Synthesis and Functionalization of Allenes and Enones Catalyzed by Gold and Copper Complexes

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Thèse présentée en vue de l'obtention du grade conjoint de Docteur en sciences de l'Université catholique de Louvain et de Docteur de l'Université Paris-Saclay (spécialité chimie organique)

2017

Université catholique de Louvain

Institut de la Matière Condensée et des Nanosciences (IMCN)

Molécules, Solides et Réactivité (MOST)

Université Paris-Saclay

Ecole Polytechnique

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Remerciements

Si les premiers mots d'un manuscrit de thèse sont parmi les plus difficiles à écrire, il en est de même pour les derniers qui composent cette section de remerciements. Ces quatre années ont été un apprentissage au métier de chercheur, tantôt décourageant, tantôt jubilatoire, toujours passionnant. Au terme de celles-ci, je tiens à remercier toutes les personnes qui y ont contribué de près ou de loin.

Tout d'abord, je tiens à remercier mes promoteurs de thèse, les Professeurs Olivier Riant et Fabien Gagosz, pour la confiance qu'ils m'ont accordée au cours de ces quatre ans. A présent que cette thèse touche à sa fin, je peux enfin confirmer ce que vous me disiez avant de la commencer : oui, vous êtes bel et bien aussi fous l'un que l'autre.

Monsieur Riant, Chef, je ne sais plus exactement quand je me suis décidé à venir faire mon mémoire dans votre labo, mais les événements qui ont suivi me confortent chaque jour un peu plus dans ce choix. Merci pour votre patience, votre optimisme (même face à des résultats qui me paraissaient désespérants), et surtout votre ouverture d'esprit et passion communicatives envers des domaines interdisciplinaires de la chimie que je n'aurais jamais envisagés comme accessibles. Enfin, merci pour les discussions autres que scientifiques que nous avons pu avoir avec vous, allant de goûts littéraires jusqu'aux derniers potins des alentours. Ce fut un réel plaisir de travailler dans votre groupe, et qui sait, peut-être que le futur nous amènera à collaborer de nouveau…

Fabien, merci à toi pour avoir accepté cette cotutelle avec l'enthousiasme qui est le tien. Après mon début de thèse un peu compliqué au niveau des résultats, j'arrivais timidement à Palaiseau, et tu as vite su me mettre à l'aise.

Merci pour ton dynamisme et ta capacité à rebooster un doctorant qui arrive vers toi avec un résultat peu probant. Je garde l'image du tableau vierge de ton bureau se remplissant rapidement de nouvelles idées qui s'éloignent de plus en plus du problème initial. Là où je pensais qu'un problème finissait en cul-de-sac, tu montrais qu'une dizaine de portes de sorties étaient à notre disposition. Merci aussi pour ta confiance quant à l'écriture du chapitre de livre RSC, et pour tes conseils avisés lors de chacune des corrections de manuscrits ou de publications. Je te souhaite bon courage à Ottawa et espère que ton groupe là-bas prendra rapidement son essor.

Je tiens ensuite à remercier le Professeur Sophie Hermans, le Professeur Alexandre Alexakis, le Docteur Raphaël Dumeunier, le Professeur Bastien Nay et le Professeur Yann Garcia pour avoir accepté d'évaluer ce manuscrit. Vos remarques et questions ont permis de pousser plus loin la réflexion sur un nombre certain de points du manuscrit, et ce dernier ne s'en porte que mieux.

Je tiens à adresser un remerciement spécial au Professeur Sophie Hermans qui m'avait encadré durant mon projet de bac 3 sur la métathèse des oléfines, il y a de cela quelques années. Ce projet avec vous a été mon premier contact avec la catalyse homogène, thématique que je n'ai plus quittée depuis, et je reste convaincu que votre encadrement et vos conseils ont contribué à mon intérêt envers ce domaine.

Que ce soit à Louvain-la-Neuve ou à Palaiseau, les labos ne tourneraient pas de la même façon sans l'aide quotidienne de plusieurs personnes. Du côté belge, je me souviens avoir été accueilli par la dame haute en couleur qu'est notre Chanchan. Merci à toi d'avoir ajouté ton grain de folie au quotidien, et d'être toujours là pour nous aujourd'hui. Je pense souvent à toi en voiture, que ce soit en changeant de vitesse, ou en véhiculant un auto-stoppeur… Merci pour tout et profite bien d'une retraite bien méritée. Merci aussi à

Audrey pour toute l'aide apportée, surtout en cette fin de thèse. Les petites discussions sur le pas de porte de ton bureau me manqueront, ainsi que les pauses Cup'Inn que nous aurions décidément dû faire plus souvent. Bon courage à toi pour la suite. Merci à Francis, mon nounours, pour l'aide quotidienne au laboratoire, pour les pauses câlins après une manip' foirée, mais surtout pour tous les bons moments passés ensemble, allant des jeux de sociétés à l'escape room organisée, en passant par les terrains de beach. Et quoi qu'on en dise, sache que c'est toi « le concierge » de l'étage, même si je me faisais épingler par le Chef plus souvent…

Dans l'aile du LSO de Polytechnique, c'est grâce à l'aide quotidienne de Béatrice que le labo tourne comme il faut. Merci à toi pour ta gentillesse, ta patience, et ton aptitude à rattraper les bêtises de chacun, telle une déprotonnation au NaH mal balisée… Profite bien de la retraite, sans trop penser à la chimie radicalaire. Merci également à Brigitte pour l'aide administrative ainsi que pour toutes les discussions plus ou moins sérieuses que nous avons eues en buvant un thé ou lors de mes visites dans ton bureau.

En quatre ans et sur deux sites géographiques, j'ai eu l'occasion de rencontrer un grand nombre de personnes qui ont rendu cette thèse inoubliable. Si la place me manque pour remercier chacun individuellement comme il se devrait, soyez sûrs que je n'en pense pas moins et que les moments passés avec vous justifient à eux seuls cette thèse.

A Palaiseau, je garde bien en mémoire les moments passés dans notre salle de pause, que ce soit en pause thé qui se transformait souvent en débat politique, ou bien durant les afterworks qui ont rythmé nos semaines avec des bières dont je ne commenterai pas la qualité.

Je commencerai par remercier Geoffroy, avec qui j'ai travaillé sur le projet des allènes-CF_3. Même si la collaboration à distance n'a pas toujours rendu les choses faciles, je pense que nous en sommes tous deux sortis grandis et

que nous pouvons être fiers du résultat. Où que tu poursuives ton parcours (du côté de l'Asie du Sud-Est peut-être ?), je te souhaite bon vent et du succès dans ce que tu entreprendras.

Un grand merci au Dr. Pierre Faudot dit Bel, pour la thèse au contenu de qualité qu'il m'a fournie (et je ne parle pas seulement du contenu scientifique). Nos discussions philosophiques ponctuées de choses « aberrantes » ou « farfelues » me manquent beaucoup, et j'espère que ton retour en France sera synonyme de retrouvailles pour nous.

Il y avait le gros proton au LSO, mais les radicaux et le titane n'étaient pas en reste non plus. Merci à Lucile, petit Fabien, Vincent R. et Vincent J. pour l'accueil (pour les uns) et pour la relève (pour les autres). Une petite pensée particulière pour Lulu à qui je souhaite une carrière extraordinaire (ce qui est déjà bien parti) et pour Vincent R. avec qui les échanges de données quotidiens permettent une productivité optimale.

Merci aux permanents du LSO que j'ai connus lors de mes passages : Sam, Yvan et Laurent pour votre gestion quotidienne du laboratoire et les discussions (scientifiques ou non) toujours captivantes que j'ai pu avoir avec vous.

La liste est encore longue, et je ne peux m'empêcher d'avoir une pensée pour tous. Merci à Alix, Aude, Diane, Olesya, Praewpan, Stefanie, Alexander, Andrey, Azmi, David, Ben, Gabriela, Guilhem, Guillaume, Ling, Pierre S., Qi, Qing, Rafal, Ricardo, Shiguang, Songhze.

Le LSO est une petite bulle dans une grande école, et la vie y a été agréable grâce à vous.

Du côté de mon Alma Mater, un roman serait probablement nécessaire pour remercier individuellement tout le monde.

Je tiens tout d'abord à remercier les « anciens » (pour ne pas dire « vieux ») du labo qui m'ont accueilli il y a cinq ans, quand j'étais jeune et innocent. Je garde de cette période un souvenir extraordinaire, entre l'année de mémoire

et la découverte du labo Riant, l'ambiance a été au rendez-vous et les résultats au beau fixe. Merci à Yoyo et Hélène pour avoir incarné le « mal » en nous faisant sortir si souvent à l'Onlywood, à Fady pour son encadrement durant le mémoire et son suivi pendant ces années de thèse, à Vivi pour sa motivation sans faille et pour m'avoir permis de partager ma passion des calendriers, à Carl pour sa confiance et pour son affection en soirée. Les soirées Only bien mouvementées avaient des protagonistes récurrents. Merci à Seb et Alice, à Gégé et Edouard, à Flo et Alex, à Thomas, à Charly, à Fleur, à Loïc et Nath, et à Xavier et Carla pour toutes ces belles années et ces moments intenses. Enfin je tiens également à remercier Yoshiko pour toutes ces années à nos côtés, ainsi que Claver, Zainab, et Affef.

Après les anciens, il me faut également remercier les très anciens. Elo, Nico, Jess, c'est un réel plaisir de vous voir à chaque event, et je trouve toujours ça aussi génial de me dire qu'on continue à s'inviter les uns les autres alors que nous ne nous sommes jamais cotoyés au labo.

Heureusement, la nouvelle génération n'est pas en reste ! Depuis mon arrivée, j'ai eu l'occasion de voir débarquer une bande d'énergumènes qui donnent au labo, voire au bâtiement, son ambiance aussi colorée. Merci à Audric pour son admiration communicative de Lukaku, à Seb pour ses SMS attachants de 4 h du matin (que je n'ai malheureusement plus), à Anto avec qui nous formions un duo « Statler et Waldorf » imparable (même si je maintiens que tu as une nette longueur d'avance sur moi pour les commérages), à Mathieu pour ses jeux de mots de mauvais goût (voire de mauvaise allène), à Florence pour tous nos moments potins (en particulier sur l'ancien répertoire UCL… RIP), à Marion pour l'accent chaleureux qu'elle nous a ramené du sud et pour son amour du pastis. Thank you Kiran for your help and your advices during our collaboration on the boroacylation project. I hope that you will enjoy your last months in Europe and I wish you the best for the

future. Bon courage à Gilles aussi, qui entame sa thèse cette année-ci. C'est évidemment un plaisir de voir que certains projets seront poursuivis et j'espère qu'ils te porteront chance et que tu en tireras autant de satisfaction que moi. Même si je ne les ai cotoyés que peu de temps, la promo de mémorants Phoenix-Camille-Stouse avec notre Antonin-nin-nin me laisse un souvenir d'une bonne cuvée. Je vous souhaite bien sûr également le meilleur pour l'avenir.

Il y a les anciens, il y a les nouveaux, et il y a celui qui transcende le temps. Merci à Coco pour tous les moments partagés : les pauses Chemistry by Design, les verres en tête à tête (oui oui), Werchter, l'élaboration et le partage de TP's, la chasse de Pokémon (au début pour moi)… Je te souhaite une bonne fin de thèse, histoire que l'on arrête de te vanner avec ça.

Une pensée particulière pour les étudiants que j'ai eu l'occasion d'encadrer. Isabel, Aubin, Phoenix, ce fut un plaisir de travailler avec vous et j'espère que votre carrière future vous donnera pleine satisfaction.

Bon courage également aux derniers arrivés, nos nouveaux mémorants. Céline, Maud, Audric, Gilles, Boris, bonne chance pour votre mémoire, et portez fièrement les couleurs du labo Riant.

Merci aux Professeurs Devillers, Tinant, Hautier, Gohy et Elias pour m'avoir autorisé à participer aux activités didactiques de l'Ecole de Chimie. Merci également au personnel didactique et assistants de l'Ecole de Chimie pour m'avoir accueilli, particulièrement Catherine, Tommy, Pascale, Corentin avec qui j'ai collaboré directement. L'assistanat est une tâche dans laquelle j'ai été ravi de pouvoir m'investir, et j'espère y avoir apporté quelque chose de positif.

Le bâtiment Lavoisier est un petit monde où il fait bon vivre. Merci aux membres des différents groupes occupant les différentes ailes de notre QG. Je ne compte plus les bons moments passés, une proportion non négligeable

ayant eu lieu dans notre sacro-sainte caféteria du 3ème. Bon courage à tous pour la suite.

La recherche fonctionnerait beaucoup moins bien sans les nombreuses aides des différentes plateformes technologiques. Merci à tous les intervenants sur ces plateformes, et particulièrement à Cécile Le Duff et à Laurent Collard, pour leur aide apportée sur les analyses RMN et HPLC respectivement.

Merci à tous les membres de l'ACIM et des Comités STEL que j'ai cotoyés durant ces quelques années. Bien qu'un peu chronophages, ces activités extra-labo m'ont permis de passer d'excellents moments et d'apprendre pas mal de choses. Si c'était à refaire, je m'y réinvestirais sans hésiter.

I would like to address a special acknowledgement to you, César, for your daily presence and friendship. Since we met during my Erasmus in St Andrews in 2012, we have never stopped keeping in touch through the years, speaking about serious and non serious business, from organometallic chemistry to Glee songs. I wish you all the best for the future.

Les chimistes, c'est bien, mais heureusement qu'il y a aussi du beau monde à côté. Merci à mes amis pour leur présence quotidienne et indispensable. Merci aux Gembloutois avec qui les contacts sont gardés depuis bientôt dix ans (aïe), et merci aux volleyeurs gembloutois et nivellois.

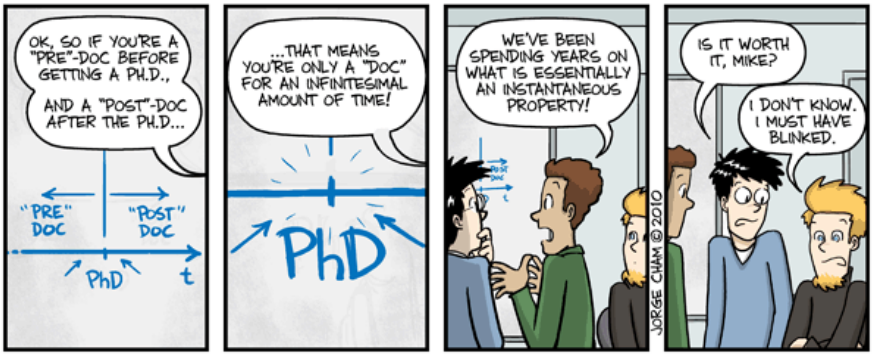
Merci au FNRS pour le soutien financier indispensable qu'ils ont prodigué à travers ma bourse FRIA.

Je tiens à remercier ma famille pour leur soutien inconditionnel qu'ils m'apportent depuis des années. En particulier, merci à vous, Maman et Papa, pour vos encouragements à nous pousser, Pauline, Thomas et moi, à poursuivre nos passions. Merci pour votre soutien moral et financier durant toutes ces années d'étude, et bien plus encore. Merci pour tout.

Enfin, je tiens à remercier Nathan pour sa présence au quotidien. Si la chimie est loin d'être ta tasse de thé, et que tu en as une image pratique quelque peu

caricaturale, ton écoute et ton humour dans les moments moins évidents ont été un soutien considérable. Merci également de m'encourager dans mes projets professionnels, même si cela rend notre vie de couple un peu plus compliquée. Enfin, et c'est sans doute le plus important, merci simplement d'être là, et de me rendre heureux chaque jour depuis notre rencontre.

Ma thèse vue par Nathan



PhD Comics

“3 reactions a day, keeps the promotor away”

found on “Not Voodoo X”

Abstract

During the last decades, transition metal catalysis has become an essential tool in organic synthesis. Each year, thousands of publications report the development of new reactions mediated by metal complexes. This manuscript depicts our contribution to this field.

The first chapter presents a general comparison of the reactivity of coinage metals (Cu, Ag, Au) complexes in catalysis, with a special focus on their ability to perform electrophilic activation (Au) or nucleophilic transfer (Cu) reactions. Representative examples are given to illustrate these concepts.

In the second part of the manuscript, the synthesis of trifluoromethylated allenes and enones by gold(I) catalysis is reported. A general method for the preparation of CF_3-allenes has been developed based on a gold(I)-mediated 1,5-hydride shift. The scope and limitations of the method, as well as some subsequent transformations of the products are described.

Using similar substrates, a gold(I)-catalyzed [3,3]-acetate rearrangement was applied to the preparation of CF_3-enones. The employment of this method into a one-pot procedure involving a subsequent Diels-Alder reaction is also reported.

The third part focuses on the copper(I)-catalyzed borofunctionalization of allenes. The recent reports from the literature are reviewed, and our contributions to this area of research are described through the study of a new copper(I)-catalyzed allene boroacylation method.

Finally, preliminary results on the elaboration of a copper(I)/gold(I) catalytic one-pot process are presented.

Résumé

Depuis plusieurs décennies, la catalyse par les métaux de transition est devenue un outil incontournable pour la synthèse organique. Chaque année, des milliers de publications décrivent le développement de nouvelles réactions effectuées en présence de complexes organométalliques.

Le premier chapitre de ce manuscrit présente une comparaison générale de la réactivité des métaux du groupe 11 (Cu, Ag, Au), avec une attention particulière sur leur capacité à réaliser des réactions d'activation électrophile (Au) ou des transferts de nucléophiles (Cu). Des exemples représentatifs sont donnés pour illustrer ces concepts.

Dans la seconde partie, la synthèse d'allènes et d'énones trifluorométhylés par catalyse à l'or(I) est détaillée. Une méthode générale de préparation d'allènes-CF_3 a été développée par un transfert d'hydrure-1,5 induit par un complexe d'or(I). Les limites de la méthode ainsi que certaines applications des produits sont décrites.

Dans la même idée, un réarrangement-[3,3] d'acétates propargylique catalysé par l'or(I) a été appliqué à la synthèse d'énones-CF_3. L'incorporation de cette méthode dans un processus monotope avec une réaction de Diels-Alder est également présentée.

La troisième partie est centrée sur les réactions de borofonctionnalisation d'allènes catalysées par le cuivre(I). Les récents développements de ce domaine sont passés en revue, et notre contribution à ce sujet est détaillée.

Enfin, un travail préliminaire sur l'élaboration d'un processus monotope impliquant une catalyse coopérative cuivre(I)/or(I) est présenté.

Abbreviations

Ac	:	Acetyl
Ad	:	Adamantyl
Ar	:	Aryl
BDP	:	1,2-Bis(DiphenylPhosphino)benzene
BINAP	:	2,2'-bis(diphénylphosphino)-1,1'-binaphtyle
Bn	:	Benzyl
BPin	:	Pinacolatoboryl
Bz	:	Benzoyl
cat.	:	Catalytic
Cp*	:	PentamethylCycloPentadienyl
Cy	:	Cyclohexyl
DBM	:	DiBenzoylMethane
DBU	:	1,8-DiazaBicyclo(5.4.0)Undec-7-ene
DCM	:	Dichloromethane
DCyPE	:	1,2-Bis(DiCyclohexylPhosphino)Ethane
DIAD	:	Diisopropyl azodicarboxylate
Dipp	:	Di*iso*propylphenyl
DMAP	:	DiMethylAminoPyridine
DMF	:	DiMethylFormamide
DM-Segphos	:	5,5′−Bis[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole
DMSO	:	DiMethylSulfOxide

dppb	:	1,2-bis(DiPhenylPhosphino)Benzene
dppe	:	1,2-bis(DiPhenylPhosphino)Ethane
dppf	:	1,1′-bis(DiPhenylPhosphino)Ferrocene
DTBM-Segphos	:	5,5′-Bis[di(3,5-Di-Tert-Butyl-4-Methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole
ee	:	Enantiomeric Excess
Et	:	Ethyl
equiv	:	Equivalent(s)
EWG	:	Electron Withdrawing Group
HMPA	:	HexaMethylPhosphoramide
HOMO	:	Highest Occupied Molecular Orbital
HSAB	:	Hard and Soft Acids and Bases
IMes	:	1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
iPr	:	Isopropyle
IPr	:	1,3-bis(2,6-diisopropylphenyl)imidazo-2-ylidene
LDA	:	Lithium DiisopropylAmide
LG	:	Leaving Group
LUMO	:	Lowest Unoccupied Molecular Orbital
mcpba	:	*Meta*-ChloroPerBenzoic Acid
Mes	:	Mesityl
MTBE	:	Methyl *Tert*-ButylEther
NaHMDS	:	Sodium bis(trimethylsilyl)amide
NIS	:	*N*-iodosuccinimide
Me	:	Methyl

Mes	:	2,4,6-trimethylbenzyl (mesityl)
min	:	Minute(s)
Ms	:	Methanesulfonyl (mesyl)
MTBE	:	Methyl *tert*-butyl ether
NaHMDS	:	Sodium bis(trimethylsilyl)amide
nd		Not determined
NMR	:	Nuclear Magnetic Resonance spectroscopy
NHC	:	*N*-Heterocyclic Carbene
NIS	:	*N*-IodoSuccinimide
NMP	:	*N*-Methyl-2-Pyrrolidone
Nu	:	Nucleophile
phen	:	Phenanthroline
Ph	:	Phenyl
Piv	:	Pivaloyl
PMHS	:	Poly(MethylHydroSiloxane)
rt	:	Room Temperature
SET	:	Single Electron Transfer
S_N2	:	Nucelophilic Substitution (2^{nd} order)
(S,S)-Ph-bpe	:	1,2-bis((2S,5S)-2,5-diphenylphospholano)-ethane
*t*Bu	:	*Tert*-butyl
*t*BuBox	:	2,2′-Isopropylidenebis[(4S)-4-*tert*-butyl-2-oxazoline]
*t*BuXPhos	:	2-Di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl
TBAF	:	*Tert*-Butyl Ammonium Fluoride

TBAI : *Tert*-Butyl Ammonium Iodide

TBAT : Tetrabutylammonium difluorotriphenylsilicate

TBDPS : *Tert*-ButylDiPhenylSilyl

TEMPO : 2,2,6,6-TEtraMethyl-1-PiperidinylOxy

TIPS : Triisopropylsilyl

Tf : Trifluoromethanesulfonyl (triflyl)

TFA : TriFluoroAcetic Acid

TFAA : TriFluoroAcetic Anhydride

THF : TetraHydroFuran

THP : TetraHydroPyran (protecting group)

TMS : TriMethylSilyl

Tol : Tolyl

Ts : Toluenesulfonyl (tosyl)

XPhos : 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

List of Publications

The following publications and book chapter have been reported during this PhD:

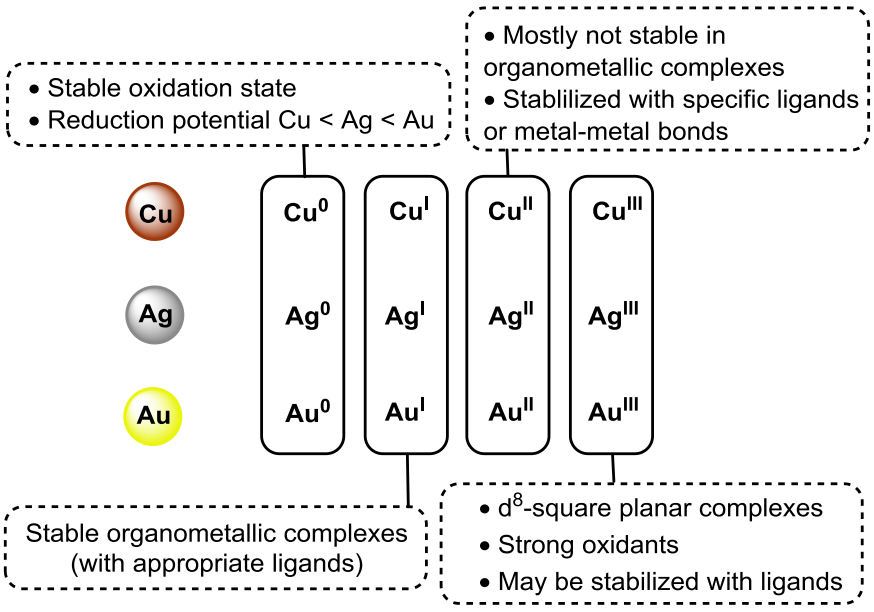
1. F. Nahra, Y. Macé, A. Boreux, F. Billard, O. Riant, *Chem. - Eur. J.* **2014**, *20*, 10970 – 10981; *Versatile Cu^{I}/Pd^{0} Dual Catalysis for the Synthesis of Quaternary α-Allylated Carbonyl Compounds: Developments, Mechanistic Investigations and Scope*.
2. A. Boreux, G. H. Lonca, O. Riant, F. Gagosz, *Org. Lett.* **2016**, *18*, 5162-5165; *Synthesis of Trifluoromethyl-allenes by Gold-Catalyzed Rearrangement of Propargyl Benzyl Ethers*.
3. A. Boreux, N. Marion, F. Gagosz, "*NHC–Copper, –Silver and –Gold Complexes in Catalysis*". In S. Díez-González (Ed.), *N-Heterocyclic Carbenes: From Laboratory Curiosities to Efficient Synthetic Tools: Edition 2* (pp. 421 – 455), **2017**, Royal Society of Chemistry, Cambridge.
4. A. Boreux, K. Indukuri, F. Gagosz, O. Riant, **2017**; under revision; *Acyl Fluorides as Efficient Electrophiles for the Copper-Catalyzed Boroacylation of Allenes*.

Table of Contents

Chapter I: General Introduction: Coinage Metals Complexes as Catalysts – Reactivity of Gold and Copper Complexes

I. General Considerations on Coinage Metal Complexes

The group 11 elements, called "coinage metals", have always fascinated humankind and have been used during centuries to make jewels or decorative objects. Since the beginning of the elements classification by Mendeleïev, their similarities in terms of structure and properties have been pointed out by scientists. The particular electronic configuration of copper, silver and gold ([Ar] $3d^{10}$ $4s^1$, [Kr] $4d^{10}$ $5s^1$ and [Xe] $4f^{14}$ $5d^{10}$ $6s^1$ respectively) where a single electron remains on the external s orbital reveals a common feature between these elements. In this continuity, the three metals exhibit a similar behavior in organometallic complexes at their different oxidation states (Scheme I-1).



Scheme I-1. Properties of the coinage metals at their most common oxidation states

In each of these oxidation states, some nuances have to be made to explain the differences of reactivity between these metals.

- Oxidation state 0: All coinage metals are relatively stable in their elementary form. As shown by their standard reduction potential, the nobler is the metal, the harder it is to oxidize it in aqueous medium: $E°_{Cu^{2+}/Cu}$ = 0.34 V < $E°_{Ag^{+}/Ag}$ = 0.80 V < $E°_{Au^{3+}/Au}$ = 1.52 V.[1] Therefore, the preparation of active electrophilic gold catalysts requires the use of a strong oxidant, such as *aqua regia*. As this oxidation state displays only few interesting reactivities in the context of organic transformation, it will not be the subject of discussion in this manuscript.
- Oxidation state +I: although the dispropotionation of aqueous copper(I) or gold(I) salts is thermodynamically favoured, coinage metal(I)-based organometallics complexes are often stable thanks to the use of appropriate ligands. In the field of homogeneous catalysis, this oxidation state is probably the one majorly exploited for silver and gold. Catalytic transformations involving organometallic copper(I) complexes are also a subject of intense research. As the +I oxidation state of copper and gold was mainly involved throughout this PhD, the specific properties of copper(I) and gold(I) complexes will be detailled in the next paragraph.
- Oxidation state +II: Copper(II) is known to be the most stable oxidation state of copper in aqueous media and with inorganic ligands. However, the fast reductive elimination of copper(II) organometallics complexes usually leads to the generation of a stable copper(0) species and makes them relatively prompt to decomposition. Moreo-

[1] https://www.webelements.com

ver, silver(II) and gold(II) complexes tend to disproportionate. Their isolation requires some stabilization brought by appropriate chelating ligands (Cu, Ag, Au) or by metal-metal bonds (Au).[2] Except for the use of copper(II) inorganic complexes used as copper precatalysts, this oxidation state will not be the subject of further discussions in this manuscript.

- Oxidation state +III: Coinage metals complexes adopt a square planar geometry induced by the d^8 electronic configuration of this oxidation state. Although several complexes of this type have been isolated and characterized, they behave as strong oxidant and ligands are necessary to stabilize them. Copper(III) species are often postulated as intermediates in several transformations, but their isolation remains rare.[3] Silver(III) compounds are mainly based on inorganic and chelating ligands, and are not frequent in organometallic chemistry. Finally, several gold(III) species can be isolated and characterized, and they can be used as a gold source for catalytic transformations.

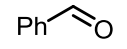
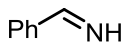
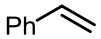
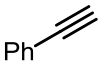
The +I oxidation state will be the most depicted in this manuscript, and some attention will be given to gold(III) as well. More especially, the interaction

[2] For a previous PhD thesis from our group presenting a related introduction, see: "Développement de nouvelles réactions catalysées par l'or, l'argent ou le cuivre pour la synthèse de molécules hétérocycliques" by C. Gronnier (2013, supervisor: F. Gagosz).

[3] For selected examples, see: (a) S. H. Bertz, S. Cope, M. Murphy, C. A. Ogle, B. J. Taylor, *J. Am. Chem. Soc.* **2007**, 129, 7208–7209; (b) A. E. King, L. M. Huffman, A. Casitas, M. Costas, X. Ribas, S. S. Stahl, *J. Am. Chem. Soc.* **2010**, *132*, 12068-12073; (c) B. Yao, Z.-L. Wang, H. Zhang, D.-X. Wang, L. Zhao, M.-X. Wang, *J. Org. Chem.* **2012**, *77*, 3336–3340.

and reactivity of metal complexes with carbon-carbon unsaturated bonds will be the basis of the methods developed during this PhD.

All coinage metal complexes and salts can behave as Lewis acids. Depending on the nature of the Lewis base which is in presence, the strength of the interaction can fluctuate. In order to make this consideration quantitative, Y. Yamamoto reported a theoretical work on the interaction between several metal salts and σ- or π-donating functional groups, such as an aldehyde, imine, alkene or alkyne (Scheme I-2).[4]

		CuCl	$CuCl_2$	AgCl	AuCl	$AuCl_3$
σ		-156.5	-106.3	-110.4	-138.5	-150.2
		-216.7	-172.4	-165.7	-224.2	-252.3
π		-140.6	-75.7	-102.1	-156.9	-154.0
		-138.5	-59.8	-94.6	-145.2	-136.0

Scheme I-2. Coordination enthalpy ($kJ.mol^{-1}$) of Lewis acids with several functional groups involving σ or a π bonds

All coordination patterns are exothermic, but some trends can be found by comparing several chosen cases:

- By comparing the aldehyde row to the alkene and alkyne rows, it turns out that the gold salts are the only ones that present a better affinity for the carbon-carbon unsaturated bonds than for the oxygen atom. Gold complexes can be considered as more carbophilic than the corresponding copper and silver salts. Though, the latters still display some affinity for those unsaturations as the associated trans-

[4] Y. Yamamoto, *J. Org. Chem.* **2007**, *72*, 7817-7831.

formation is exothermic. Copper and silver are therefore also able to induce some transformations on alkenes and alkynes.

- A closer look at the same table rows also allows the comparison of the carbophilicity of several oxidation states of the same metal. The energy gap between an aldehyde and an alkyne is relatively higher for $CuCl_2$ than for CuCl. This trend is even stronger for gold, where $AuCl_3$ displays a less exothermic coordination energy towards the alkyne than the aldehyde. On the contrary, AuCl coordination is more favourable towards the triple bond *versus* the aldehyde. These facts can be related to the Hard and Soft Acids and Bases (HSAB theory) which also indicates the good affinity of harder cations (Cu^{II}, Au^{III}) with harder Lewis bases (heteroatoms) and of softer cations (Cu^{I}, Au^{I}) with softer Lewis bases (unsaturated carbon-carbon bonds).
- In all columns, the strongest energy is associated to the coordination of the metal to the imine. This has as consequence the inhibition of coinage-metal catalyzed reactions by basic nitrogen atoms.

This simplified model was able to show the general trends in the reactivity of coinage metals towards several Lewis bases, and so their potential to activate several functional groups in catalysis.

The next paragraph will have as goal to describe briefly the general reactivity of gold and copper catalytic species in carbon-carbon unsaturated bonds activation.

II. Gold Catalysis in Electrophilic Activation of Carbon-Based Unsaturations

II.1. Relativistic Effects in Gold Complexes

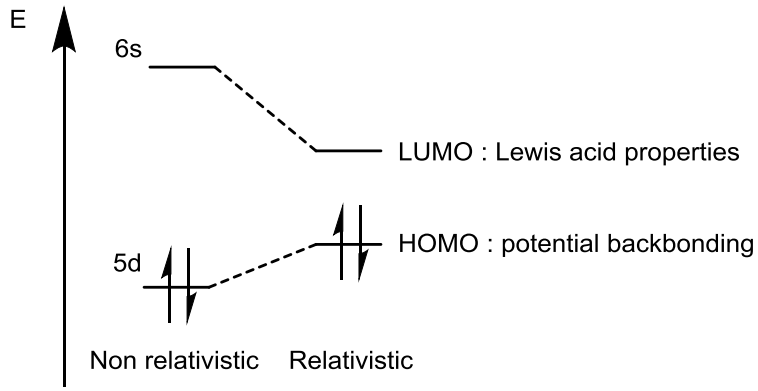
The use of gold complexes in homogeneous catalysis remains a recent advance in the field of organic synthesis, mostly due to the assumed chemical inertia of metallic gold. Gold possesses the electronic configuration [Xe] $4f^{14}$ $5d^{10}$ $6s^{1}$, where a single electron remains on the external 6s orbital. Due to this configuration, Au^{I} (d^{10}) and Au^{III} (d^{8}) complexes can be commonly found, under linear and square planar geometry respectively. As stated above, both types of complexes exhibit exceptional Lewis acid properties, and tend to be more carbophilic than their copper or silver analogs.

Other characteristics of gold are quite peculiar as it does not follow the trends from the previous periods of the periodic table. Its radius is quite small, its electronegativity is one of the highest among the transition metals (2.54, close to the carbon electronegativity of 2.55) and its optical properties provide its golden colour.

All these specificities find their origin in relativistic effects encountered in the case of heavy elements. In the case of gold, several studies have shown the link between these relativistic aspects and its properties.[5] Relativistic effects can be attributed to a heavy nucleus surrounded by electrons with high speed. The consequence is a relative increase of the eletron mass, and so a decrease of the Bohr radius. The 6s and 6p orbitals of gold are affected by this phenomenon, and the contraction of these orbitals is correlated with the stabilization of the 6s orbital, which is the LUMO in the case of Au^{I}

[5] (a) P. Pyykkö, *Angew. Chem. Int. Ed.* **2004**, *43*, 4412-4456; (b) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395-403.

complexes (Scheme I-3). The energy lowering of this orbital induces improved Lewis acid properties for gold compared to a considered non relativistic analog. Besides, the contraction of these orbitals induces a better shielding effect from the nucleus toward the d and f orbitals. This leads to a diffusion of these orbitals and so to an increase of their energy. The 5d orbital (HOMO) of Au^{I} species undergoes this energy raise, which also affects the electronic properties by allowing a potential backbonding of the gold electrons towards the ligands.

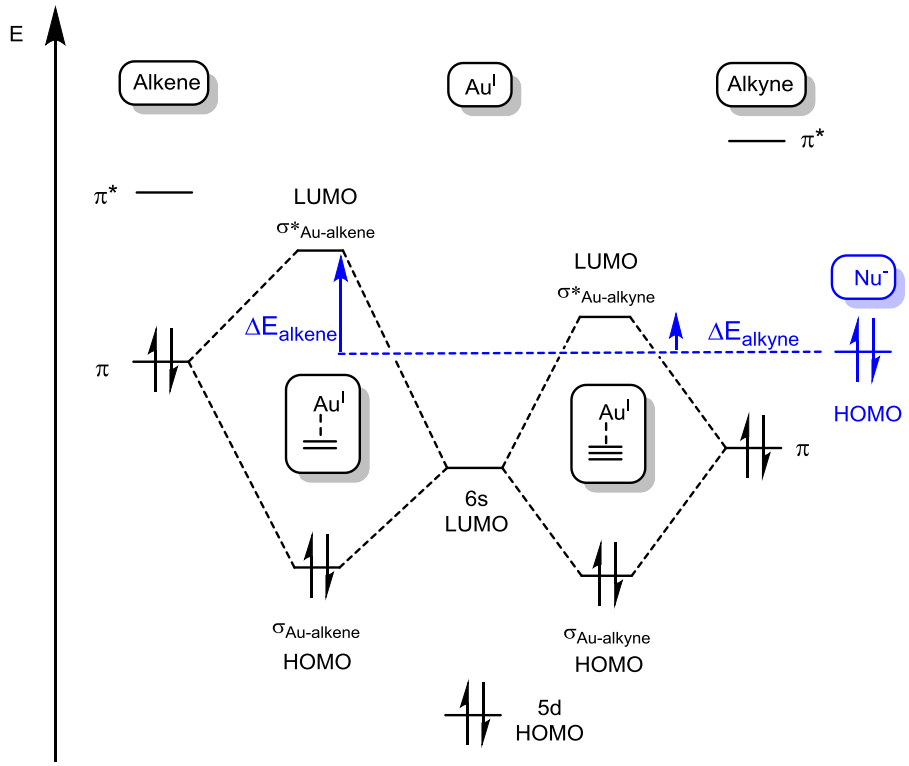


Scheme I-3. Relativistic effects on the energy of Au^{I} HOMO and LUMO

Starting from these considerations, the electrophilic activation of carbon-carbon unsaturations by gold(I) complexes can be discussed (Scheme I-4). The 6s orbital of the gold (LUMO) interacts with a π orbital of the unsaturation (HOMO) to form a stabilizing metal-ligand bond. This activation leads to the creation of a new LUMO (σ* metal-ligand) that can interact with the HOMO of a nucleophile in the medium (alcohol, amine,…). Therefore, this phenomenon is at the origin of the activation of unsaturations by gold complexes.

The reactivity order of alkynes *versus* alkenes can also be deducted from this consideration. The LUMO generated by the interaction between gold(I) and an alkyne being lower in energy, the energy gap $\Delta E_{Au\text{-}alkyne}$ is smaller than

with an alkene. Alkynes behave as better electrophiles when activated by gold than alkenes, and allenes display an intermediate reactivity in this reaction pathway.

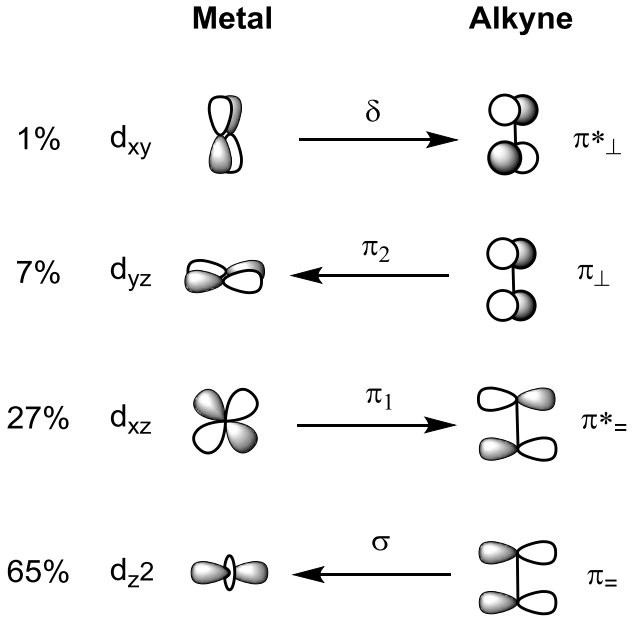


Scheme I-4. Activation of carbon-carbon unsaturations by gold(I) complexes

In Scheme I-4, the bond between the gold center and the alkene/alkyne is represented as a simple interaction between the 6s orbital of the metal and the π orbital of the ligand. This interaction is actually more complex and involves several orbitals from the metal (5d, 6s, 6p orbitals) and from the ligand (π and π* orbitals). A more detailled model showing several components of the gold-acetylene bond based on the 5d orbitals of the metal is presented in Scheme I-5.[6]

[6] A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449.

In this model, the predominant interaction appears to be the donation from the π bond of the alkyne to the d_{z2} orbital of the metal (65%). The retrodonation from the d_{xz} orbital to the π* orbital of the alkyne constitutes the first π bond of this metal-ligand interaction (27%). Finally, minor contributions involving the perpendicular π-system of the alkyne constitute the last fraction of the bond.



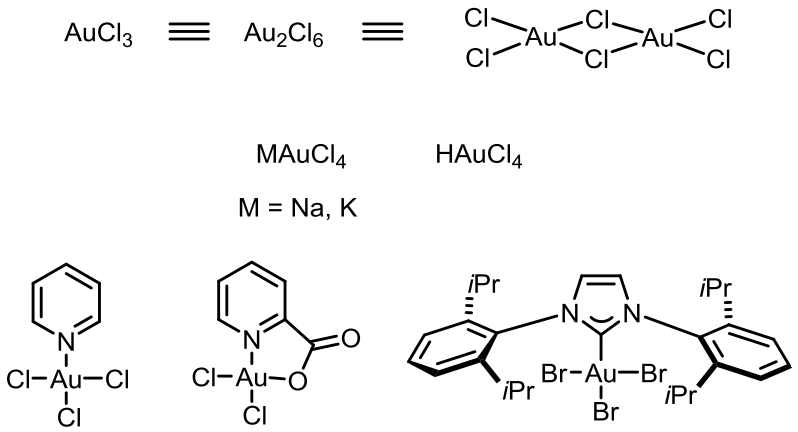
Scheme I-5. Qualitative molecular orbital diagram showing the components of a metal/alkyne interaction (adaptated from reference 6)

II.2. Structures and Preparation of Gold Catalysts

The aim of this paragraph is to describe the general structures of typical gold salts and complexes that are used in catalysis. An emphasis is given on the structures that will interest us in the context of this PhD research. Two families of gold catalysts will be considered: gold(III) and gold(I) species.

Gold(III) complexes

With their [Xe] $4f^{14}$ $5d^{8}$ $6s^{0}$ configuration (d^{8}), gold(III) complexes adopt a square planar geometry. As mentioned earlier, asides from their Lewis acid properties, they also behave as oxidants. Several gold(III) salts are commercially available, and constitute the first synthetic intermediates obtained from elementary gold after an oxidative treatment (Scheme I-6). $AuCl_3$, or Au_2Cl_6, is a very hygroscopic gold dimer. Other complexes based on the tetrachloroaurate(III) anion ($AuCl_4^-$) are obtained by the oxidation of gold(0) by *aqua regia*. More sophisticated complexes can be prepared by the use of stabilizing ligands, such as a pyridine, a chelating picolinate or a NHC.



Scheme I-6. Described gold(III) salts and complexes

Even if these complexes can potentially be used as a gold source for the activation of carbon-carbon unsaturated bonds, their trend to coordinate heteroatomic function, their lack of selectivity and the limitations of modulability on the ligands make them so far less interesting than their gold(I) homologs.

Gold(I) complexes

Gold(I) complexes possess a [Xe] $4f^{14}$ $5d^{10}$ $6s^{0}$ configuration (d^{10}) and exhibit most of the time a linear geometry.[7] Ligands are necessary to stabilize these complexes and a counteranion is present to balance the positive charge of the gold(I) nucleus. Depending on the nature of this counteranion, two general configurations of gold(I) complexes are presented on Scheme I-7. If a coordinating counteranion is used, a linear complex including the counteranion in the coordination sphere is obtained (complex A). On the contrary, the use of a non-coordinating counteranion leads to the formation of a cationic complex bearing two neutral ligands (complex B). When a bidentate ligand is used, double coordination of the metal centre is usually observed. In the case of gold(I), the disposition of this metal to form linear complexes leads to the formation of two gold-containing species, with one ligand linked to each gold centre (complex C).[8] In this case, studies have showed that aurophilic interactions between the two gold atoms existed and contributed to the conformational stability of the complex.

This list of encountered gold complexes geometries in not exhaustive, as complexes or clusters with higher coordination numbers can be prepared.[9] However, this is given to highlight the complexes usually employed as precatalysts in gold electrophilic catalysis, and so the species that will be considered in the following sections of this manuscript.

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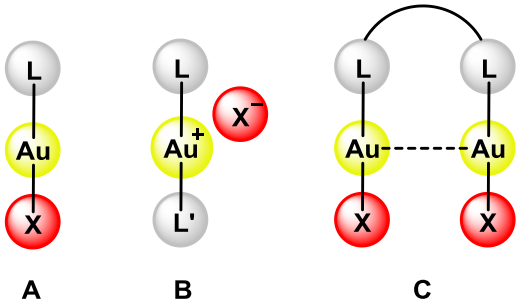
[7] M. A. Carvajal, J. J. Novoa, S. Alvarez, *J. Am. Chem. Soc.* **2004**, *126*, 1465-1477.

[8] For the original reports of this family of complexes, see: (a) H. Schmidbaur, A. Wohlleben, F. Wagner, O. Orama, G. Huttner, *Chem. Ber.* **1977**, *110*, 1748-1754; (b) M.-C. Brandys, M. C. Jennings, R. J. Puddephatt, *J. Chem. Soc., Dalton Trans.* **2000**, 4601-4606.

[9] A. Blumenthal, H. Beruda, H. Schmidbaur, *J. Chem. Soc., Chem. Commun.* **1993**, 1005-1006.



L, L' = neutral ligands (phosphorus-based, NHC, MeCN, Me_2S,...)
X = counteranion (Cl, Br, OTf, NTf_2, SbF_6,...)

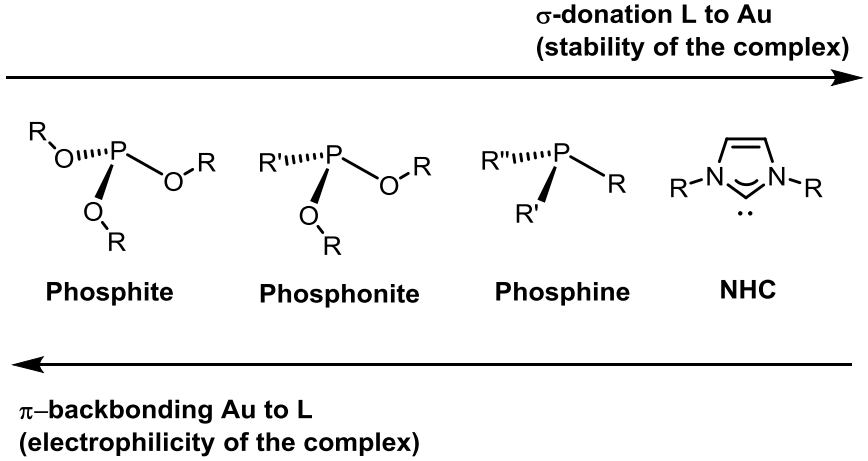
Scheme I-7. Possible configurations of gold(I) complexes

Both the nature of the coordinating ligand as well as the counteranion used are important to define the reactivity of a gold catalyst. The combination of those two parameters leads to a large possibility for the design of gold(I) catalysts.

Numerous families of neutral ligands are depicted in the literature. The ones that will be involved during this PhD work are represented on Scheme I-8.

- *N*-Heterocyclic Carbenes (NHC's): This carbene-type ligand characterize itself by a strong σ-donating ability associated with generally poor π-backbonding from the gold to the ligand. These properties make the corresponding gold complexes relatively electron-donating and able to stabilize cationic intermediates.
- Phosphites: At the other extremity, phosphites display relatively poor σ-donating properties and are very strong π-acceptors. This gives to the gold complexes a high electrophilic character and makes them very efficient as Lewis acids. This high reactivity is also reflected in the poor stability of these complexes and their trend to decompose in reactions media.
- Phosphines and phosphonites: At intermediates positions between NHC's and phosphites, these phosphorus-based ligands combine σ-

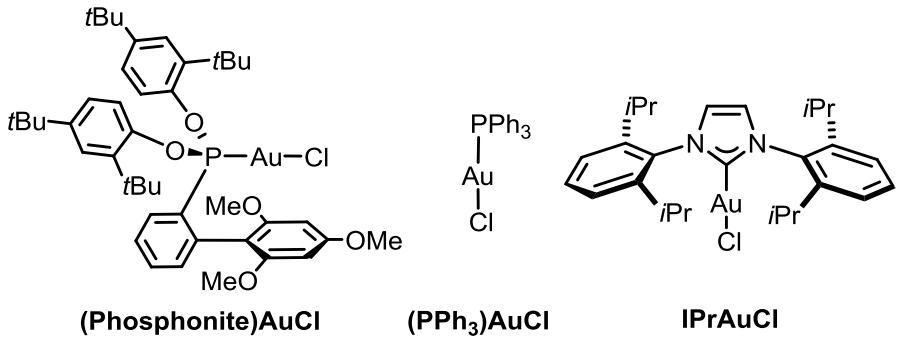
donation and π-backbonding at several proportions. The corresponding complexes are relatively stable and display nice reactivity. On the opposite of phosphonites which are quite exotic moieties, phosphines are probably the most standard ligands used in gold catalysis, with the triphenylphosphine PPh_3 as the simplest example. Many more sophisticated phosphines were developed during the last decades and several examples will be used in this manuscript.



Scheme I-8. Families of ligands used in combination with gold(I)

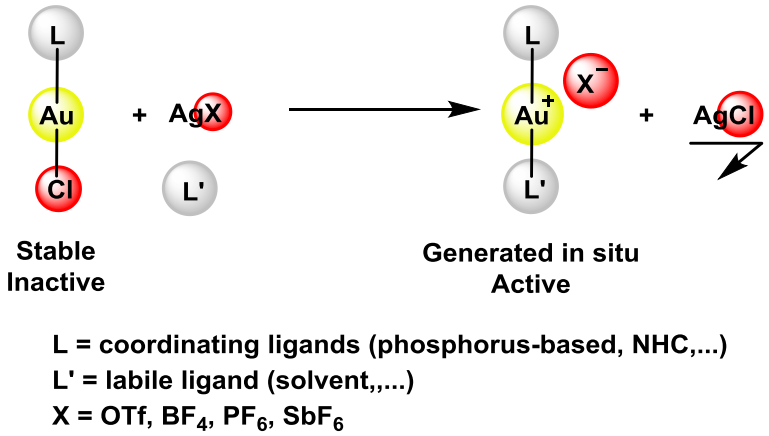
Concerning the counteranion, the main issue is to find a compromise between the stability and the reactivity of the complex.[10] Gold(I) chloride complexes are usually very stable but suffer from a low activity in catalysis (Scheme I-9). These species are most of the time used as the gold precursor which must be activated by the abstraction of the chloride.

[10] For a review on the counterion effect in gold catalysis, see: M. Jia, M. Bandini, *ACS Catal.* **2015**, *5*, 1638-1652.



Scheme I-9. Examples of gold(I) chloride complexes: stable but non active catalysts

This abstraction can be carried out by the addition of a silver(I) salt that generates a silver chloride precipitate and releases the active gold complex. This strategy allows the generation this species in situ by the addition of silver(I) trilfate, tetrafluoroborate, hexafluorophosphate or hexafluoroantimonate.



Scheme I-10. In situ generation of an active gold species from a gold(I) chloride complex and a silver salt

The use of copper salts as the additive instead of silver has also been developed. By adding copper(II) triflate to a gold chloride complex, the group of

Bezzenine-Lafollée and Gandon observed a cooperative effect of gold and copper, and better results were obtained than with the silver triflate analog.[11] However, this method has been a matter of some debate. Indeed, the presence of silver or copper in the reaction medium does not allow to identify the real nature of the active species and to know when the added cation is still playing a role.[12] This is why the isolation of stable and active gold complexes has been the subject of research.

Two counteranions leading to the formation of isolable complexes have become currently used in the field of gold(I) catalysis. The first one has been reported by Gagosz and co-workers in 2005 and relies on the use of the bis(trifluoromethylsulfonyl)imidate species NTf_2^-.[13] The reaction between a gold(I) chloride and $AgNTf_2$ leads to the isolation of a stable gold complex containing this weakly coordinating anion. It ensures the stability of the gold(I) precatalyst and is labile enough to be an active catalyst. Some examples of reported catalyst are presented on Scheme I-11.

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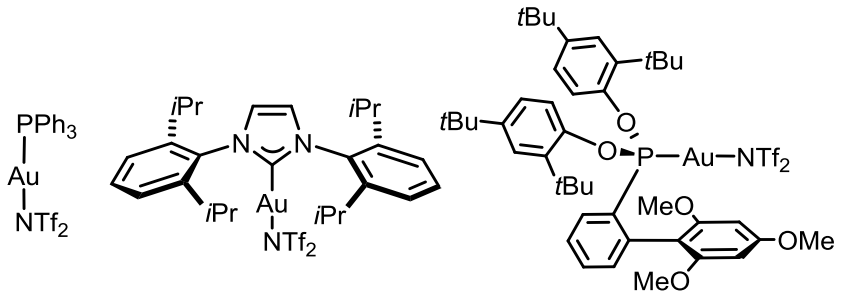
[11] A. Guérinot, W. Fang, M. Sircoglou, C. Bour, S. Bezzenine-Lafollée, V. Gandon, *Angew. Chem. Int. Ed.* **2013**, *52*, 5848-5852.

[12] For selected reports discussing the active catalytic species generated by a mixture of gold and silver complexes, see: (a) D. Weber, M. R. Gagné, *Org. Lett.* **2009**, *11*, 4962-4965; (b) D. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X. Liu, J. L. Petersen, X. Shi, *J. Am. Chem. Soc.* **2012**, *134*, 9012-9019.

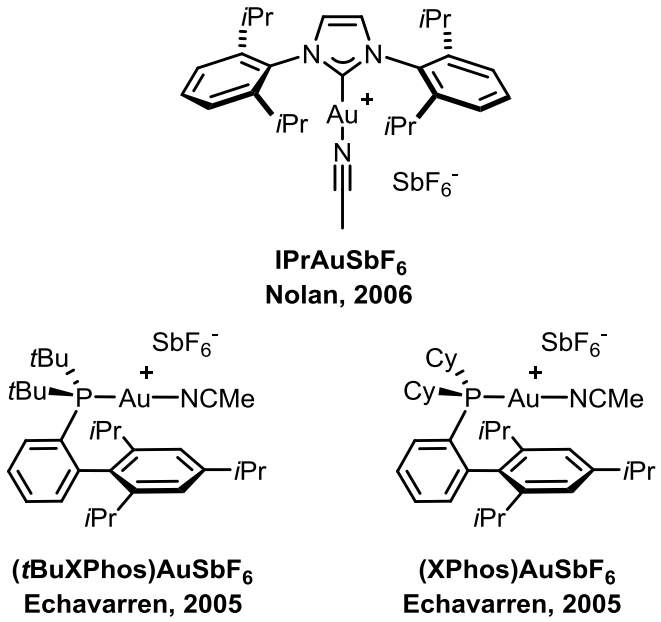
[13] (a) N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133-4136; (b) L. Ricard, F. Gagosz, *Organometallics*, **2007**, *26*, 4704-4707; (c) G. Henrion, T. E. J. Chavas, X. Le Goff, F. Gagosz, *Angew. Chem. Int. Ed.* **2013**, *52*, 6277-6282.



Scheme I-11. NTf_2-gold(I) complexes as stable and active catalysts (Gagosz and co-workers)

Another development was reported by the group of Echavarren on phosphine-gold complexes in 2005.[14a] By abstracting the chloride of the gold precatalyst with silver(I) hexafluoroantimonate in the presence of acetonitrile, a cationic complex bearing the nitrile as the second ligand and hexafluoroantimonate can be isolated (Scheme I-12). The same transformation was applied on NHC-gold complexes by the group of Nolan in 2006.[14b] This method represents another general way to prepare active yet bench-stable gold(I) catalysts from the corresponding chloride complexes.

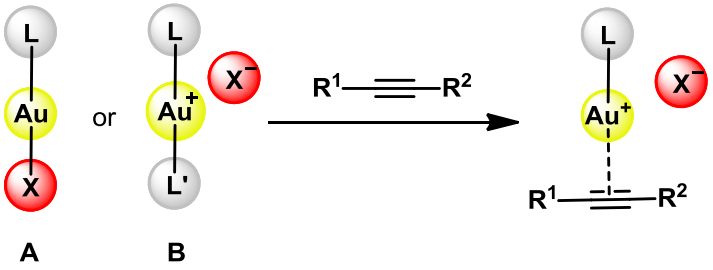
[14] (a) C. Nieto-Oberhuber, S. López, M. P. Muñoz, D. J. Cárdenas, E. Buñuel, C. Nevado, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2005**, *44*, 6146-6148; (b) P. de Fremont, E. D. Stevens, M. R. Fructos, M. Mar Diaz-Requejo, P. J. Perez, S. P. Nolan, *Chem. Commun.* **2006**, 2045-2047



Scheme I-12. Cationic complexes with SbF_6^- as counteranion

II.3. General Reactivity of Gold Complexes

As shown previously, gold(I) complexes display good Lewis acid properties and can interact with carbon-carbon bond unsaturations, such as alkynes (Scheme **I-13**). The preferential linear geometry adopted by gold complexes induces a ligand exchange between the counteranion (**A**) or the labile ligand (**B**) and the π-system (here an alkyne) to activate. The resulting complex consists in a linear structure where the activated alkyne is at 180° of the ligand that modulates the steric and electronic properties of gold. As explained previously (Scheme I-4), this interaction enhances the electrophilic properties of the alkyne. The attack of nucleophiles on this activated system constitutes the pillar of electrophilic homogeneous gold catalysis and leads to a high number of developments in this field.



Scheme I-13. Coordination of an alkyne to a gold(I) precatalyst

The attack of a nucleophile on a gold-activated triple bond occurs in an *anti* fashion to generate a vinylgold intermediate (Scheme I-14). The main options for this intermediate rely on its capture by an electrophilic species. In most of the early reports, a proton was used to regenerate the gold catalyst via a protodeauration step (Scheme I-14, pathway a).[15] In some cases, an electrophilic source of halogen can be used for this deauration step (Scheme I-14, pathway b).[16] Besides, in some particular occasion, the trapping of the electrophile can occur on the β-position of the gold, leading to the formation of a cationic species (Scheme I-14, pathway c). Depending on the ligand on the gold atom, the latter can possess some carbene character. Strong electrophilic ligands (e.g. a phosphite) favour the carbocationic form whereas σ-donor ligands stabilize the carbene. This behavior opens a wide range of reactivity which has also been exploited in organic synthesis.[17]

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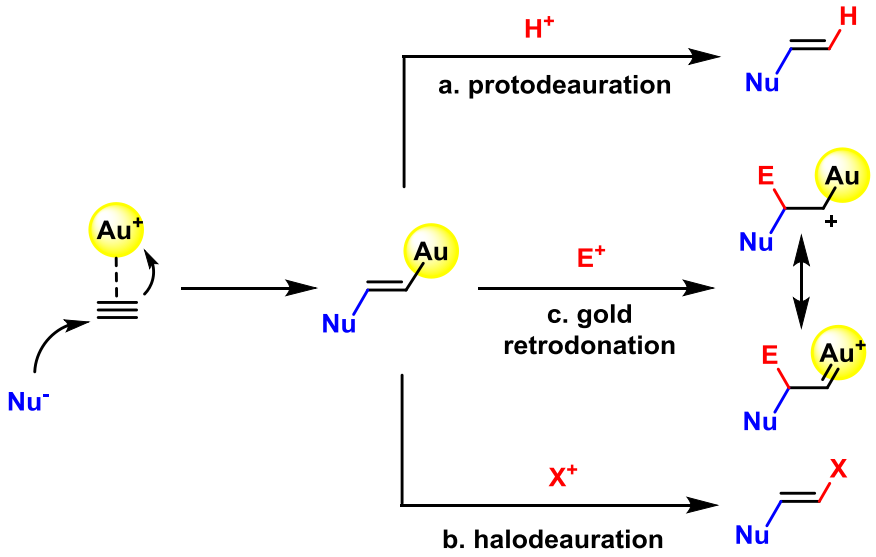
[15] For a recent book chapter on the gold-catalyzed formal addition of HX to alkynes, see: E. Genin, V. Michelet, *The Chemistry of Organogold Compounds*, **2014**, Pt. 2, 901–960.

[16] A. Corma, A. Leyva-Pérez, M. J. Sabater, *Chem. Rev.* **2011**, *111*, 1657-1712.

[17] For recent reviews on the synthesis and reactivity of gold carbenes, see: (a) Y. Wang, M. E. Muratore, A. M. Echavarren, *Chem. - Eur. J.* **2015**, *21*, 7332-7339; (b)



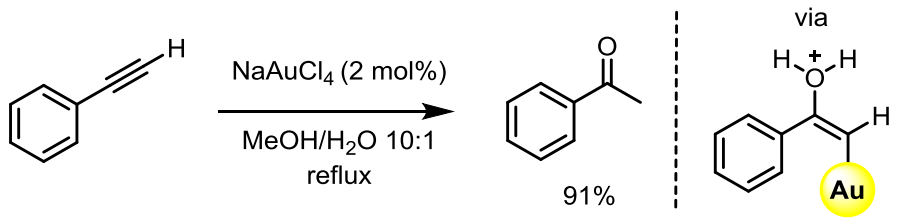
Scheme I-14. General mechanistic pathways for gold-catalyzed alkyne functionalizations

Because of the large number of reports in the field of gold catalysis, an exhaustive overview is difficult to give in a concise manner. The next paragraphs will have as purpose to present the first developments in gold catalysis as well as selected and representative examples to illustrate the general reactivity. Even if some examples have also been reported with alkene or allene substrates, we will focus our attention on alkynes which are the most common moiety involved in gold(I) catalysis.

H.-S. Yeom, S. Shin, *Acc. Chem. Res.* **2014**, *47*, 966-977; (c) L. Zhang, *Acc. Chem. Res.* **2014**, *47*, 877-888.

Addition of heteroatoms on alkynes

The first example of a gold-catalyzed hydration of alkynes was reported by Thomas and co-workers in 1976 with $HAuCl_4$.[18] In 1991, the group of Fukuda and Utimoto obtained acetophenone starting from phenylacetylene by using catalytically $NaAuCl_4$ as a catalyst (Scheme I-15).[19] An improved system using a gold(I) precatalyst activated by a Brönsted acid was reported by the group of Hayashi and Tanaka in 2002.[20] In all cases, this reaction proceeds with a Markovnikov selectivity and acts as a nice alternative to the analogous alkyne hydration reaction catalyzed by mercury salts.



Scheme I-15. Example of gold-catalyzed alkyne hydration by Utimoto in 1991

Since then, a lot of developments have been carried out in order to improve the catalytic systems in terms of catalyst loading[21] and of selectivity for internal unsymmetrical alkynes.[22] Nowadays, this reaction can also be used as

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[18] R. O. C. Norman, W. J. E. Parr, C. B. Thomas, *J. Chem. Soc., Perkin Trans. 1*, **1976**, 1983-1987.

[19] Y. Fukuda, K. Utimoto, *J. Org. Chem.* **1991**, *56*, 3729-3731.

[20] E. Mizushima, K. Sato, T. Hayashi, M. Tanaka, *Angew. Chem., Int. Ed.* **2002**, *41*, 4563-4565

[21] For a publication using a NHC-gold catalyst with a loading decreased until 10 ppm, see: N. Marion, R. S. Ramon, S. P. Nolan, *J. Am. Chem. Soc.* **2009**, *131*, 448-449. However, the authors do not precise the amount of silver salt that they added to activate the gold, which could also behave as a catalyst for this transformation.

[22] J. A. Goodwin, A. Aponick, *Chem. Commun.* **2015**, *51*, 8730-8741.

a benchmark reaction to assess the activity of new ligands complexed to gold(I).[23]

Besides the addition of water, gold(I) complexes have also showed to efficiently promote the addition of various heteronucleophiles onto alkynes (Scheme I-16).[15] Alcohols were the first examples developed concomitantly with water. For instance, they can be added in an inter- (Scheme I-16 (a)[24]) or intramolecular (Scheme I-16 (b)[25]) fashion to furnish a ketal or an enol ether function. In the same vein, nitrogen-based nucleophiles were employed to functionalize alkynes in order to deliver several structural motifs, such as an imine (Scheme I-16 (c)[26]) or an oxazolidinone (Scheme I-16 (d)[27]).

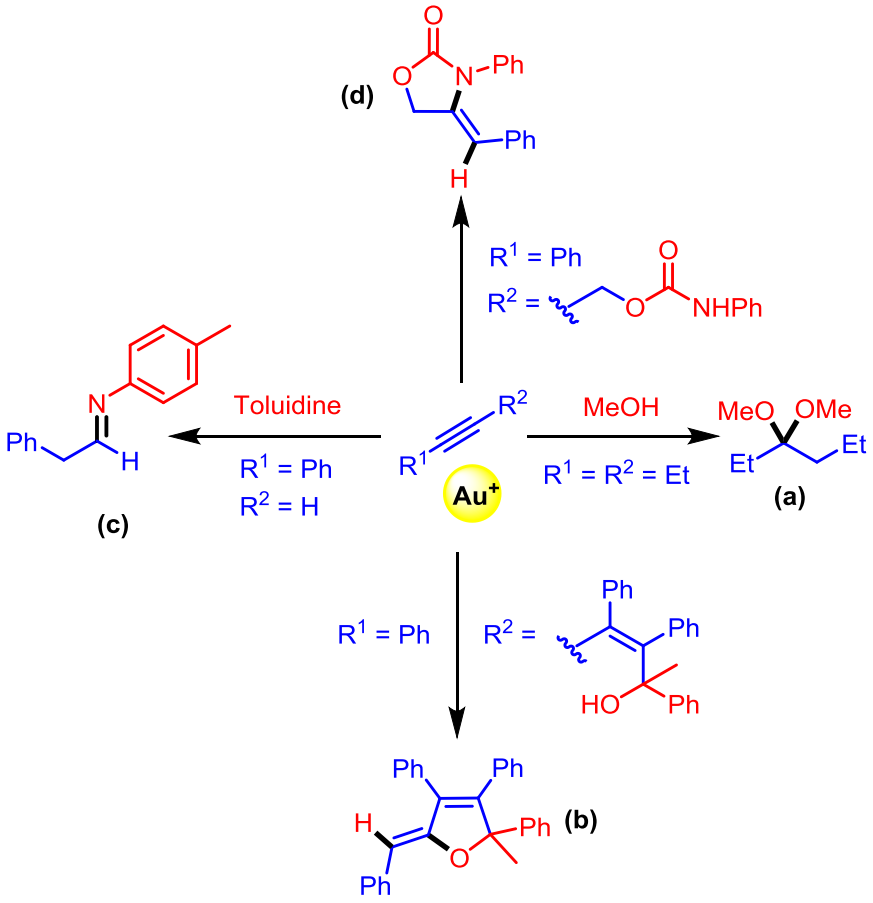
[23] « Développement de nouveaux complexes d'or et leur application en catalyse homogène » by P. Faudot dit Bel (2015, supervisor: F. Gagosz).

[24] J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem. Int. Ed.* **1998**, *37*, 1415-1418.

[25] Y. Liu, F. Song, Z. Song, M. Liu, B. Yan, *Org Lett.* **2005**, *7*, 5409-5412.

[26] Y. Fukuda, K. Utimoto, *Synthesis* **1991**, 975-978

[27] S. Ritter, Y. Horino, J. Lex, H.-G. Schmalz, *Synlett* **2006**, 3309-3313.



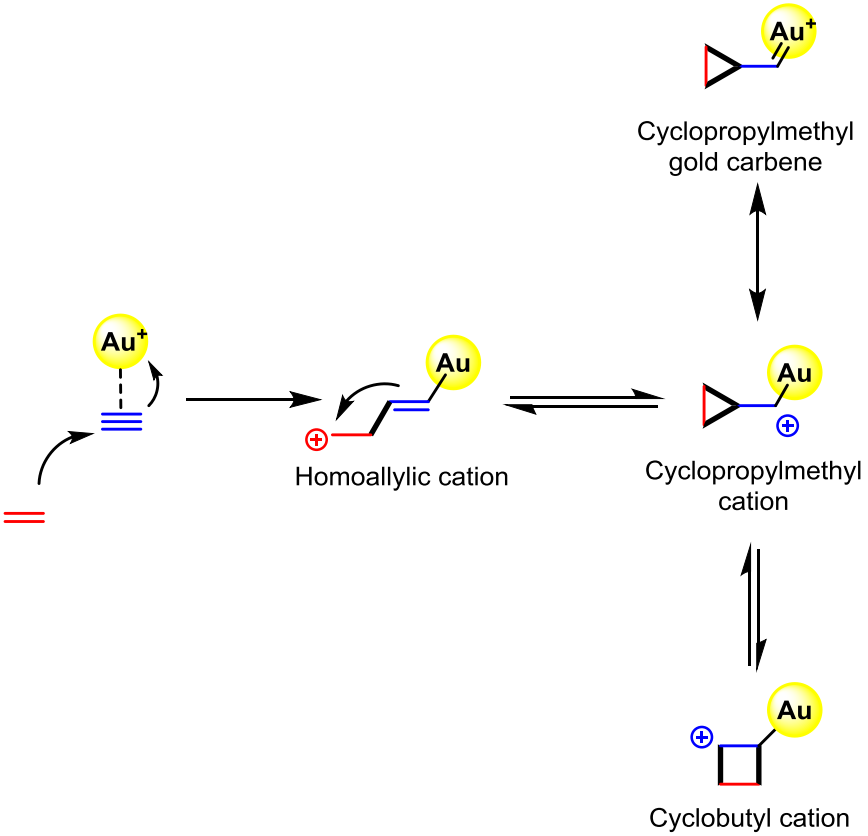
Scheme I-16. Selected examples for the gold-catalyzed addition of heteronucleophiles onto alkynes

Enynes cycloisomerisations

Besides the addition of heteroatoms on alkynes, enyne cycloisomerization is also known as a benchmark reaction in the field of gold catalysis.[28] The main mechanistic pathways are presented on the Scheme I-17. The transformation is initiated by the addition of a nucleophilic alkene on the gold-activated

[28] Selected reviews: a) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326-3350; b) R. Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, *115*, 9028-9072.

alkyne that leads to the formation of a carbon-carbon bond with the generation of a gold-stabilized homoallylic cation. The structure of this intermediate is actually not fixed and it exists as an equilibrium between several limit forms (cyclopropylmethyl cation, cyclopropyl gold carbene, cyclobutyl cation). Several factors, such as the nature of the ligand, the temperature, the solvent… can push the equilibrium toward one of these limit forms and so enhance one specific reactivity of this intermediate.



Scheme I-17. Reaction intermediates in the gold-catalyzed enyne cycloisomerization

As mentioned previously, electron-donating ligands would favour the formation of a gold-carbene type intermediate, whereas electron-withdrawing

ligands would lead to the generation of carbocationic species. The formation of these intermediates is reflected in the isolation of "carbene-type" or "carbocation-type" products. Therefore, this transformation can be regarded as a benchmark test for new gold catalysts in order to get some insight in their electronic properties and their propention to favour one intermediate or the other.

When carried out on unactivated alkenes and alkynes, enyne cycloisomerizations are most of the time performed in an intramolecular fashion. This corresponds to a cyclization reaction and several variations can be observed depending on the substrate geometry, but also on the nature of the catalyst (Scheme I-18).

Endo-type cyclizations (upper part) generate a bicyclic motif bearing an endocyclic gold-carbene. Several evolutions for this intermediate can be envisioned, and some selected examples are given below: a proton elimination followed by a protodeauration (a, b)[29] or associated to a cyclopropane ring-opening (c)[30] can lead to the formation of various structural motifs.

The *exo*-type cyclization (lower part) produces an exocyclic gold carbene which can also lead to various products. For example, its trapping by a nucleophile such as methanol generates the corresponding cyclic product (d).[31] More complex rearrangements can occur and lead to diene products in which the original alkene and alkyne moieties have been completely mixed up

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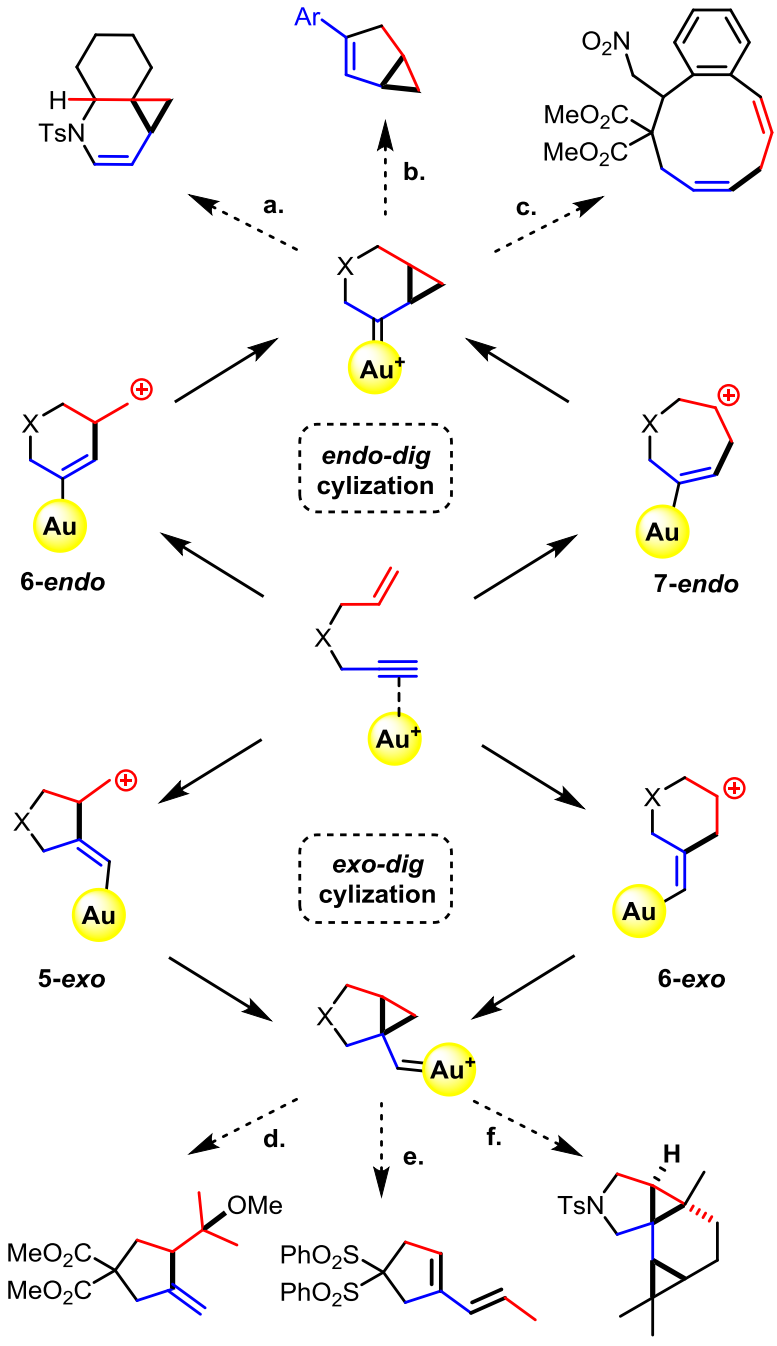
[29] a) C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406; b) M. R. Luzung, J. P. Markham, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 10858-10859.

[30] E. Comer, E. Rohan, L. Deng, J. A. Porco, *Org. Lett.* **2007**, *9*, 2123-2126.

[31] C. Nieto-Oberhuber, M. P. Munoz, S. Lopez, E. Jimenez-Nunez, C. Nevado, E. Herrero-Gomez, M. Raducan, A. M. Echavarren, *Chem. - Eur. J.* **2006**, *12*, 1677-1693.

(e).[29a] An intramolecular cyclopropanation involving the generated gold carbene and the alkene can produce fancy polycyclic structures (f).[29a]

These few examples are far from covering the whole field of enynes cycloisomerization but are given to highlight the impressive potential and possibilities of such type of transformation.



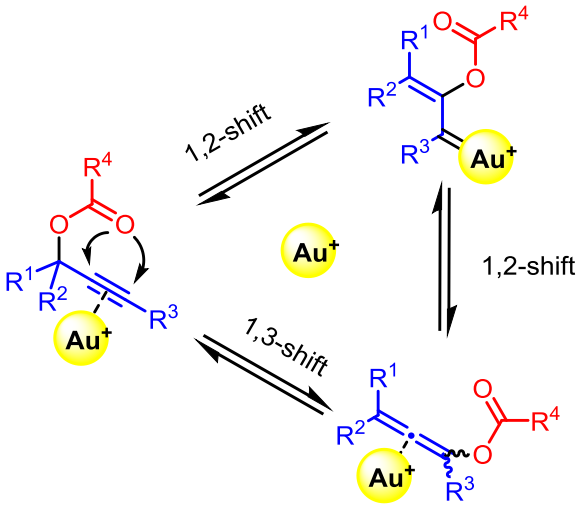
Scheme I-18. General mechanism for gold-catalyzed enynes cycloisomerization

Miscellaneous transformations

Since the report of the first gold-catalyzed transformations, the number of publications in the field has exponentially increased so that this metal has become one of the most investigated in homogeneous catalysis. While the classical reactivity of gold(I) complexes towards alkynes has been described in the previous sections, the large variety of transformations involving this reactivity makes difficult their comprehensive listing. We will just mention some of the other types of transformations mediated by gold(I) which have been the subject of an increasing interest during the last years:

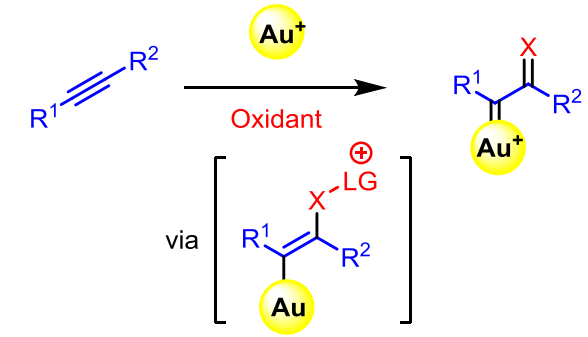
- Propargylic esters rearrangements: A wide range of gold-catalyzed reactions are also based on an initial rearrangement of a propargyl ester via a 1,2- or 1,3-shift (Scheme I-19).[32] Depending on the nature of the ligand and the reaction conditions, the predominant species can react further and pull the equilibrium toward the formation of the product. As this transformation was involved in a project during this PhD, the literature associated will be detailed later in this manuscript (p.134).

[32] N. Marion, S. P. Nolan, *Angew. Chem. Int. Ed.* **2007**, *46*, 2750-2752.



Scheme I-19. General mechanism for the gold-catalyzed propargyl ester rearrangements

- Generation of α-oxo- or α-imino-gold carbenes: If the nucleophile attacking the alkyne also possesses a leaving group on its reactive centre, it can be described as ambivalent. In this context, this species allows the generation of gold carbenes on the α-position of the carbonyl or iminyl function (Scheme I-20). This strategy is often described as an alternative to the use of diazo compounds for the generation of carbenes and its development has been the subjects of several studies in the past years.[17c]



Oxidant	X =	Leaving group (LG)
Pyridine *N*-oxide	O	Pyridine
Sulfoxide	O	Sulfide
Azide	NR	N_2

Scheme I-20. Generation of gold carbenes by the use of ambivalent nucleophiles

- Oxidative additions on gold(I) complexes: On the contrary to palladium(0) or rhodium(I) complexes, gold(I) catalyst are not prompt to undergo an oxidative addition step, because of the low stability of the resulting gold(III) species. Several groups have been recently working on the generation of these gold(III) intermediates, by the use of external oxidants[33] or by designing specific gold(I) complexes.[34] Advances toward the use of Au(I)/Au(III)-based cross-couplings have been carried out through these studies.

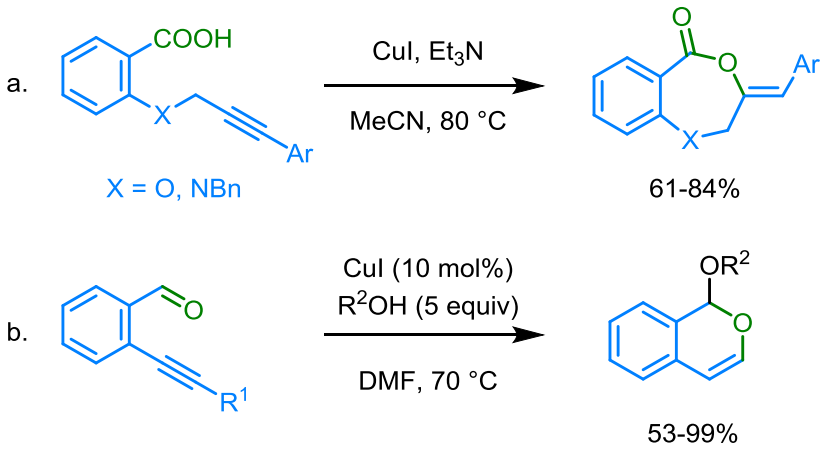
[33] Selected example: W. E. Brenzovich, D. Benitez, A. D. Lackner, H. P. Shunatona, E. Tkatchouk, W. A. Goddard, F. D. Toste, *Angew. Chem. Int. Ed.* **2010**, *49*, 5519-5522.

[34] a) M. Joost, A. Zeineddine, L. Estévez, S. Mallet−Ladeira, K. Miqueu, A. Amgoune, D. Bourissou, *J. Am. Chem. Soc.* **2014**, *136*, 14654-14657; b) M. Joost, L. Estévez, K. Miqueu, A. Amgoune, D. Bourissou, *Angew. Chem. Int. Ed.* **2015**, *54*, 5236-5240.

III. Copper Catalysis: From Electrophilic Activation to Nucleophilic Transfers

III.1. Copper(I)-Mediated Reactions on Alkynes: Electrophilic or Nucleophilic?

Even if copper(I) salts and complexes also possess soft Lewis acid properties, this does not constitute the main reactivity of such entities. In the field of electrophilic alkynes activation, some examples catalyzed by copper(I) species have been reported in the literature (Scheme I-21).[35,36] However, most of these examples are limited to intramolecular functionalization and require relatively high temperatures as compared to similar gold-catalyzed reactions.

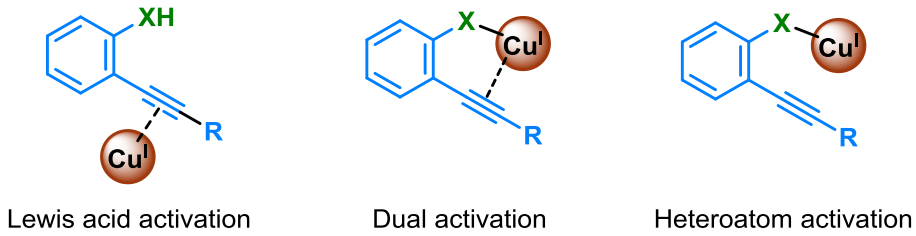


Scheme I-21. Examples of copper-catalyzed electrophilic activation of alkynes

[35] Selected examples: a) G. Chaudhuri, N. G. Kundu, *Chem. Soc., Perkin Trans. 1*, **2000**, 775; b) N. T. Patil, Y. Yamamoto, *J. Org. Chem.* **2004**, *69*, 5139-5142.

[36] For a more detailed review of this field of the literature, see the corresponding section in the PhD thesis of C. Gronnier (ref. 2).

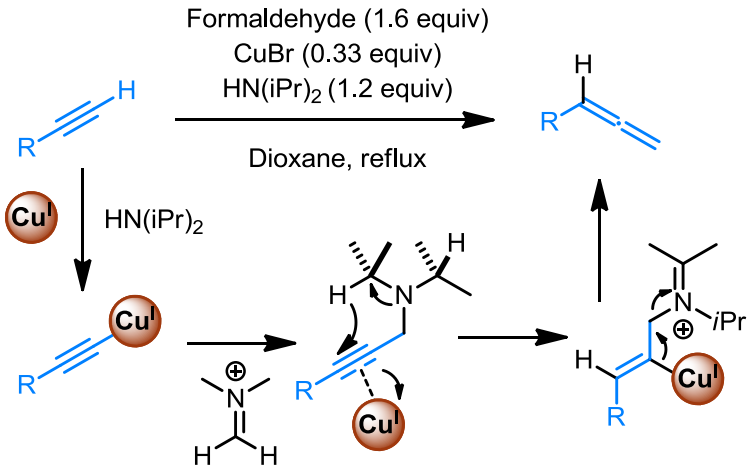
A precise mechanism for the activation of alkynes remains elusive in these reports. Even if the same electrophilic activation than in gold(I) catalysis can be applied for this transformation (Scheme I-22, left part), other types of reactivity can be invoked. Indeed, the Lewis acidity of copper(I) complexes is in competition with the ability of copper to activate pronucelophiles in order to promote their addition on unsaturations (Scheme I-22, right part). A cooperative action of both cannot be excluded (Scheme I-22, middle part).



Scheme I-22. Potential types of activation by copper(I) complexes

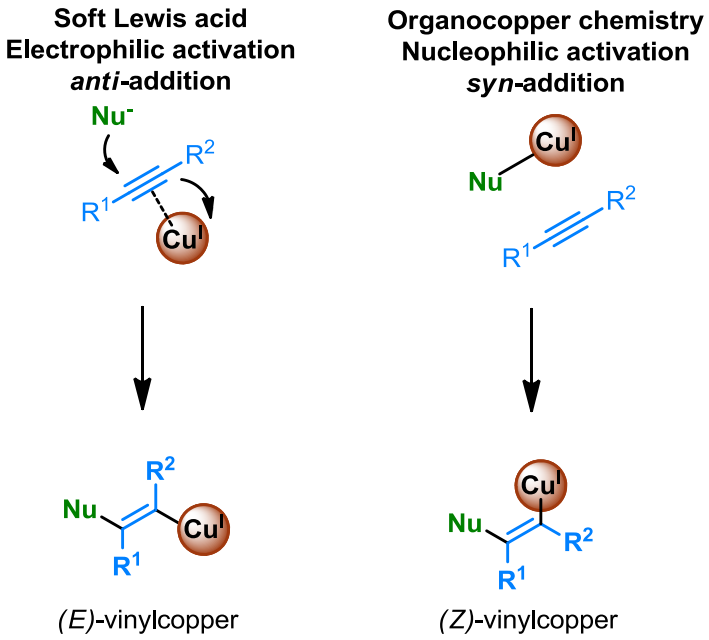
An illustrative reaction where copper exhibits these two abilities is the homologation of alkynes by the Crabbé reaction (Scheme I-23).[37] A copper-assisted deprotonation of a terminal alkyne produces a nucleophilic alkynyl-copper species. The reaction of this intermediate with a generated iminium leads to the formation of a propargylic amine. Then, the electrophilic activation of the alkyne by copper(I) induces a 1,5-hydride shift which generates a vinylcopper intermediate. Its subsequent fragmentation furnishes an allene, an imine and regenerates the copper(I) catalyst.

[37] P. Crabbé, H. Fillion, D. Andre, J.-L. Luche, *J. Chem. Soc., Chem. Commun.* **1979**, 859-860.



Scheme I-23. Mechanism of the Crabbé reaction involving electrophilic and nucleophilic activation by the copper catalyst

This nucleophilic activation by copper(I) complexes constitutes nowadays an entire field of reasearch in copper catalysis. Whereas the previously discussed Lewis acid properties of copper(I) complexes lead to the *anti*-addition of nucleophiles onto alkynes (Scheme I-24, left part), the addition of nucleophiles onto alkynes involves a *syn*-addition of the reagent to generate the vinylcopper intermediate (Scheme I-24, right part). In the next section, the use of copper catalysis to transfer several element-based nucleophiles (B, Si, H,…) on unsaturations will be discussed.



Scheme I-24. Two mechanistic pathways involved in copper catalysis

III.2. Copper(I)-Catalyzed Activation of Silanes, Borosilanes and Bis(pinacolato)diboron

Essentially issued from the chemistry of organocuprates, the use of organocopper species has become during the last decades a key tool in organic synthesis.[38] More especially, the catalytic generation of organocopper entities, such as Cu-B,[39] Cu-Si[40] or Cu-H[41] intermediates have led to the development of elaborated and synthetically useful methods.

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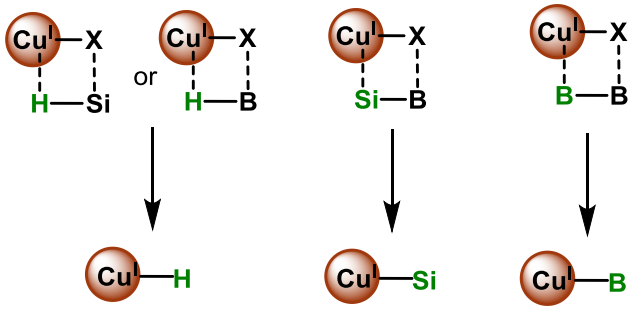
[38] *The chemistry of organocopper compounds* (Eds.: Z. Rappoport, I. Marek), Wiley, Chichester, UK, **2009**.

[39] For recent examples, see: (a) K. Kato, K. Hirano, M. Miura, *Angew. Chem. Int. Ed.* **2016**, *55*, 14400-14404; (b) X. Li, F. Meng, S. Torker, Y. Shi, A. H. Hoveyda,

The generation of these active species is believed to occur via a common pathway presented on Scheme I-25. A copper(I) precatalyst bearing a hard counteranion (fluorine or oxygen-based) undergoes a σ-metathesis with a pronucleophile in order to generate the organocopper species with the release of a stable by-product (containing a Si-X or B-X bond).



Scheme I-25. Generation of Cu-H, Cu-Si and Cu-B species from the Cu-X precatalyst (X = F or OR)

Depending on the nature of the starting pronucleophile, a different active species can be generated:

- Cu-H: Although copper hydrides were at first described and used as stoichiometric reagents,[42] catalytic generation of copper hydride species has rapidly become a reliable tool in organic synthesis. Nowadays, copper hydrides can be easily produced by the reaction between a copper precatalyst and a silane or a borane. The hydride can then be transferred onto a desired electrophile, such as a carbon-

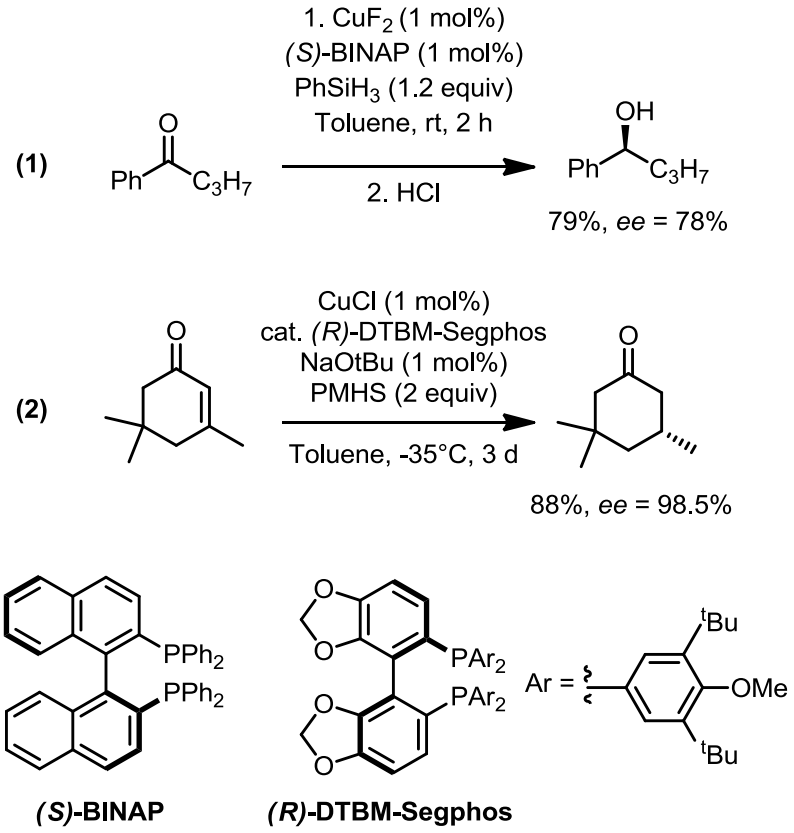
Angew. Chem. Int. Ed. **2016**, *55*, 9997-10002; (c) M. Guisán-Ceinos, A. Parra, V. Martín-Heras, M. Tortosa, *Angew. Chem. Int. Ed.* **2016**, *55*, 6969-6972.

[40] M. Oestreich, E. Hartmann, M. Mewald, *Chem. Rev.* **2013**, *113*, 402-441.

[41] C. Deutsch, N. Krause, B. H. Lipshutz, *Chem. Rev.* **2008**, *108*, 2916-2927.

[42] W. S. Mahoney, D. M. Brestensky, J. M. Stryker, *J. Am. Chem. Soc.* **1988**, *110*, 291-293.

yl compound (Scheme I-26 (1))[43] or a Michael acceptor (Scheme I-26 (2)).[44] Enantioselective versions of such transformations have been described and have proven their efficiency.[41] Additional details on the developments of this transformation and their involvement in tandem processes will be given in Chapter V.



Scheme I-26. 1,2- and 1,4-reductions mediated by copper hydrides

[43] S. Sirol, J. Courmarcel, N. Mostefai, O. Riant, *Org. Lett.* **2001**, *3*, 4111-4113.

[44] B. H. Lipshutz, J. M. Servesko, T. B. Petersen, P. P. Papa, A. A. Lover, *Org. Lett.* **2004**, *6*, 1273-1275.

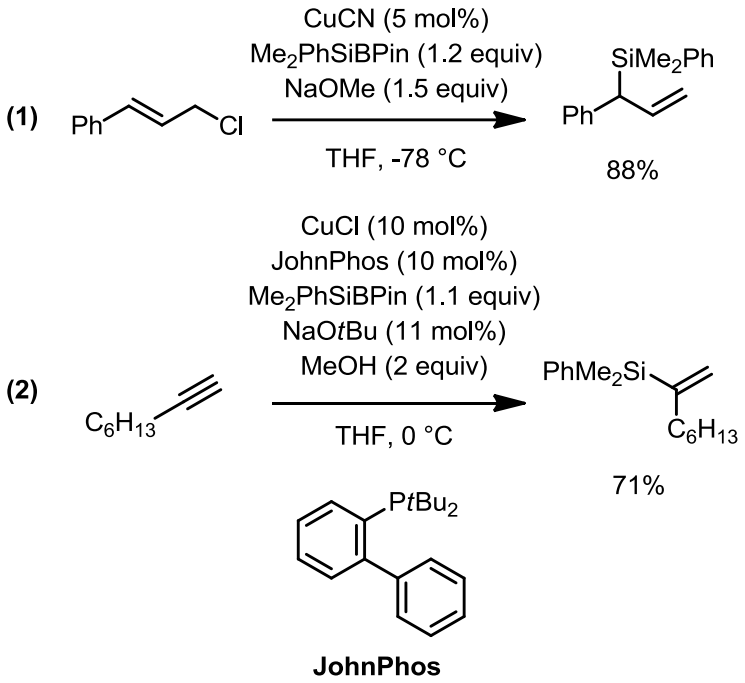
- Cu-Si: Copper-mediated transfers of silylcuprates have been already known for decades.[45] However, the transposition to neutral copper-catalyzed transformations turns out to be more recent, probably due to the lack of suitable reagents possessing a transferable silicon moiety. The emergence of this field might be related to the development of a stable silylboronate, the Suginome's reagent,[46] which can easily be employed as a nucleophilic silicon equivalent in the presence of copper complexes. This strategy has been exploited in conjunction with several common electrophiles and has shown its efficacy. For instance, we can mention the cupration of carbon-carbon unsaturations, using allyl chlorides[47] or alkynes[48] as substrates (Scheme I-27). These methods represent a straightforward route for the synthesis of alkyl and vinylsilanes, respectively, which are both useful building blocks in organic synthesis.

[45] For a review, see: R. K. Dieter in *Modern Organocopper Chemistry* (ed. N. Krause), chapter 3, p. 79-144.

[46] M. Suginome, T. Matsuda, Y. Ito, *Organometallics* **2000**, *19*, 4647-4649.

[47] D. J. Vyas, M. Oestreich, *Angew. Chem. Int. Ed.* **2010**, *49*, 8513-8515.

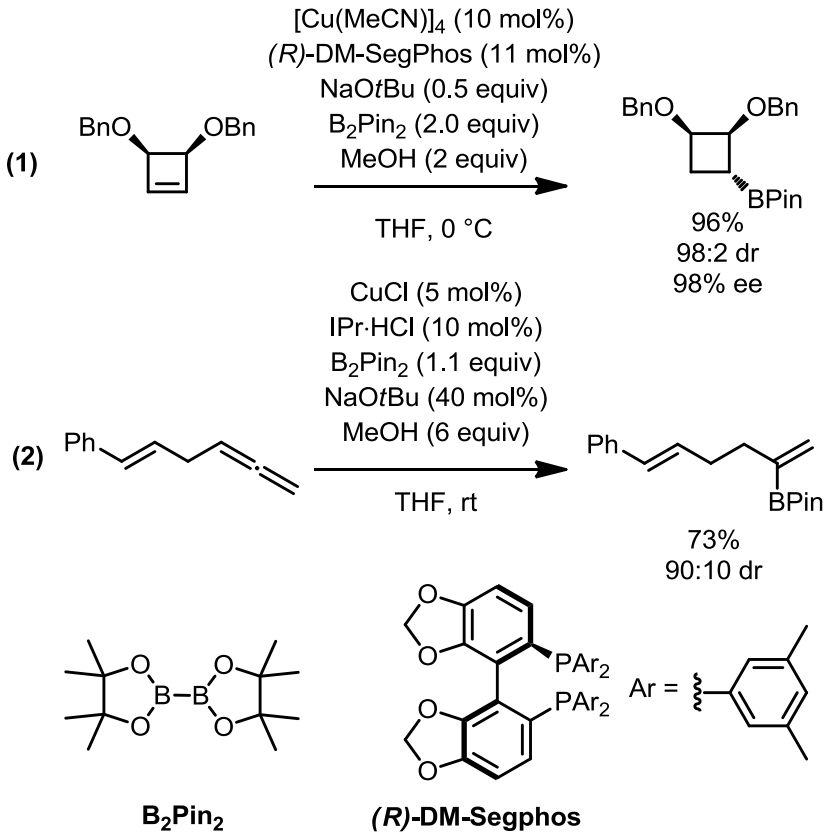
[48] P. Wang, X.-L. Yeo, T.-P. Loh, *J. Am. Chem. Soc.* **2011**, *133*, 1254-1256.



Scheme I-27. Copper-catalyzed addition of silicon onto allyl groups and alkynes

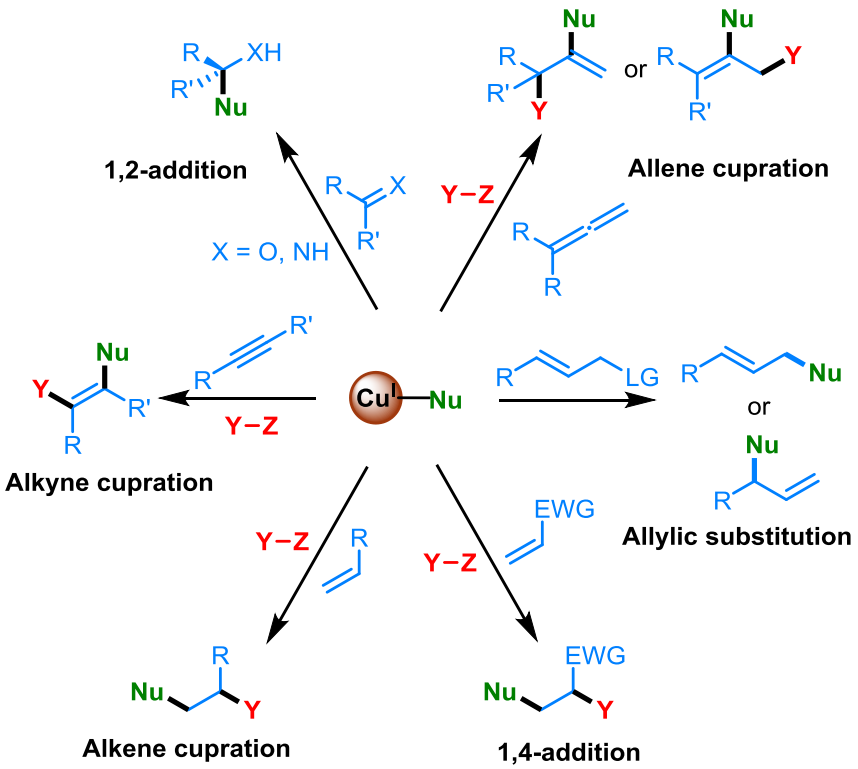
- Cu-B: During the 20 last years, reports on boron transfers using bis-boron compounds have exponentially increased in the field of transition metal catalysis. The use of copper-boron nucleophilic species generated by a copper source with B_2Pin_2 has found numerous applications in the synthesis of organoboron compounds. For example, well established transformations in the field of copper catalysis such as alkene[39c] or allene[49] functionalization were developed with Cu-B nucleophiles and led to the synthesis of alkyl- or vinylboron species (Scheme I-28). More details on the development of copper-catalyzed boron transfers will be given in Chapter IV.

[49] F. Meng, B. Jung, F. Haeffner, A. H. Hoveyda, *Org. Lett.* **2013**, *15*, 1414-1417.



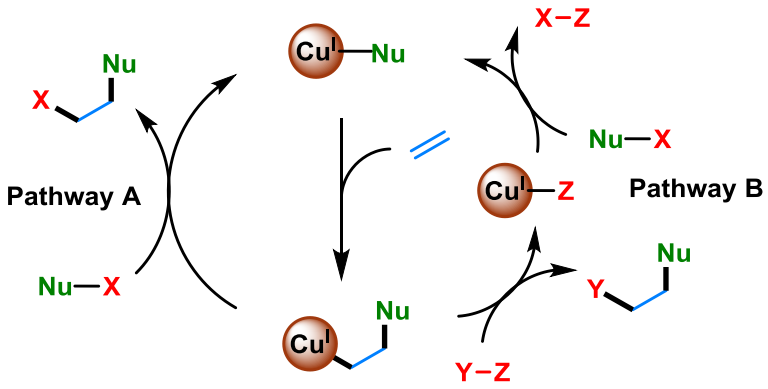
Scheme I-28. Copper-catalyzed borylation of alkenes and allenes

As briefly described above, copper-catalyzed nucleophilic transfers have found applications in the synthesis of various structural motifs. A common mechanistic scheme is involved in these transformations. In each case, a nucleophilic organocopper species is catalytically generated. Once it has been formed, it can evolve in several directions depending on the nature of the electrophile in presence. Functionalizations of allenes, allyl moieties, Michael acceptors, alkenes, alkynes and carbonyls are some examples of the variety of transformations which are accessible using this chemistry (Scheme I-29).



Scheme I-29. Various copper-catalyzed transformations of unsaturations

From a mechanistic point of view, the reaction of a Cu(I)-nucleophile species with an alkene can proceed following two dinstinct pathways as depicted in Scheme I-30.



Scheme I-30. Mechanistic pathways for the copper-catalyzed functionalization of unsaturations

Pathway A describes the difunctionalization of an unsaturation by a unique species Nu-X. Once the copper-nucleophile species Cu-Nu is generated, it can add on the unsaturation (represented here as an alkene). The organocopper intermediate subsequently reacts with an additional equivalent of the Nu-X species to regenerate the Cu-Nu species. Accordingly, the X part of the reagent is incorporated in the final compound. This method allows quite an efficient incorporation of the reagent Nu-X onto the unsaturation. This mechanism if often postulated in the case of a 1,2-addition on carbonyl functions.

Pathway B is a little bit more complex and is present in most of the copper-catalyzed transformations that will be discussed in this manuscript. In this case, the difunctionalization of the unsaturation occurs following a domino process involving three components and the catalyst. The addition of the Cu-Nu species adds onto the unsaturation to generate an organocopper intermediate, which then reacts with another electrophile (X-Z). This second step

releases the desired compound and leads to the formation of a second intermediate Cu-Z. The choice of Z as a hard anion (oxide, fluoride…) is related to the formation of a reactive copper species which is then able to regenerate the Cu-Nu species by a σ-metathesis reaction with an equivalent of the Nu-X reagent. The nature of the Y-Z electrophile is variable (proton, aldehyde, ketone…) and this method allows therefore a large range of functionalization. More details on the functionalization of carbon-carbon unsaturations (alkenes, alkynes, allenes) with B_2Pin_2 will be given in Chapter IV.

III.3. Structure and Preparation of Copper(I) Complexes

Copper(I) possesses a [Ar] $3d^{10}$ $4s^0$ electronic configuration, which confers it a relative stabilitiy in the presence of ligands. Contrarily to gold(I), copper(I) complexes can display various geometries around the metal centre. This paragraph will briefly present the structures and preparation of the complexes that have been used during this PhD research work.

Coordination in copper(I) complexes

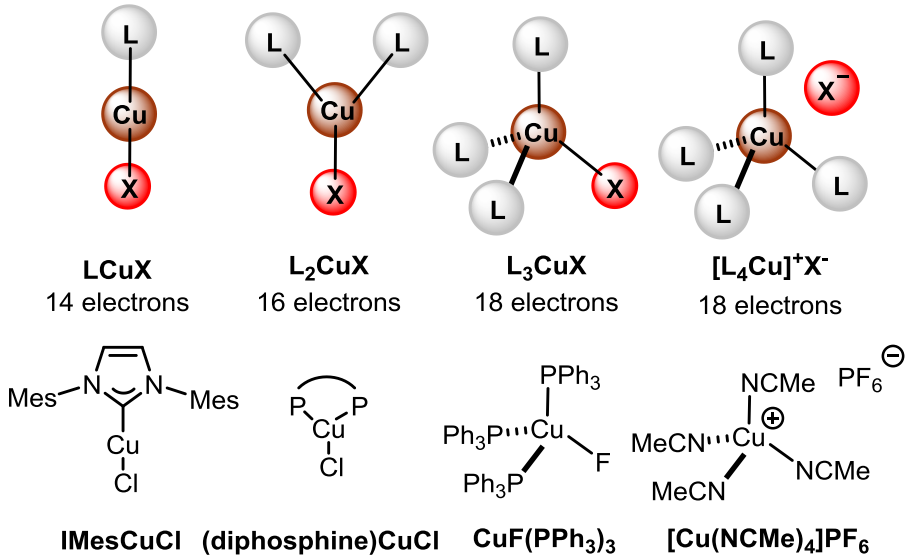
Main categories are represented on Scheme I-31 with an example for each of them:

- Linear geometry: Copper complexes can display a linear geometry surrounded by a neutral (L) and an anionic (X^-) ligand. Complexes from this category usually contain a bulky electron-donating L ligand in order to stabilize the copper centre which is relatively deficient in electrons (14 electrons). The IMesCuCl species constitutes a representative example.
- Trigonal geometry: The lack of electrons encountered in the case of linear complexes can be counterbalanced by the addition of another

neutral L ligand. This additional ligand allows the metal centre to reach a 16 valence electrons, which improves its stability. The two L ligands are often linked together as a chelating ligand. So, monomeric biphosphine ligand-copper complexes can be drawn with this representation. Bulky phosphines-based complexes, such as [(Xantphos)CuCl] complexes are given below as examples. However, monomeric complexes from this family are often in equilibrium with their dimeric form in non-coordinating solvents or in the solid state.[50]

- Tetrahedral geometry: This geometry is the most encountered in copper complexes.[7] The 18 electrons rule is respected in tetracoordinated complexes. Both neutral complexes (L_3CuX) and cationic complexes ([(L_4Cu]X) have been reported. The first type monophosphine-copper complexes, such as [$CuF(PPh_3)_3$] and dimeric copper complexes bearing diphosphines ([(diphosphine)$CuCl]_2$). The popular cationic complex [$(MeCN)_4Cu]PF_6$ which possesses 4 labile acetonitrile ligands also adopts a tetrahedrical geometry.

[50] (a) S. R. Harutyunyan, F. López, W. R. Browne, A. Correa, D. Peña, R. Badorrey, A. Meetsma, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2006**, *128*, 9103-9118; (b) G. Hattori, K. Sakata, H. Matsuzawa, Y. Tanabe, Y. Miyake, Y. Nishibayashi, *J. Am. Chem. Soc.* **2010**, *132*, 10592-10608.

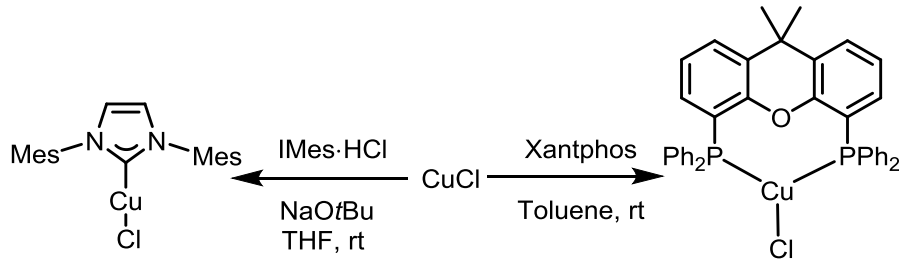


Scheme I-31. Several geometries observed in copper(I) complexes

Preparation of copper(I) complexes

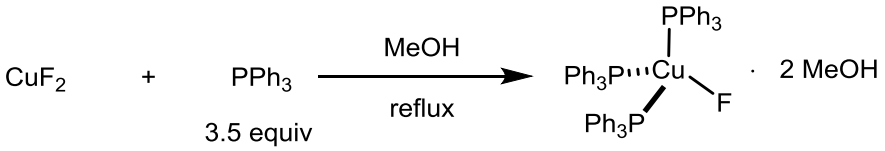
Even if catalytically active copper species can be generated in situ by the mixing of copper(I) or copper(II) salts ($Cu(OAc)_2$, CuCl, $Cu(OTf)_2$…) with a ligand, a wide range of copper complexes can be prepared and isolated.

As described above, phosphines and NHC's are the most common ligands used in copper(I) catalysis. Copper chloride derivatives stabilized by these ancilliary ligands are easily obtained starting from the air sensitive copper(I) choride (Scheme I-32). NHC-copper chlorides can be obtained directly from the NHC salt by deprotonation with sodium *tert*-butoxide. The simple mixing of copper chloride with a diphosphine allows the preparation of the corresponding complex. Both types of complexes are air-stable but might display poor reactivity because of the strong copper-chloride bond. Displacement of this chloride ion for a fluoride or *tert*-butoxide usually allows the conversion of the complex into a catalytically active species.



Scheme I-32. Synthesis of copper chloride complexes sarting from CuCl salt

Besides, fluorotris(triphenylphosphine)copper(I) $CuF(PPh_3)_3$ complex is also a stable and active copper precatalyst, which can easily be prepared from copper(II) fluoride (Scheme I-33).[51]

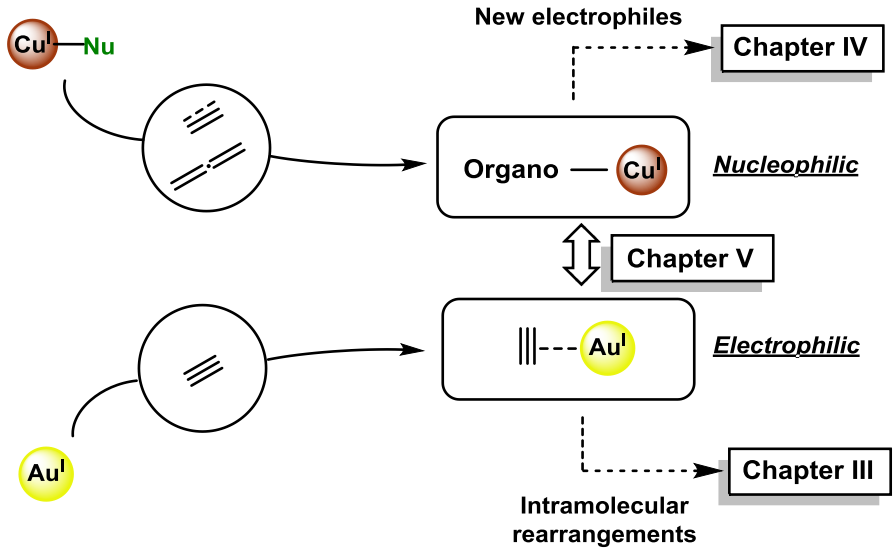


Scheme I-33. Synthesis of $CuF(PPh_3)_3$ from copper fluoride

[51] D. J. Gulliver, W. Levason, M. Webster, *Inorg. Chim. Acta* **1981**, *52*, 153-159.

Chapter II: General Objectives

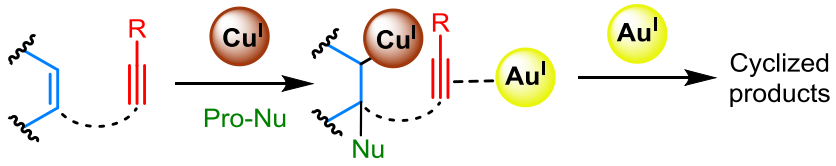
As presented previously, gold(I) and copper(I) catalysis are two areas of intense research in terms of new method developments and new applications in organic synthesis. At the beginning of this PhD work, our purpose is to contribute to these topics by elaborating new catalytic systems based on the intresic reactivity of these metals. As presented on Scheme II-1, several aspects of this reactivity will be covered with the involvement of generated organocopper and organogold species.



Scheme II-1. General objectives of this PhD research

On one side, the reaction of copper-nucleophiles complexes with carbon-carbon unsaturated bonds (alkenes, alkynes, allenes) is known to generate nucleophilic organocopper species. On the other side, gold-activated alkynes are well-studied electrophilic complexes.

The first idea of this PhD is to develop a dual process combining these two specific properties in which the nucleophilic organocopper will be able to react with the gold-activated alkyne (Scheme II-2).



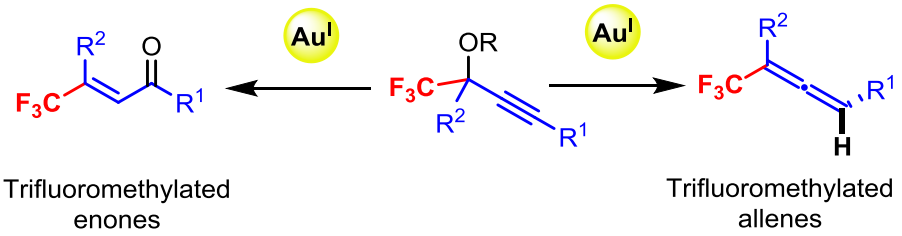
Scheme II-2. Objectives of the fifth chapter of this PhD

For this project, an intramolecular dual catalysis will be targeted by designing the reactive moeities with regards to several aspects, such as the ease of synthesis, the functional compatibility and the valorization of the chosen patterns in synthesis. All these aspects will be discussed in the Chapter V of this manuscript.

Considering the individual reactivities of organocopper(I) and organogold(I) complexes that have been discussed in the bibliographic part of this manuscript, a large amount of new developments are also envisaged on these topics.

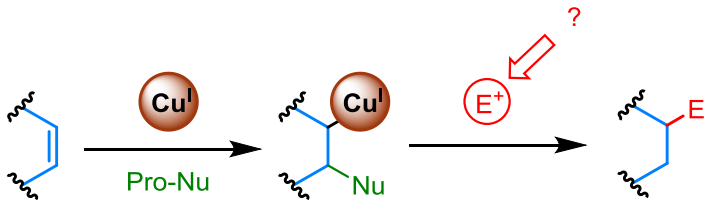
The involvement of electrophilic gold-alkyne complexes in various rearrangements is nowadays well known in the field. In Chapter III, we aim to prepare valuable trifluoromethylated scaffolds from easily accessible starting materials using gold-catalyzed rearrangements. The application of gold-catalyzed transformations to the synthesis of fluorinated substrates can allow a straightforward synthesis of these structural motifs. Among others, CF_3-allenes and CF_3-enones will be targeted by applying these methods to trifluoromethylated propargyl alcohol derivatives (Scheme II-3).

The scope and limitations of these transformations will be studied, as well as the synthetic applications of the trifluoromethylated products.



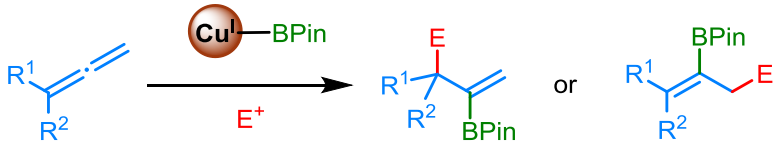
Scheme II-3. Synthesis of trifluoromethylated allenes and enones by gold-catalyzed rearrangements

Besides, the generation of nucleophilic organocopper species by the cupration of unsaturated carbon-carbon bonds have known an increasing interest over the past decade. The trapping of these species by various electrophiles is still an area of intense research (Scheme II-4). In addition to our interest in the elaboration of a dual catalysis system with organogold complexes, we also envision to study new selected organic electrophiles for this functionalization step.



Scheme II-4. Development of copper-catalyzed difunctionalizations of unsaturated C-C bond (represented here as an alkene) using new electrophiles

As several types of carbon-carbon unsaturations and pronucleophiles are nowadays described and available for such transformations, we will focus on the use of allenyl moieties in combination with copper-boron nucleophiles (Scheme II-5).



Scheme II-5. Copper-catalyzed boroamination and boroacylation of allenes

The potential of such transformation with chosen electrophiles, as well as its scope will be studied in Chapter IV.

Chapter III: Gold-Catalyzed Synthesis of Fluorinated Allenes and Enones

The work on the synthesis of fluorinated allenes reported in this chapter was carried out in collaboration with Geoffroy Lonca (PhD student in the laboratory of Prof. Gagosz, Ecole Polytechnique).[52]

The work on the synthesis of trifluoromethylated enones reported in this chapter was carried out in collaboration with Aubin Lambion (trainee from the Institut Paul Lambin in the laboratory of Prof. Riant, UCL).

[52] « Development of new gold- and copper-catalyzed reactions for organic synthesis» by G. Lonca (2017, supervisor: F. Gagosz)

I. Introduction: Interests and Syntheses of Fluorine-Containing Compounds

The introduction of fluorine atoms into organic molecules has been proven to induce a modification on their physical and chemical properties, thus favouring their use as bioactive compounds.[53] These interesting properties can result from several contributions of the fluorine atoms:

- Metabolic stability: The replacement of a C-H bond (412 $kJ.mol^{-1}$) by a stronger C-F bond (485 $kJ.mol^{-1}$) improves the stability of the compound at key positions where oxidation could occur commonly.
- pKa modification: Due to the high electronegativity of the fluorine atom, acidity and basicity properties of the functional groups nearby will be influenced. The acidity of carboxylic acids and alcohols close to fluorine will be enhanced whereas the basicity of amines will be decreased. This modification of the pKa can have a significant impact on the bioavailability of the compounds, and thus on their global activity.
- Conformation modification: The stereoelectronic effects induced by fluorine atoms can lead to a different conformation of the chemical bonds into space. A change in conformations can lead to improving the interactions between the compound and its target.

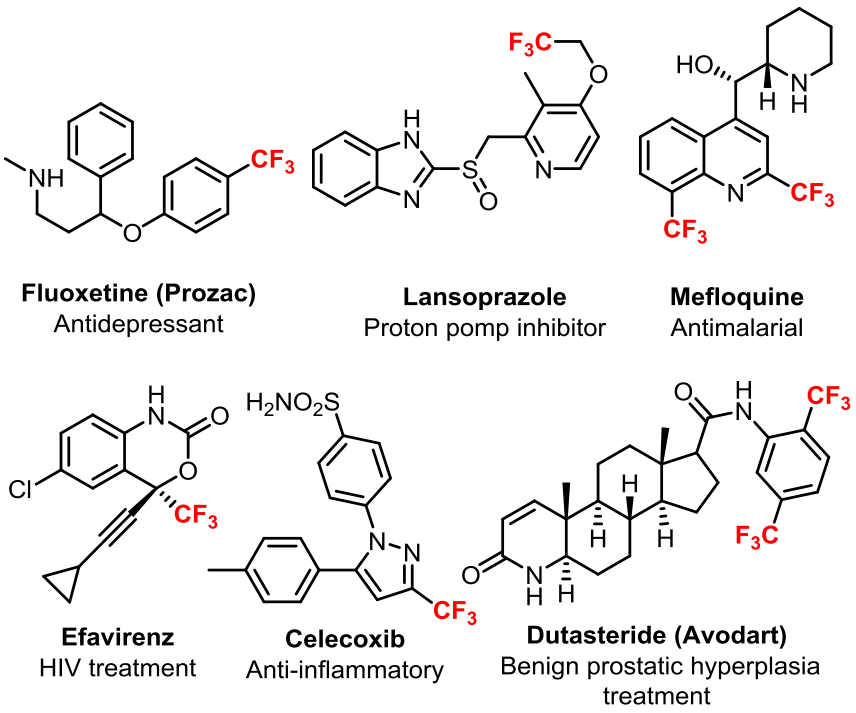
[53] (a) J. Wang, M. Sanchez-Rosello, J. L. Acena, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432-2506; (b) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315-8359; (c) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Acena, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422-518.

- Lipophilicity: Related to the previous properties, the modification of the hydrophobicity of a compound will influence its ability to dissolve into the cellular membranes and thus to penetrate into the tissues.

All these effects of fluorinated bioactive compounds contribute to the continuing discovery and their increasing introduction to drug market. Nowadays, about 25% of marketed drugs contain at least one fluorine atom.

In particular, the trifluoromethyl group (or CF_3 group) has been intensely used to replace methyl groups in compounds relevant to medicinal or agrochemical applications (Scheme III-1).[54]

[54] Adapted from the *Tetrahedron Chair Lectures* of the 15th *Belgian Organic Synthesis Symposium* presented by Prof. V. Gouverneur.



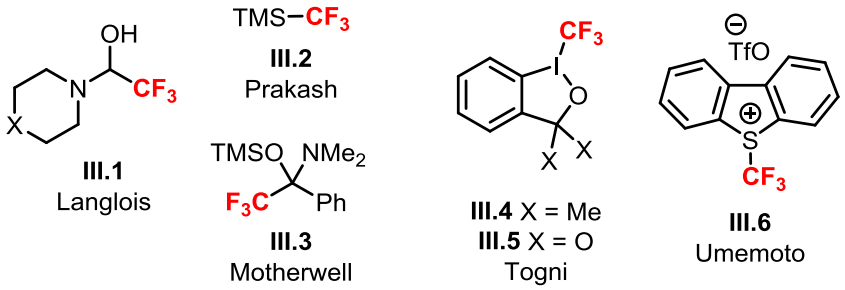
Scheme III-1. Top-selling drugs containing the CF_3 group[54]

The development of synthetic methods directed to the synthesis of such functionalized compounds has known an increasing success during the last years.[55] More especially, the preparation and the application of trifluoromethylating reagents for the late functionalization of organic compounds by a CF_3 moiety has been the subject of intense successful research. A few examples are presented on Scheme III-2. The transfer of a nucleophilic trifluoromethyl group can be performed by using the reagants described by the groups of Langlois (**III.1**),[56] Ruppert and Prakash

[55] Selected review: C. Alonso, E. Martinez de Marigorta, G. Rubiales, F. Palacios, *Chem. Rev.* **2015**, *115*, 1847-1935.

[56] T. Billard, Bernard R. Langlois, G. Blond, *Eur. J. Org. Chem.* **2001**, 1467-1471.

(**III.2**)[57] and Motherwell (**III.3**).[58] Under specific conditions, these reagents allows the formal release of CF_3^- which is able to undergo nucleophilic additions. Various electrophilic reagents were also developed, among which the Togni's ester (**III.4**) and alcohol (**III.5**),[59] as well as the Umemoto's reagent (**III.6**).[60] These reagents were also used in processes involving radical-based mechanisms.



Scheme III-2. Selected examples of trifluoromethylating reagents

The main advantage of trifluoromethylation methods relies on the late introduction of the CF_3 group thus limiting a potential loss in the yield of the CF_3-compound all along the synthesis.

However, some of these reagents are quite expensive or require several synthetic steps. Another strategy would consist in starting a synthesis by using cheap fluorine or trifluoromethyl sources and to convert them into versatile reaction intermediates (Scheme III-3). Fluoride ions and fluoroform **III.6** remain the most simple and accessible sources of fluorine and trifluoromethyl group, respectively. Besides, ethyl trifluoroacetate is also a relatively

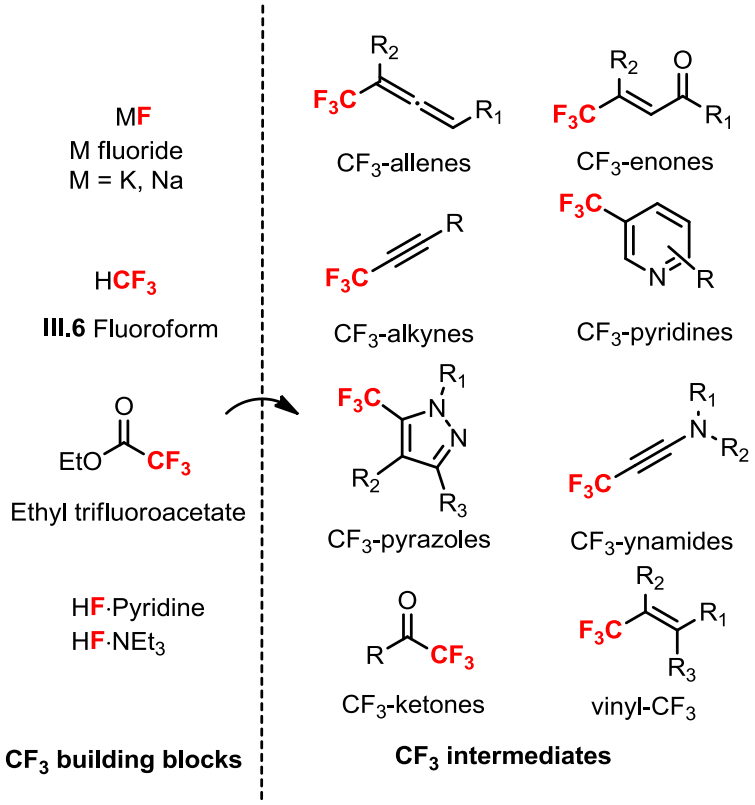
[57] I. Ruppert, K. Schlich, W. Volbach, *Tetrahedron Lett.* **1984**, *25*, 2195-2198.

[58] W. B. Motherwell, L. J. Storey, *Synlett* **2002**, 646-648.

[59] P. Eisenberger, S. Gischig, A. Togni, *Chem. – Eur. J.* **2006**, *12*, 2579-2586.

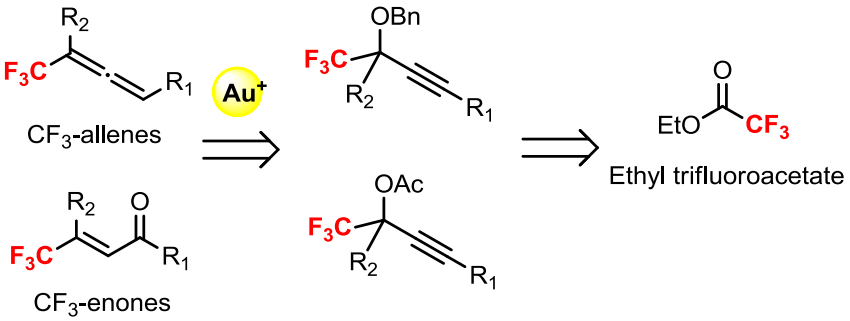
[60] For a review, see: H. Li, *Synlett* **2012**, *23*, 2289-2290.

cheap and stable source of trifluoromethyl moiety that can be easily turned into other functional groups. Methods to convert these small building blocks into the chemical functions presented on the right side of Scheme III-3 would be of great interest as they can potentially be used as synthetic intermediates for the preparation of bioactive compounds.



Scheme III-3. Synthesis of versatile CF_3-intermediates from simple building blocks

During this PhD work, we were interested in the preparation of two fluorinated moieties: CF_3-allenes and CF_3-enones. The syntheses to access them are both based on a gold-catalyzed rearrangement from a fluorinated propargyl alcohol derivative, which can be easily accessed from ethyl trifluoroacetate in a few steps (Scheme III-4).



Scheme III-4. Retrosynthesis of the targeted trifluoromethylated allenes and enones

This chapter will be divided in two subsections. The first part will be dedicated to the synthesis of trifluoromethylated allenes via a gold-catalyzed hydride shift. In the second part our results on the synthesis of trifluoromethylated enones by a gold-catalyzed [3,3]-acetate rearrangement will be presented and dicsussed.

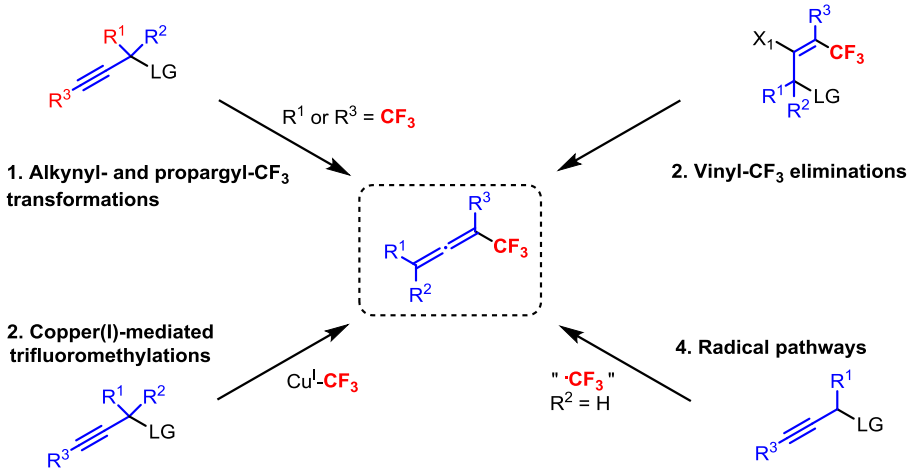
II. Synthesis of CF_3-Allenes by 1,5-Hydride Shift

II.1. Known Syntheses of CF_3-Allenes

Whereas numerous methods are reported for the preparation of standard allenes,[61] general strategies for the synthesis of their trifluoromethylated analogs remain rare in the literature. However, several reports describe the obtention of substituted CF_3-allenes. This paragraph aims at giving an overview of these strategies, which have been divided into four categories (Scheme III-5). The first one focuses on the transformations of alkynyl- or propargyl-CF_3 compounds involving the rearrangement of the alkyne back-

[61] Themed issue on allenes: B. Alcaide, P. Almendros, *Chem. Soc. Rev.* **2014**, *43*, 2886-2887 and the references cited therein.

bone into the allene moiety. The second category refers to elimination processes developed on vinyl-CF_3 species bearing a leaving group on the allylic position. Copper(I)-mediated direct trifluoromethylations of alkynes constitute the third category. Finally, other radical pathways allowing the formation of CF_3-allenes will be presented.

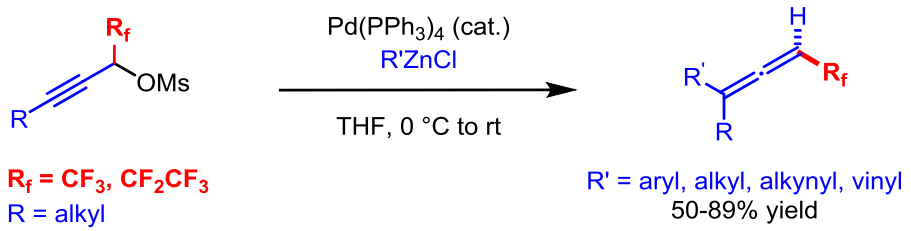


Scheme III-5. Different pathways toward the synthesis of CF_3-allenes

Transformations of Alkynyl- and Propargyl-CF_3 Compounds

One of the most practical manners to synthesize trifluoromethyl allenes consists in the transformation of a compound that already contains the trifluoromethyl group, such as an alkyne moiety. In 2000, Konno and co-workers reported the palladium-catalyzed coupling of fluoralkyl propargyl mesylates with organozinc reagents (Scheme III-6).[62]

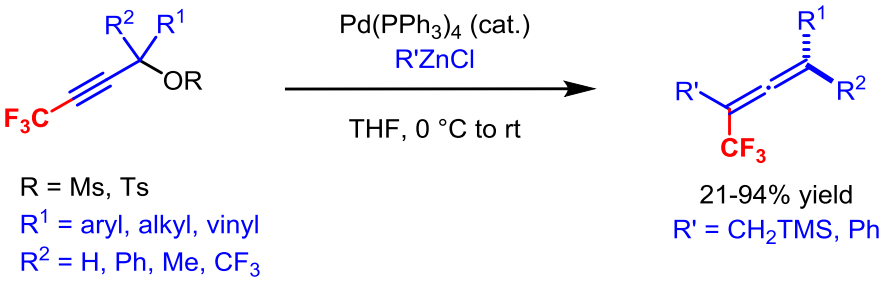
[62] T. Konno, M. Tanikawa, T. Ishihara, H. Yamanaka, *Chem. Lett.* **2000**, 1360-1361.



Scheme III-6. Palladium-catalyzed coupling of propargyl-CF_3 with organozinc reagents

When enantiopure propargylic mesylates were used, this transformation proceeded with a central-to-axial conversion of chirality to furnish the CF_3-allenes with excellents *ee* of 94-96%.

A similar transformation involving CF_3-alkynes was used by the group of Shimizu to produce tertiary and quaternary CF_3-allenes in moderate to good yields (Scheme III-7).[63]



Scheme III-7. Palladium-catalyzed coupling of CF_3-alkynes with organozinc reagents

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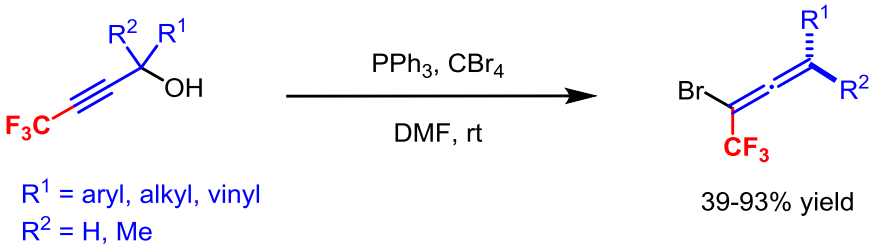
[63] (a) M. Shimizu, M. Higashi, Y. Takeda, G. Jiang, M. Murai, T. Hiyama, *Synlett* **2007**, 1163-1165; (b) M. Shimizu, M. Higashi, Y. Takeda, M. Murai, G. Jiang, Y. Asai, Y. Nakao, E. Shirakawa, T. Hiyama, *Future Med. Chem.* **2009**, *1*, 921-945; (c) For a similar transformation using a copper-mediated addition of phenylgrignard reagent on the propargyl-CF_3, see: R. Zeng, Z. Ma, C. Fu, S. Ma, *Adv. Synth. Catal.* **2014**, *356*, 1343-1358.

Rearrangements of CF_3-propargylic alcohol derivatives have also been exploited for the synthesis of CF_3-allenes possessing other functional groups, such as a bromide (Scheme III-8),[64] tosylate[65] or a phosphonate.[66]



Scheme III-8. Synthesis of CF_3-bromoallenes from CF_3-alkynes

Finally, terminal CF_3-allenes have been observed as rearrangement products from CF_3-butatriene-rhodium complexes.[67] Even if the corresponding reports allow a mechanistical understanding in coordination chemistry, they do not provide an efficient synthetic route to CF_3-allenes, due to the stoichiometric amount of rhodium that is required.

Eliminations of Vinyl-CF_3 Compounds

Another direct precursor of a CF_3-allene can be found on a vinyl-CF_3 moiety bearing an appropriate leaving group. A simple elimination reaction allows the formation of the second unsaturation leading to the allene (Scheme III-9).

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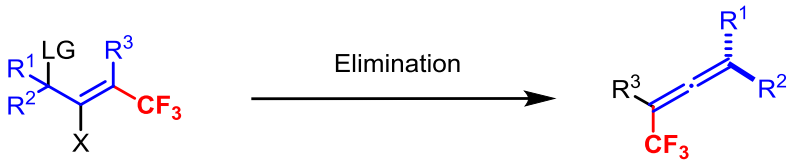
[64] Y. Watanabe, T. Yamazaki, *Synlett* **2009**, 3352-3354.

[65] (a) Y. Watanabe, T. Yamazaki, *J. Fluorine Chem.* **2010**, *131*, 646-651; (b) T. Yamazaki, Y. Watanabe, N. Yoshida, T. Kawasaki-Takasuka, *Tetrahedron* **2012**, *68*, 6665-6673.

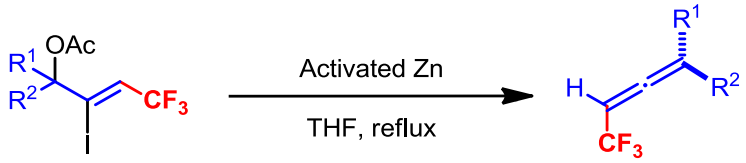
[66] P. Li, Z.-J. Liu, J.-T. Liu, *Tetrahedron* **2010**, *66*, 9729-9732.

[67] (a) H. Werner, M. Laubender, R. Wiedemann, B. Windmueller, *Angew. Chem. Int. Ed.* **1996**, *35*, 1237-1239; (b) H. Werner, R. Wiedemann, M. Laubender, B. Windmueller, P. Steinert, O. Gevert, J. Wolf, *J. Am. Chem. Soc.* **2002**, *124*, 6966-6980.



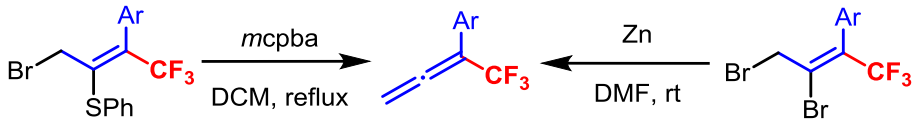
Scheme III-9. Elimination of vinylic and allylic substituents of a vinyl-CF_3

With this strategy, the synthesis of substituted CF_3-allenes from vinyliodides was reported by Yamazaki in 2006. Their simple treatment with zinc dust allowed the elimination of the acetate on the propargylic position to yield the desired allenes (Scheme III-10).[68]



Scheme III-10. Synthesis of CF_3-allenes from vinyliodides

Following a similar method, 1-aryl-1-trifluoromethylallenes could be easily accessed from vinylsulfides or vinylbromides (Scheme III-11).[69]



Scheme III-11. Synthesis of 1-aryl-trifluoromethylallenes from substituted vinyl-CF_3

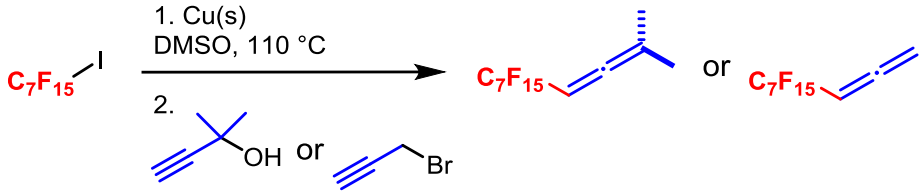
Copper-Mediated Trifluoromethylations

The first synthesis of perfluorinated allenes relating to a copper-mediated reaction was reported in 1974 by Coe and Milner.[70] By stirring perfluoro-*n*-

[68] T. Yamazaki, T. Yamamoto, R. Ichihara, *J. Org. Chem.* **2006**, *71*, 6251-6253.

[69] (a) H. Y. Han, M. S. Kim, J. B. Son, I. H. Jeong, *Tetrahedron Lett.* **2006**, *47*, 209-212; (b) B. Sam, T. P. Montgomery, M. J. Krische, *Org. Lett.* **2013**, *15*, 3790-3793.

heptyl iodide in the presence of metallic copper in DMSO, the corresponding organocopper could be generated. Subsequent addition of a propargylic bromide or alcohol led to the formation of the perfluorinated allene (Scheme III-12). A further study on the scope of this method was reported in 1990 by Hung.[71]



Scheme III-12. Synthesis of perfluorinated allenes by alkynes cupration

A similar strategy to synthetize perfluorinated or difluoromethylated allenes was described by Burton and co-workers using an improved procedure to generate the organocopper species (Scheme III-13).[72] By adding a copper(I) salt (CuI, CuBr, CuCl, CuCN) to a pre-formed [CF_3-Cd] or [CF_3-Zn] complex, an in situ metathesis allowed high-yielding formation of the corresponding organocopper reagent at low temperature.[73] A recent report described the extension of the scope to other perfluorinated chains (vinyl, aryl…) and to the use of catalytic amounts of copper.[74]

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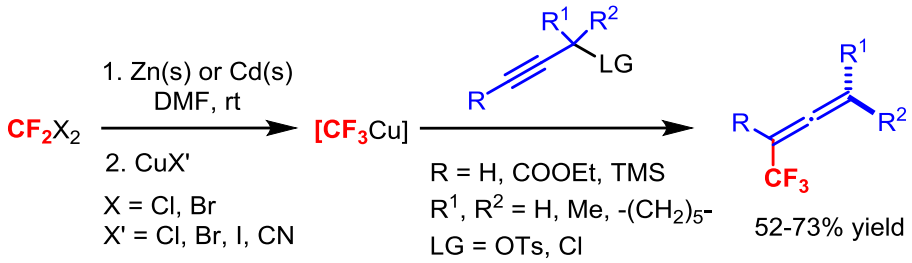
[70] P. L. Coe, N. E. Milner, *J. Organometal. Chem.* **1974**, *70*, 147-152.

[71] M. H. Hung, *Tetrahedron Lett.* **1990**, *31*, 3703-3706.

[72] (a) D. J. Burton, G. A. Hartgraves, J. Hsu, *Tetrahedron Lett.* **1990**, *31*, 3699-3702. Similar transformation in: (b) J. P. Bouillon, C. Maliverney, R. Merenyi, H. G. Viehe, *J. Chem. Soc., Perkin Trans. 1* **1991**, 2147-2149.

[73] (a) D. M. Wiemers, D. J. Burton, *J. Am. Chem. Soc.* **1986**, *108*, 832-834; (b) D. J. Burton, S. W. Hansen, *J. Am. Chem. Soc.* **1986**, *108*, 4229-4230.

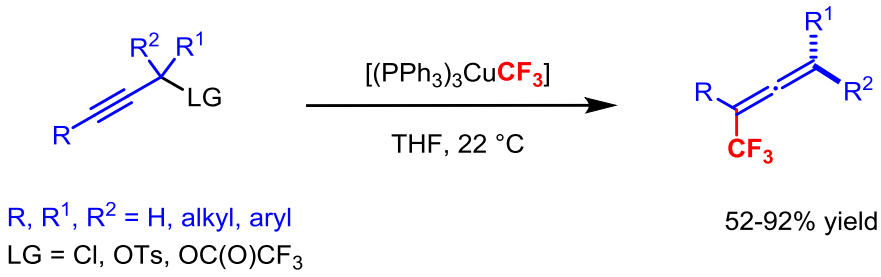
[74] D. J. Burton, G. A. Hartgraves, *J. Fluorine Chem.* **2009**, *130*, 254-258.



Scheme III-13. Novel synthesis of [Cu-CF_3] species for the synthesis of CF_3-allenes

However, these methods involve sensitive and undefined [Cu-CF_3] reagents, which can lead to issues of chemo- and regioselectivity. Furthermore, the use of organocadmium reagents is not very attractive because of the toxicity related to this element.

In 2012, the group of Szabó reported the synthesis of secondary and tertiary CF_3-allenes from propargylic chlorides, tosylates or trifluoroacetates using the well defined [$(PPh_3)_3CuCF_3$] reagent (Scheme III-14).[75] This reaction proceeds under mild conditions and with a good regioselectivity towards the formation of the allenic product. By using an enantioenriched propargylic trifluoroacetate, a central-to-axial chirality conversion was observed and a chiral CF_3-allene could be obtained with in 89% *ee*.

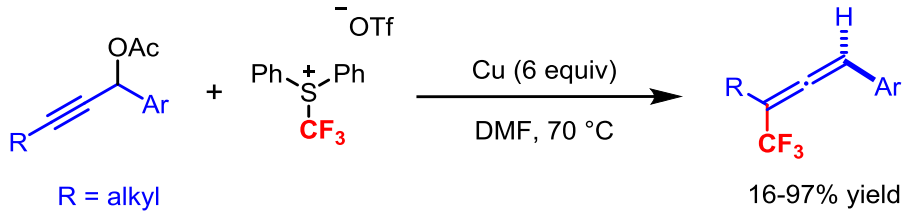


Scheme III-14. Synthesis of CF_3-allenes with [$(PPh_3)_3CuCF_3$] reagent

[75] T. S. N. Zhao, K. J. Szabo, *Org. Lett.* **2012**, *14*, 3966-3969.

Other sources of trifluoromethyl group have been recently investigated for the copper-mediated synthesis of CF_3-allenes. Ruppert-Prakash reagent TMS-CF_3 in the presence of KF turned out to be efficient and two recent reports described transformations using stoichiometric or catalytic amounts of a copper(I) salt.[76]

Electrophilic trifluoromethylation reagents have also been studied in this context. In 2014, the group of Lin and Xiao reported the synthesis of CF_3-allenes using propargyl acetates, *S*-(trifluoromethyl)diphenylsulfonium triflate $[Ph_2SCF_3]^+[OTf]^-$ in the presence of metallic copper (Scheme III-15).[77] The reaction between the sulfonium salt and the copper was believed to generate a $[CuCF_3]$ species that could lead to a formal S_N2' substitution.



Scheme III-15. Copper-mediated trifluoromethylation of propargyl acetates

In 2016, the same group described the direct CH trifluoromethylation of 3-aryl-prop-1-ynes in the presence of Togni's reagent and KF in NMP with catalytic amounts of CuI and phenantroline.[78] In this case, copper was used

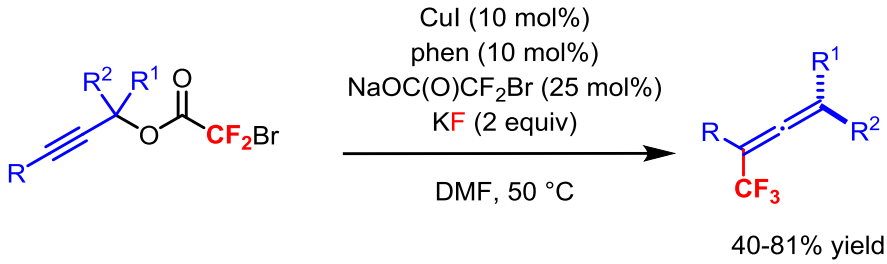
[76] (a) X. Jiang, F.-L. Qing, *Beilstein J. Org. Chem.* **2013**, *9*, 2862-2865; (b) Y. Miyake, S.-i. Ota, M. Shibata, K. Nakajima, Y. Nishibayashi, *Chem. Commun.* **2013**, *49*, 7809-7811.

[77] Y.-L. Ji, J.-J. Kong, J.-H. Lin, J.-C. Xiao, Y.-C. Gu, *Org. Biomol. Chem.* **2014**, *12*, 2903-2906.

[78] Y.-L. Ji, J.-J. Luo, J.-H. Lin, J.-C. Xiao, Y.-C. Gu, *Org. Lett.* **2016**, *18*, 1000-1003.

to promote a single electron transfer (SET) and to generate ·CF_3 radical species which can add on the propargylic substrate.

Finally, Altman and co-workers reported a ligand-controlled copper-catalyzed trifluoromethylation to synthetize CF_3-allenes (Scheme III-16).[79] Starting from propargyl bromodifluoroacetates and KF as the generator of CF_3 moiety, this method allowed a general access to CF_3-allenes from readily available propargyl alcohols as it also proceeded with an excellent regioselectivity (allene/alkyne 8 : 1 to 49 : 1).



Scheme III-16. Copper-catalyzed trifluoromethylation of propargyl bromodifluoroacetates

Other Radical Pathways

Even if radical-based mechanisms could have been proposed in some copper-mediated syntheses of CF_3-allenes, a free radical process was also described by Hu and co-workers for the preparation of perfluorinated allenes.[80] The heating of perfluorinated sulfinites R_fSO_2Na in the presence of $(NH_4)_2S_2O_8$ led to the formation of $R_f^{\cdot}$ radicals, which could react with propargyl bromides to yield CF_3-allenes. Unfortunately, the low yields obtained

[79] (a) B. R. Ambler, S. Peddi, R. A. Altman, *Synthesis* **2014**, *46*, 1938-1946; (b) B. R. Ambler, S. Peddi, R. A. Altman, *Org. Lett.* **2015**, 17, 2506-2509.

[80] C. Hu, F. Qing, W. Huang, *J. Org. Chem.* **1991**, *56*, 2801-2804.

as well as the presence of perfluorinated carboxylic acids as secondary products render this method not very effective for organic synthesis.

II.2. Gold-Catalyzed Hydride Shifts: Previous Work in our Laboratory

As described above, several methods consisting in the intermolecular S_N2' addition on propargyl compounds allow the preparation of allenyl-CF_3 functions. A recurrent drawback lies in the uncontrolled formation of the corresponding propargyl-CF_3 via a formal S_N2 reaction. This side reaction leads to the contamination of CF_3-allenes by various amounts of propargyl-CF_3, which are often difficult to separate.

To circumvent this problem, an intramolecular rearrangement, named a gold-catalyzed hydride shift, has been envisaged as a selective method towards the formation of the CF_3-allenes.

Intramolecular metal-catalyzed hydride transfers have been developed during the last decade by several groups.[81,82] In this field, our lab has focused on the elaboration of several strategies using gold complexes as catalysts.

In 2010, a gold-catalyzed 1,5-hydride shift/cyclization domino sequence for the hydroalkylation of alkynyl ethers was developed for the easy preparation of spirocyclic and fused bicyclic moieties (Scheme III-17).[83] Subsequent studies were carried out on the similar transformation with allene moieties.[84]

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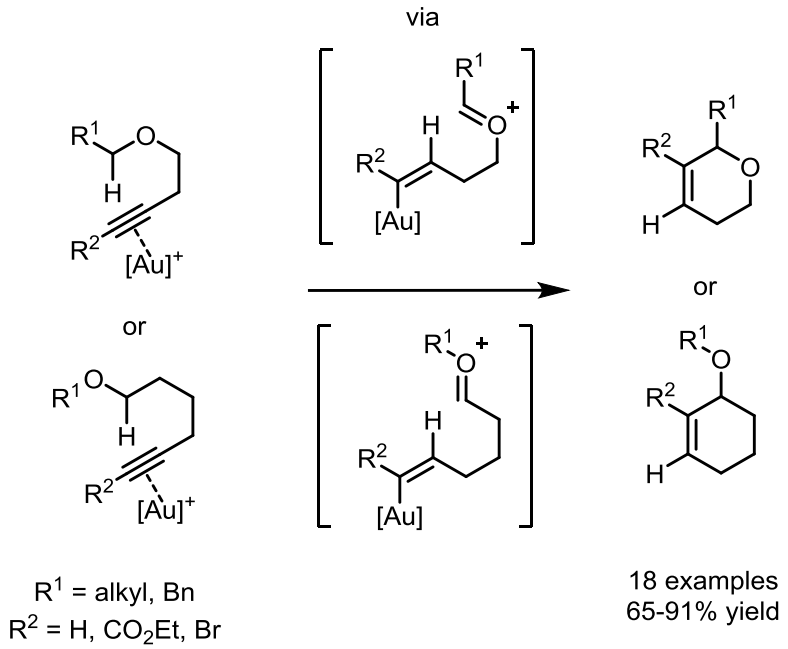
[81] M. C. Haibach, D. Seidel, *Angew. Chem., Int. Ed.* **2014**, *53*, 5010-5036.

[82] For a previous PhD thesis from our group presenting an introduction on hydride shifts, see: "Synthèse et Réactivité d'Allènes par Transferts d'Hydrures Catalysés à l'Or" by B. Bolte (2013, supervisor: F. Gagosz).

[83] I. D. Jurberg, Y. Odabachian, F. Gagosz, *J. Am. Chem. Soc.* **2010**, *132*, 3543-3552.

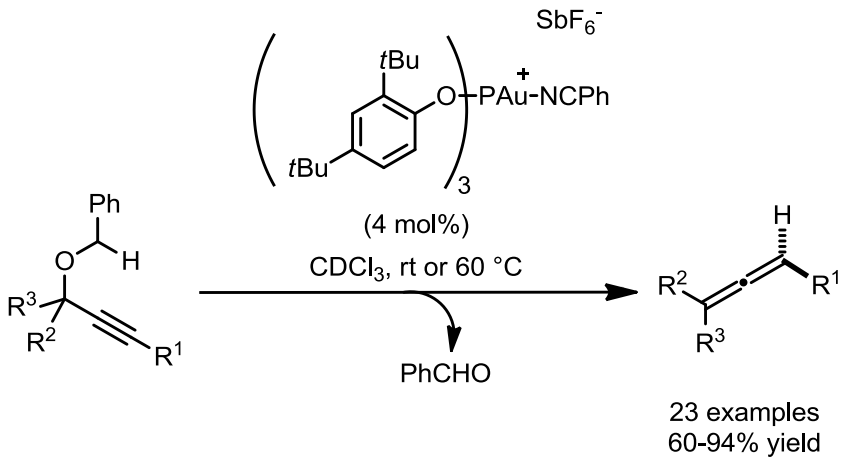
[84] B. Bolte, F. Gagosz, *J. Am. Chem. Soc.* **2011**, *133*, 7696-7699.



Scheme III-17. Gold-catalyzed 1,5-hydride shift/cyclization domino reaction

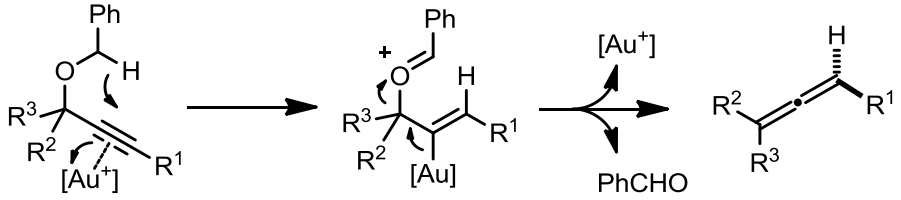
This hydride shift strategy was then applied to the synthesis of allenes. Starting with propargyl benzyl ethers, the gold-catalyzed 1,5-hydride shift allowed the preparation of di- and trisubstituted allenes by the release of benzaldehyde (Scheme III-18).[85]

[85] B. Bolte, Y. Odabachian, F. Gagosz, *J. Am. Chem. Soc.* **2010**, *132*, 7294-7296.



Scheme III-18. Gold-catalyzed synthesis of allenes via 1,5-hydride shift

Mechanistically, the 1,5-hydride shift onto the gold-activated alkyne generates a vinylgold species. This intermediate can then undergo a fragmentation to furnish the desired allene (Scheme III-19).

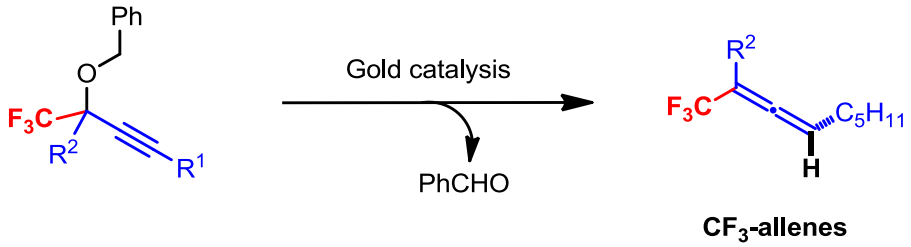


Scheme III-19. Postulated mechanism of the gold-catalyzed 1,5-hydride shift

II.4. Objectives of the Project

The recent reports in the literature showed that the synthesis of CF_3-allenes is still the subject of continuous investigations. Even if some methods have already been shown to be available for their synthesis, a widely applicable and robust route remains difficult to find. As our team previously reported the synthesis of allenes via a gold-catalyzed hydride transfer, we wanted to extend the scope of such process to the formation of trifluoromethylated

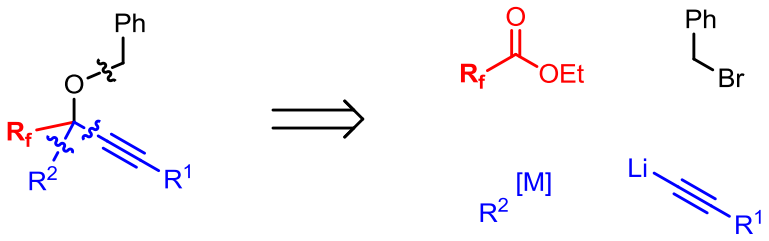
compounds, as it had not been envisioned in the first study of the scope of this reaction. (Scheme III-20).



Scheme III-20. Synthesis of CF_3-allenes from trifluoromethylated propargyl benzyl ethers

Beside its regioselectivity, this new method will provide several advantages from a synthetic point of view.

Trifluoromethylated propargyl benzyl ethers that are used as substrates can be easily prepared from cheap starting materials. A straightforward disconnection leads to a simple synthetic route starting from an alkyne, an organometallic reagent, ethyl trifluoroacetate and benzyl bromide (Scheme III-21). This would offer the opportunity to synthetize fluorinated allenes with various substitution patterns, depending on the nature of the R^1 and R^2 groups. Besides, ethyl trifluoroacetate is a very convenient CF_3 source as it is a commercially available and cheap reagent. The proposed method would avoid the use of volatile trifluoromethylated reagents such as 2-bromo-3,3,3-trifluoropropene or the prior synthesis of CF_3-alkyne moieties. Finally, other fluorinated analogs of ethyl trifluoroacetate ($HF_2CCOOEt$, CF_3CF_2COOEt…) are also accessible which could allow an extension the scope to the preparation of other fluorinated allenes.



Scheme III-21. Proposed retrosynthesis of the targeted substrates

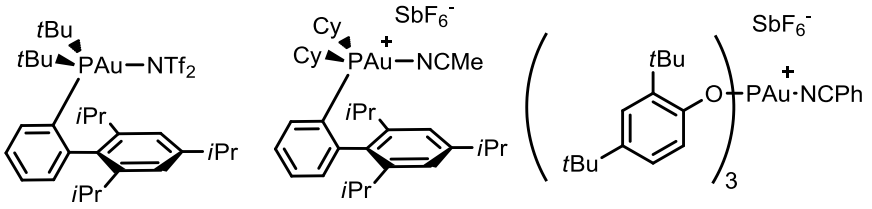
However, a few drawbacks were also considered. The synthesis of allenes via a hydride shift excludes the synthesis of tetrasubstituted allenes as one of the four substituents will be a hydrogen atom. Furthermore, the elimination of benzaldehyde from the final compound represents a moderate atom-economical efficiency of the designed process in the case of small CF_3-allenes.

With all these characteristics put together, we consider this project as a good complementary method to those previously reported in the literature.

II.5. Optimization

To validate our approach, we decided to apply the best conditions that had been found when the 1,5-hydride shift reaction was developed by Benoît Bolte in the Gagosz group in 2010.[82,85] Three gold catalysts displayed notable activities for this transformation (Scheme III-22).

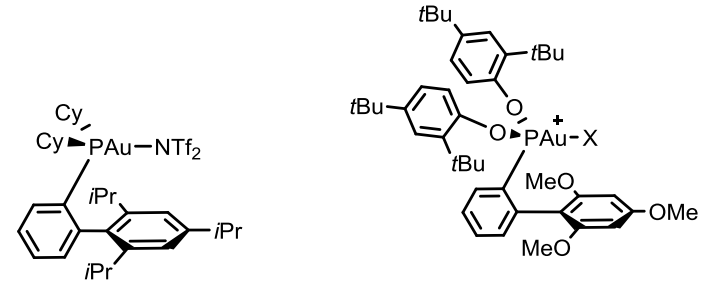
In general, Buchwald phosphines such as *t*BuXPhos or XPhos were found to be efficient ligands and allowed the conversion of many substrates in 1-3 hours at room temperature in $CDCl_3$. The phosphite ligand turned out to be a good alternative for challenging substrates, despite its low stability at higher temperature (60 °C). For this process, gold complexes possessing a NTf_2^- or SbF_6^- counteranion displayed a similar activity. Following these considerations, the catalytic activity of complexes **III.7**, **III.8** and **III.9** was then tested.



III.7 *t*BuXPhosAuNTf$_2$ **III.8** XPhosAuSbF$_6$ **III.9** PhosphiteAuSbF$_6$

Scheme III-22. Efficient gold catalysts for the synthesis of allenes via a 1,5-hydride transfer

In this study, three other catalysts were also envisaged for the optimization of the reaction conditions (Scheme III-23): the XPhosAuNTf$_2$ complex **III.10**, a recently reported PhosphoniteAuNTf$_2$ **III.11** and the PhosphoniteAuSbF$_6$ **III.12** complex. Previous work in our group had shown that the phosphonite represented a nice compromise between the Buchwald phosphine ligands, which confer a relative stability to the complexes, and the phosphite ones, which make the corresponding complexes highly reactive but somewhat unstable.[13b]



III.10 XPhosAuNTf$_2$

III.11 X = NTf$_2^-$
III.12 X = NCMe, SbF$_6^-$

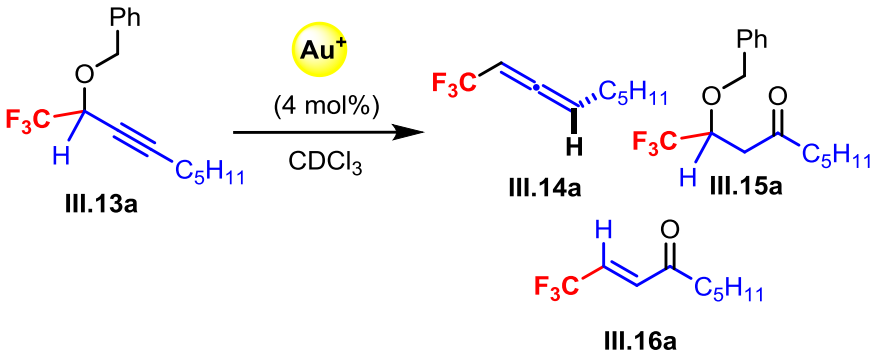
Scheme III-23. Other catalysts envisaged for the optimzation process

Our optimization study started by investigating the activity of the most efficient gold(I) catalysts under the previously reported conditions: $CDCl_3$ at room temperature or 60 °C in a sealed NMR tube at a concentration of 0.2

mol.L^{-1} for the starting material. By using 1,2-dichloroethane as an internal standard, this protocol allowed an easy monitoring of the reaction by ^{1}H or ^{19}F spectroscopy.

The results obtained during this first optimization part are presented in Table III-1. Three main products could be observed during this screening: the desired allene **III.14a**, along with the product resulting from the gold-catalyzed addition of water on the alkyne **III.15a** and product **III.16a** resulting from to the elimination of benzyl alcohol from **III.15a**. Using catalyst **III.8**, found to be optimum in the previously reported method,[85] an almost neglectable conversion of the starting material was observed (entry 1). After 24 h, only 6% yield of the product could be formed. A small amount of the side products **III.15a** and **III.16a** was also detected. The phosphite based catalyst **III.9** showed a clearly improved efficiency as 77% yield of the desired product were observed after half an hour of reaction (entry 2). The XPhosAuNTf_2 complex **III.10** was completely inactive to convert a similar substrate (entry 3), as well as complex **III.11** bearing a phosphonite ligand with a NTf_2^- counteranion (entry 4). Finally, the PhosphoniteAuSbF_6 complex **III.12** allowed a very efficient conversion of the substrate into the desired product in half an hour (entry 5).

Table III-1. First optimization of the gold catalysts



Entry	Au catalyst	T (°C)	Time (h)	Yield (%)			
				13	14	15	16
1	**III.8**	60	0.5	92	1	4	1
			1.5	92	1	4	1
			24	90	6	4	1
2	**III.9**	60	0.5	2	77	11	1
			1	2	75	10	1
3[a]	**III.10**	60	18	98	2	0	0
4[b]	**III.11**	60	1	99	1	0	0
			5.5	99	1	0	0
5	**III.12**	60	0.5	3	78	12	3
			1.5	2	77	11	3
			2.5	2	77	11	3

[a] This test was carried out on a similar substrate bearing another aliphatic chain (substrate **III.13g**); [b] For this test, only the conversion (indicated instead of the yield) was measured.

These experiments seem to indicate two important factors for the reaction to occur:

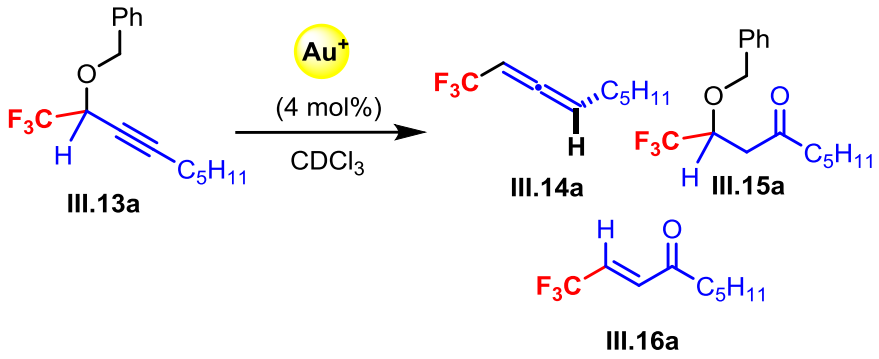
- A strong π-accepting ligand, such as a phosphonite or a phosphite, is necessary to allow the reaction to occur.

- The non-coordinating SbF_6^- is superior to NTf_2^- in term of catalytic activity.

With these promising results in hand, we decided to evaluate the catalytic activity of complexes **III.9** and **III.12** at room temperature. As shown in Table III-2, decreasing the temperature to room temperature had a detrimential effect on the kinetics of the reaction. The use of phosphite complex **III.9** required 4 hours to reach 67% yield in allene formation (entry 1), and 10 hours were necessary in the case of catalyst **III.12** to deliver the product in 74% yield (entry 2). Again, 10% yield of product **III.15a**, resulting from addition of water on the substrate, were observed. From these observations, we decided to keep the reaction temperature at 60 °C.

Since the use of phosphite ligands is known to form less stable gold complexes than their phosphine or phosphonite analogs, it was decided at this stage to pursue the investigations with the Phosphonite$AuSbF_6$ complex **III.12**. It was considered to be more appropriate as it would be less prompt to decomposition after an extended heating of the reaction medium at 60 °C. This would be useful during the scope of the reaction, when more challenging substrates might need longer reaction times.

Table III-2. Effect of the temperature on the gold-catalyzed transformations



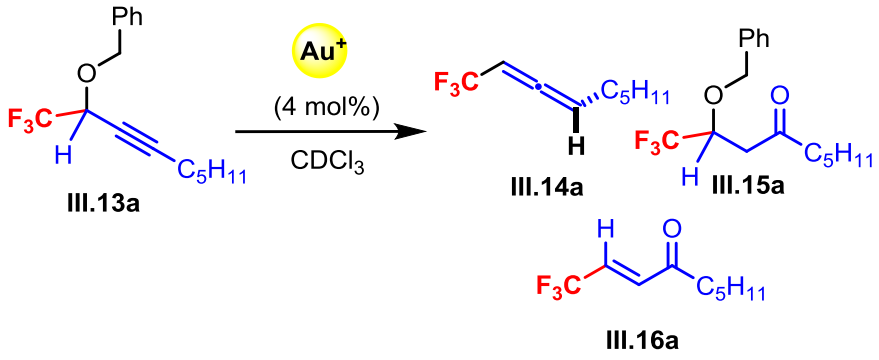
Entry	Au catalyst	T (°C)	Time (h)	Yield (%)			
				13	14	15	16
1	**III.9**	rt	0.5	63	15	10	2
			2.5	25	48	10	2
			4	10	67	10	2
			18	8	68	10	2
2	**III.12**	rt	0.7	60	20	14	1
			1.5	40	40	13	1
			8.7	28	51	13	2
			7.5	8	70	13	2
			10	5	74	13	2
			24	3	76	13	2

At this stage, the main remaining problem was the formation of by-product **III.15a**, which is probably due to the presence of water traces in chloroform. The hydration of alkynes being apparently more favourable than the desired hydride transfer, the formation of the side product **III.15a** occurs easily.

Drying $CDCl_3$ prior to its use at the reaction solvent allowed a small decrease in the amount of side product as well as an increase in the yield of allene **III.14a** (Table III-3). At 60 °C, the allene **III.14a** was obtained in 85% NMR yield (entry 1). At room temperature, 72% yield were obtained

after 72 hours (entry 2), which showed again the effect of the temperature on the transformation.

Table III-3. Influence of the drying of the solvent over molecular sieves



Entry	Au catalyst	T (°C)	Time (h)	Yield (%)			
				13	14	15	16
1[a]	**III.12**	60	1	4	85	8	1
2[a]	**III.12**	rt	72	18	72	7	1

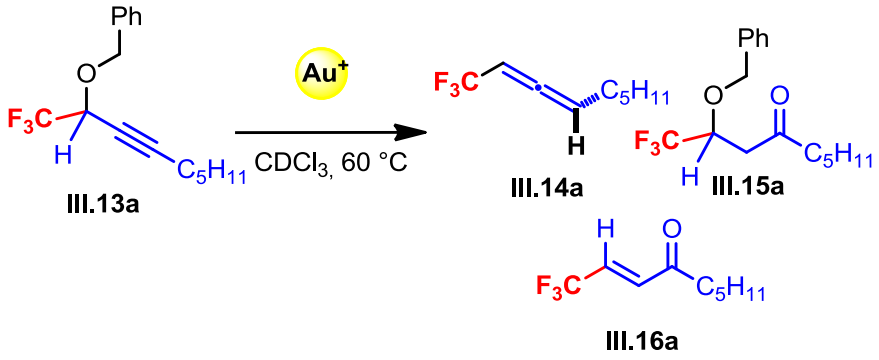
[a]The solvent was previously dried over molecular sieves 4 Å

Suitable reaction conditions for the preparation of CF_3-allenes were finally found. Heating a 0.2 $mol.L^{-1}$ solution of substrate **III.13a** in chloroform (dried over molecular sieves) in the presence of 4 mol% of PhosphoniteAuSbF_6 complex **III.12** at 60 °C was selected as an optimum protocol for the formation of CF_3-allenes.

The 4 mol% catalyst loading was selected in order to ensure an efficient and fast conversion of the starting materials into the corresponding allenes during the study of the reaction scope. However, a few tests were carried out to evaluate the limitation of the method in terms of catalyst loading for this substrate (Table III-4). 1 mol% of the PhosphiteAuSbF_6 **III.9** allowed the full conversion of the substrate in a little bit more than one hour (entry 1). For the PhosphoniteAuSbF_6 complex **III.12**, a decrease to 2 mol% loading

still led to a good conversion after 1 h of reaction (entry 2). A decrease to 1 mol% led however to an incomplete conversion of the substrate (entry 3).

Table III-4. Tests of the reaction at lower catalyst loadings



Entry	Au catalyst	Cat. Loading (mol%)	Time (h)	Yield (%)			
				13	14	15	16
1	**III.9**	1	0.5	10	69	10	2
			1.25	4	79	9	2
2	**III.12**	2	0.5	12	68	10	2
			1	5	75	10	2
			2	3	77	10	2
			19	3	77	10	2
3	**III.12**	1	1.2	24	58	11	1

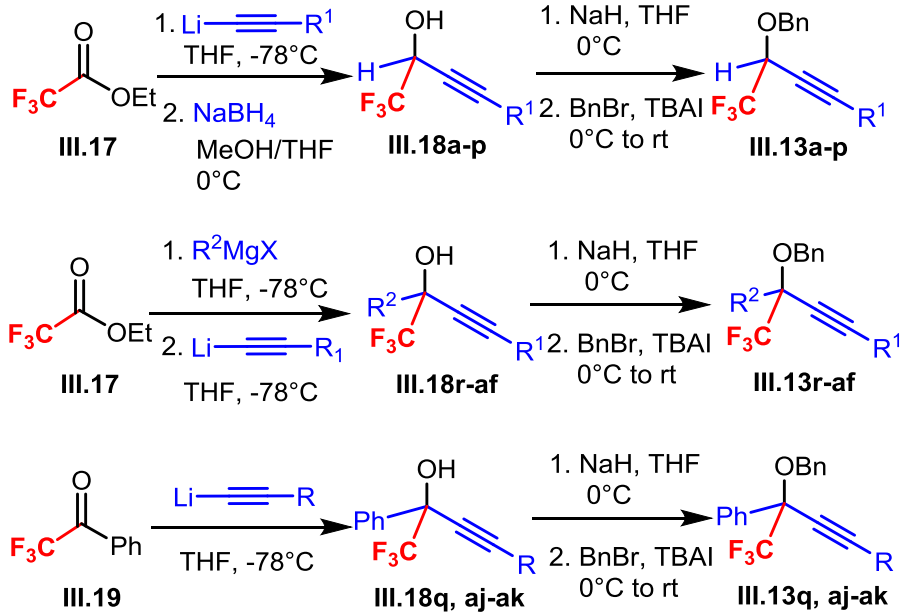
II.6. Scope of the Method

General preparation of the substrates

To study the scope of the reaction, it was required to synthetize a library of trifluoromethylated *O*-benzyl propargyl ethers. These were prepared according to modified literature procedures as described in Scheme III-24. The

detailled syntheses are reported in the experimental part of this manuscript and in the related publication.[86] The general method consisted in the nucleophilic addition of organometallic reagents onto ethyl trifluoroacetate **III.17** or the trifluoromethyl ketone **III.19** in order to access propargylic alcohols **III.18**. Most of these syntheses avoid the purification of moisture-sensitive CF_3-ketones as they are usually generated in situ. In the rare occasions we had to isolate them, an excess of the organometallic reagent during the next step ensured the regeneration of the CF_3-ketone from their hydrated form. The subsequent benzylation of these alcohols leads to the production of substrates **III.13**. This method was found to be compatible with various substitution patterns and allowed the preparation of a large number of starting materials.

[86] A. Boreux, G. H. Lonca, O. Riant, F. Gagosz, *Org. Lett.* **2016**, *18*, 5162-5165.



Scheme III-24. General ways for the synthesis of the substrates (see the experimental part for the detailed procedures and overall yields)

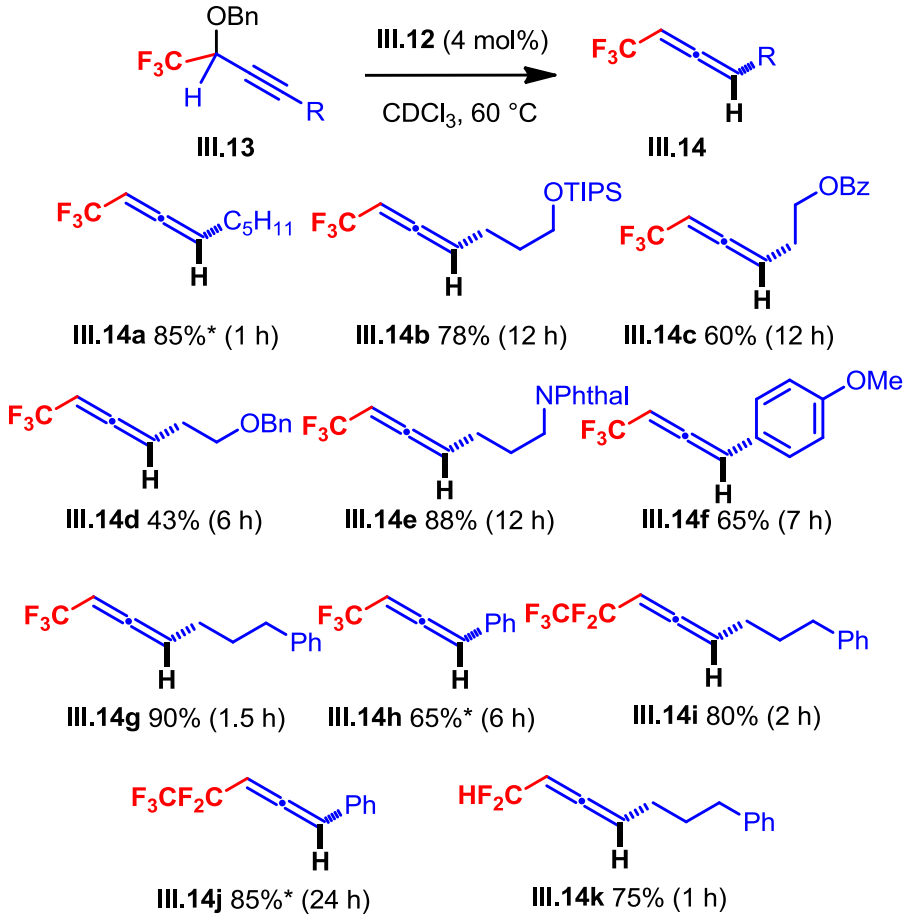
With these compounds in hand, we could start to investigate the scope of the transformation.

1,3-disubstituted allenes

We started by investigating the reactivity of *O*-benzyl ethers **III.13** obtained from secondary alcohols (Scheme III-25). Our model substrate furnished 85% of the allene **III.14a** under the optimal conditions. The extension to substrates containing protected heteroatoms was then carried out. Allenes **III.14b-d** containing a protected silylated alcohol, an ester or an ether were obtained in moderate to good yields. A phthalimide was also tolerated as the allene **III.14-e** was obtained in 88% yield after 12 hours reaction. The presence of a conjugated anisole on the alkyne led to the formation of the allene **III.14f** in 65% yield. Afterwards, the influence of the fluorinated moiety was evaluated with substrates **III.14g-k**. Aliphatic allenes **III.14g, i, k** bearing

respectively a CF_3, CF_2CF_3 and CF_2H group were obtained in very good yields after 1 to 2 hours reaction. The aromatic analogs **III.14h, j** were also well converted with 65% and 85% NMR yields.

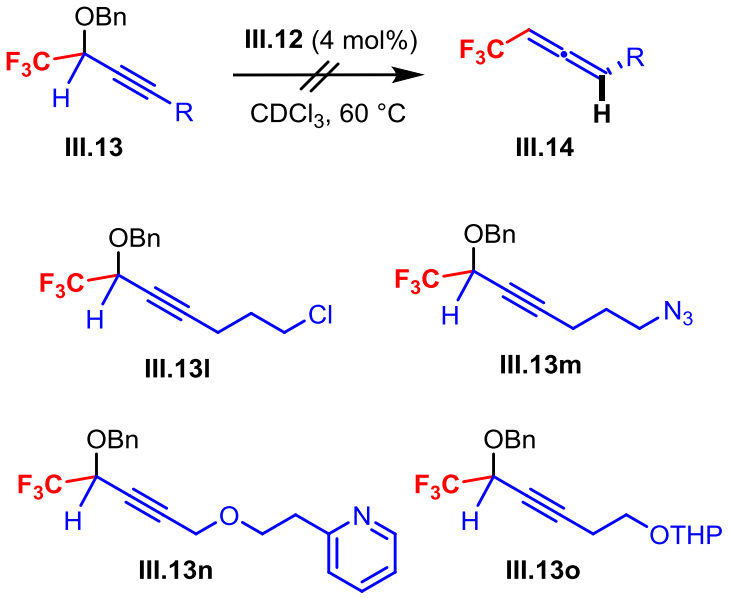
This first serie of examples already demonstrated nice tolerance of the reaction to several commonly used functional groups.



Scheme III-25. Gold-catalyzed rearrangement of secondary substrates for the synthesis of 1,3-disubstituted allenes. *NMR yield indicated due to the volatility of the product

However, the catalytic system did not tolerated the presence of several functionalities as seen in the Scheme III-26. A chloro or an azido substituent

switched off the catalytic system and no conversion could be observed. The same observation was made with a pyridine present on the side chain, as this is the case with substrate **III.13n**. The coordination of the pyridine to the gold atom may explain the deactivation of the catalyst. Finally, an alcohol protected with a THP group was decomposed during the transformation, porbably due to an unstability of this moiety in the presence of the Lewis acidic gold catalyst.

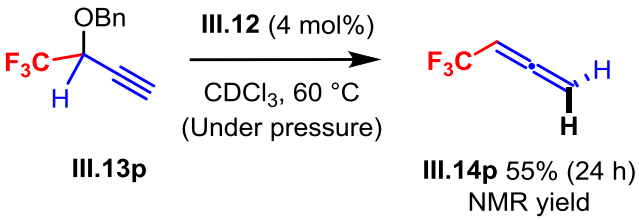


Scheme III-26. Failures for the synthesis of 1,3-disubstituted allenes

Monosubstituted allene

After the synthesis of several trifluoromethylated 1,3-disubstituted allenes, we turned our attention on the synthesis of the monosubstituted allene **III.14p** resulting from the rearrangement of the benzyl ether **III.13p** (Scheme III-27). Due to the volatility of the substrate, it was used in solution in diethylether. The formation of the allene **III.14p** was observed and a 55%

yield could be measured by ^{1}H NMR. As the boiling point of this allene had been estimated at 8-10 °C,[87] it was not possible to isolate it.

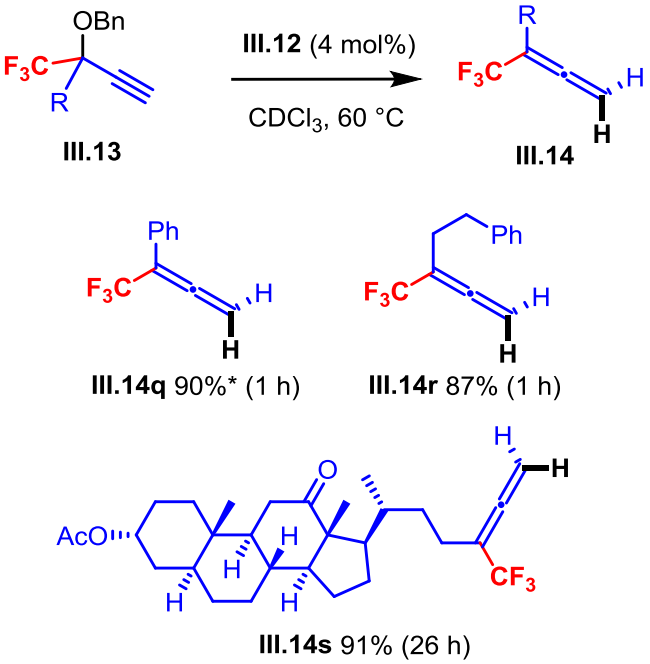


Scheme III-27. Synthesis of the monosubstituted CF_3-allene **III.14p**

1,1-disubstituted allenes

The transformation of tertiary *O*-benzyl ethers substituted by a terminal alkyne was then investigated (Scheme III-28). The aromatic substituted substrate **III.13q** was effectively converted into the corresponding allene in 90% ^{1}H NMR yield. An aliphatic chain was also tolerated at this position, as attested by the formation of allene **III.13r** in 87% yield. We also envisaged to apply our method on a more complex organic skeleton. We selected a steroid backbone and the transformation was found to be very effective. We were very pleased to isolate 91% yield of the corresponding CF_3-allene **III.14s**.

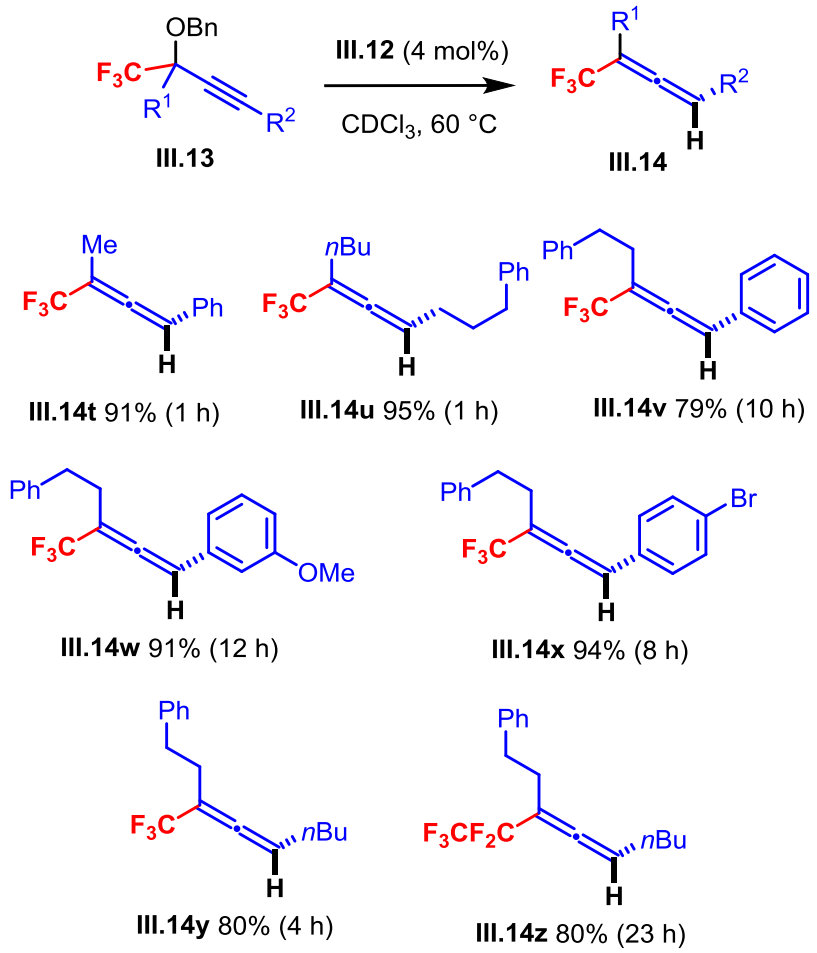
[87] J.-X. Duan, Q.-Y. Chen, *J. Chem. Soc., Perkin Trans. 1* **1994**, 725-730.



Scheme III-28. Synthesis of 1,1-disubstituted allenes by gold-catalyzed rearrangement

Trisubstituted allenes

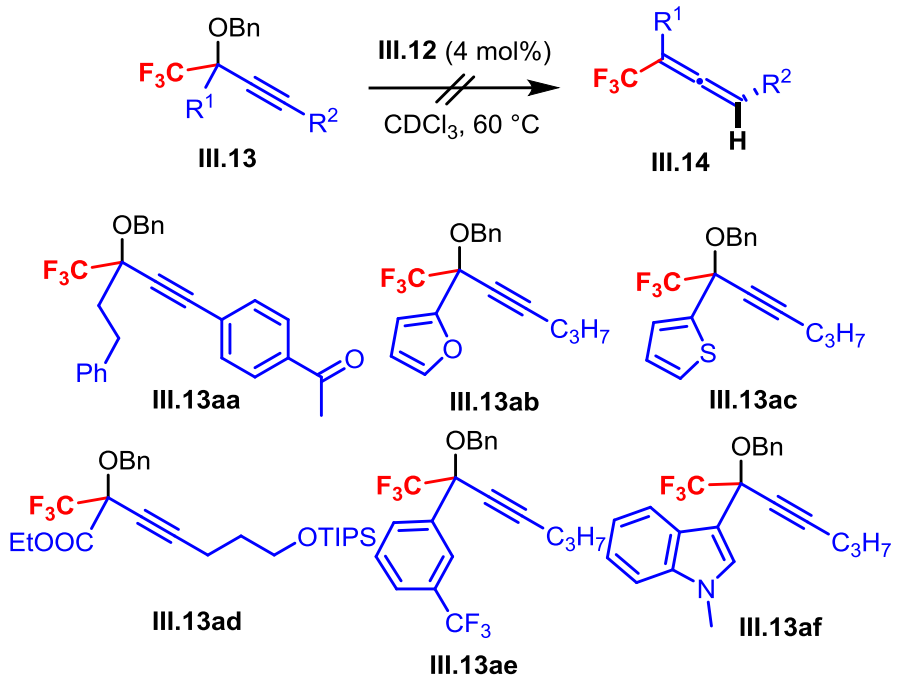
After having studied the transformation for the synthesis of disubstituted allenes, we turned our attention onto the preparation of trisubstituted CF_3-allenes possessing various types of substitution (Scheme III-29). In the case of starting materials bearing the CF_3 group and an aliphatic chain on the propargylic position, several functionalizations on the alkyne were possible: aromatic groups (substrates **III.13t,v-x**) as well as aliphatic groups (substrates **III.13u,y**) were well tolerated and the corresponding allenes could be isolated in good yields. A perfluorinated allene (**III.13z**) could also be isolated in 80% yield after 23 h reaction.



Scheme III-29. Synthesis of trisubstituted CF_3-allenes by gold-catalyzed hydride shift

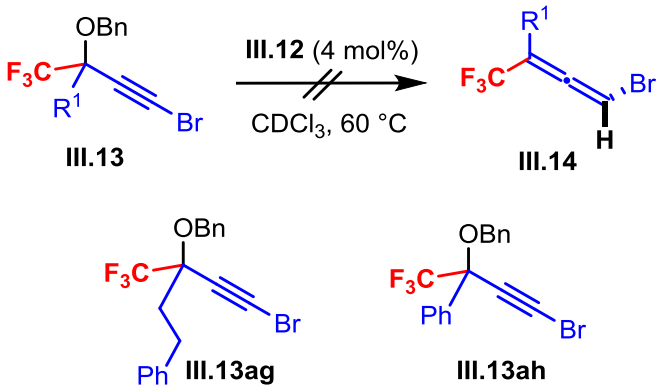
Unfortunately, several more challenging tertiary *O*-benzyl ethers led to non satisfactory results (Scheme III-30). The presence of another electron-withdrawing group than the CF_3 seemed to make the substrates inactive under the optimized conditions. This was observed in the case of an aromatic ketone (**III.13aa**), an ester group (**III.13ad**) or a CF_3-substituted aromatic group (**III.13ae**), for which the allenes could not be formed. Besides, electron-rich aromatic groups, such as a furan (**III.13ab**), a thiophene (**III.13ac**)

or a *N*-methylindole (**III.13af**) led to a decomposition of the starting material. In these cases, it was supposed that the gold catalyst reacted directly with the heteroaromatic ring or initiated the elimination of the more labile OBn group.



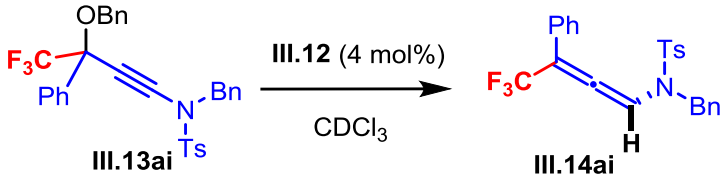
Scheme III-30. Failures for the synthesis of trisubstituted CF_3-allenes

The substitution of the alkyne by a heteroatom was also envisaged. At first, the use of bromoalkynes in the transformation was carried out (Scheme III-31). Unfortunately, the reaction with bromoalkyne **III.13ag** did not lead to any conversion. Another attempt with substrate **III.13ah** led to similar results, whereas 10% ^{1}H NMR yield of the desired product could be observed in the best case.



Scheme III-31. Attempts for the synthesis of CF_3-substituted bromoallenes

Finally, the synthesis of a CF_3-allenamide was also attempted (Scheme III-32). Starting with substrate **III.13ai**, the gold-catalyzed transformation led to mixture containing a major product, which appeared to be the desired allenamide **III.14ai**. This relatively unstable compound was isolated with acceptable purity for its characterization. After 30 minutes of reaction at 60 °C, a 40% yield of this compound was assessed by ^{1}H NMR yield. This yield was improved to 60% by carrying out the reaction at room temperature for 2 hours. Several side products were present what made the purification very difficult.



Scheme III-32. Synthesis of a CF_3-allenamide by gold-catalyzed hydride transfer

With these observations, it appeared that the chosen substrate was probably too complex to properly study the scope of this transformation. The synthesis of allenamides by this method being very interesting, it was decided to study this transformation in a separate project without the presence of the

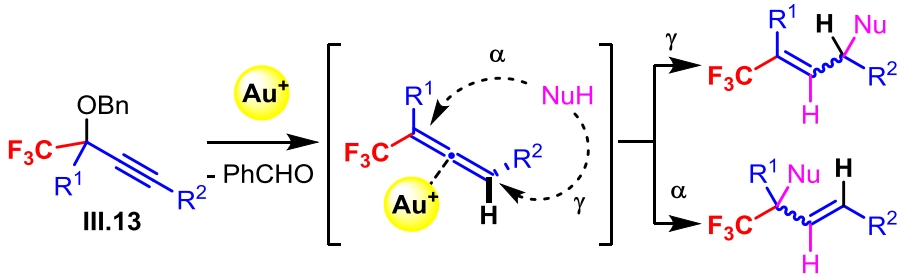
CF_3 group. This work was carried out by Dr. Qing Zhao in the laboratory of Dr. Fabien Gagosz.[88]

II.7. Post-Functionalization of CF_3-Allenes

After having been successful in the preparation of a library of allenes, we investigated their post-functionalization in an intra- and intermolecular fashion. The first part of this paragraph will be dedicated to the one-pot gold-catalyzed synthesis/intramolecular functionalization of the CF_3-allenes. The second part will focus on several intermolecular functionalizations of isolated CF_3-allenes. Other transition metal-mediated transformations will be involved in the latter case.

Intramolecular post-functionalizations

As gold remains present in the reaction medium after the formation of the allene, a one-pot transformation involving a second gold-catalyzed reaction can be envisaged. For this second reaction, a gold-catalyzed addition of a nucleophile onto the CF_3-allene has been envisaged. Depending on the nature and the position of the nucleophile, the α- or the γ-position of the substrate can be functionalized (Scheme III-33).



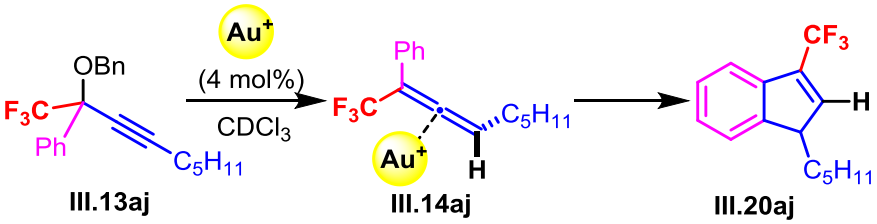
Scheme III-33. Gold-catalyzed post-functionalization of CF_3-allenes

[88] (a) "Gold catalyzed novel transformations of Ynamide" by Q. Zhao (2016, supervisor: F. Gagosz); (b) Q. Zhao, F. Gagosz, *Adv. Synth. Catal.* **2017**, *359*, 3108-3113.

The first example of this type of cascade reaction comes from an unexpected result observed during the study of the reaction scope (Table III-5). When the optimized conditions were applied to the substrate **III.13aj**, a mixture of allene **III.14aj** and indene **III.20aj** was obtained (entry 1). The formation of the indene is due to a gold-catalyzed cyclization of the phenyl group onto the allene moiety.[89] This cyclization being probably pushed forward at higher temperature, we carried out the transformation at room temperature in the presence of the PhosphiteAuSbF_6 gold catalyst **III.9** (entry 2). In this case, 81% yield of a 5:1 mixture between the allene and the indene was obtained. Even if both products were not obtained in a completely selective fashion, it was possible to favour the formation of each of them by varying the temperature of the reaction.

[89] N. Marion, S. Díez-González, P. de Frémont, A. R. Noble, S. P. Nolan, *Angew. Chem. Int. Ed.* **2006**, *45*, 3647-3650.

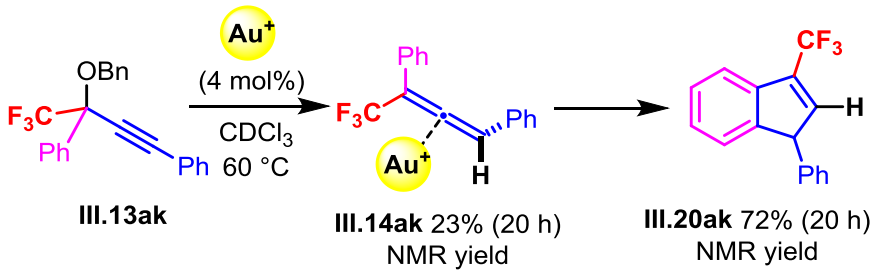
Table III-5. Synthesis of a CF_3-allene and indene by gold-catalysis



Entry	Au catalyst	Temperature (°C)	Time (h)	Yield[a] (%)	
				14	20
1	**III.12**	60	16	18	81
2	**III.9**	rt	24	81[b] (5:1 mixture)	

[a] NMR yield with 1,2-dichloroethane as an internal standard; [b] isolated yield

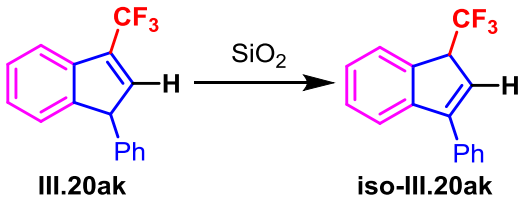
The same transformation was attempted with the substrate **III.13ak**, and the same reactivity was observed (Scheme III-34).



Scheme III-34. Gold-catalyzed rearrangement for the preparation of allene and indene

However, the clean isolation of indene **III.20ak** was not possible due to its isomerization during the flash chromatography (Scheme III-35). It is assumed that this isomerization is due to the presence of the second phenyl group, which promotes the migration of the double bond in order to give the

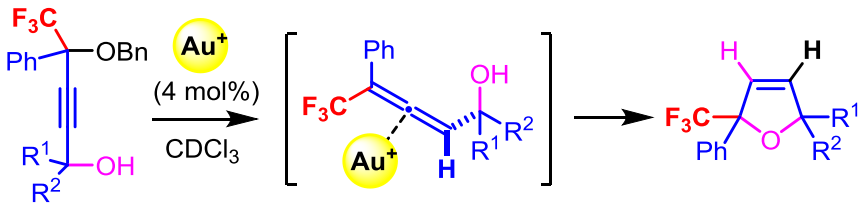
most conjugated product. This last product was previously described in the literature, which allowed its identification by ^{1}H NMR.[90]



III.20ak **iso-III.20ak**

Scheme III-35. Isomerization of the indene **III.20ak** during the purification

With these results in hand, we decided to prepare substrates possessing better nucleophilic moieties than a phenyl group. By introducing an alcohol moiety on the other propargylic position of the substrate (**III.13al,am**), a clean conversion into the corresponding CF_3-dihydrofuran was observed (Scheme III-36).[85] In this case, the allene intermediate was not observed, which led us to assume its fast capture by the nucleophilic alcohol.



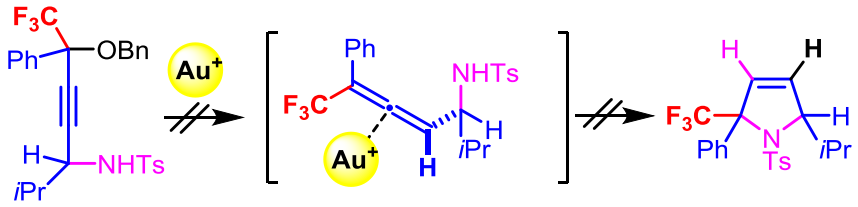
R^1= R^2= H **III.13al** **III.21al** 82% (1 h)

R^1= H, R^2= *i*Pr **III.13am** **III.21am** 88% (2 h)

Scheme III-36. Synthesis of CF_3-dihydrofurans by gold-catalyzed rearrangements

The same transformation was attempted on a propargylic tosylamine (Scheme III-37). Unfortunately, the reaction did not occur in this case and only the starting material was recovered.

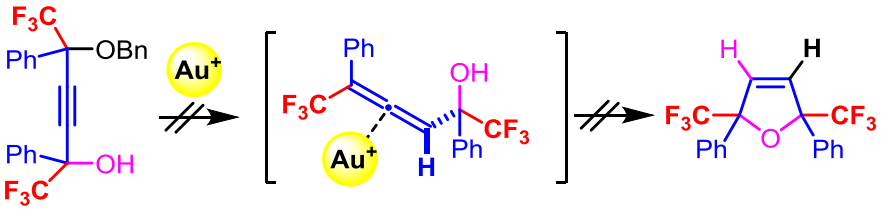
[90] G. K. Surya Prakash, F. Paknia, A. Narayanan, G. Rasul, T. Mathew, G. A. Olah, *J. Fluorine Chem.* **2012**, *143*, 292-302.



III.13an **III.14an** **III.21an** 0%

Scheme III-37. Attempt for the synthesis of an *N*-tosyl dihydropyrrole

Finally, a substrate containing a second CF_3 group on the propargylic position did not lead to any conversion (Scheme III-38). This observation can be related to the non reactivity of substrates possessing electron-withdrawing groups under the reaction conditions.

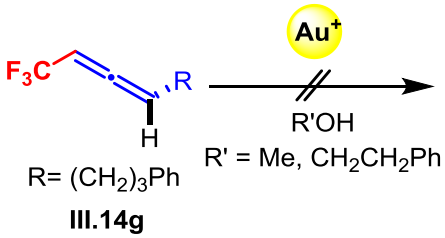


III.13ao **III.14ao** **III.21ao** 0%

Scheme III-38. Attempt for the synthesis of a bis-CF_3-dihydrofuran

Post-functionalizations with other reactions

Other types of transformations were also examined in order to functionalize the obtained CF_3-allenes. The intermolecular version of the gold-catalyzed addition of alcohols was attempted first (Scheme III-39). Suprisingly, the addition product was not observed whereas this transformation is a benchmark reaction in the field of gold catalysis. Even an aryl-substituted CF_3-allene was subjected to this transformation with success.[79b] This fact made us consider this family of allenes particularly deactivated towards electrophilic activation methods.



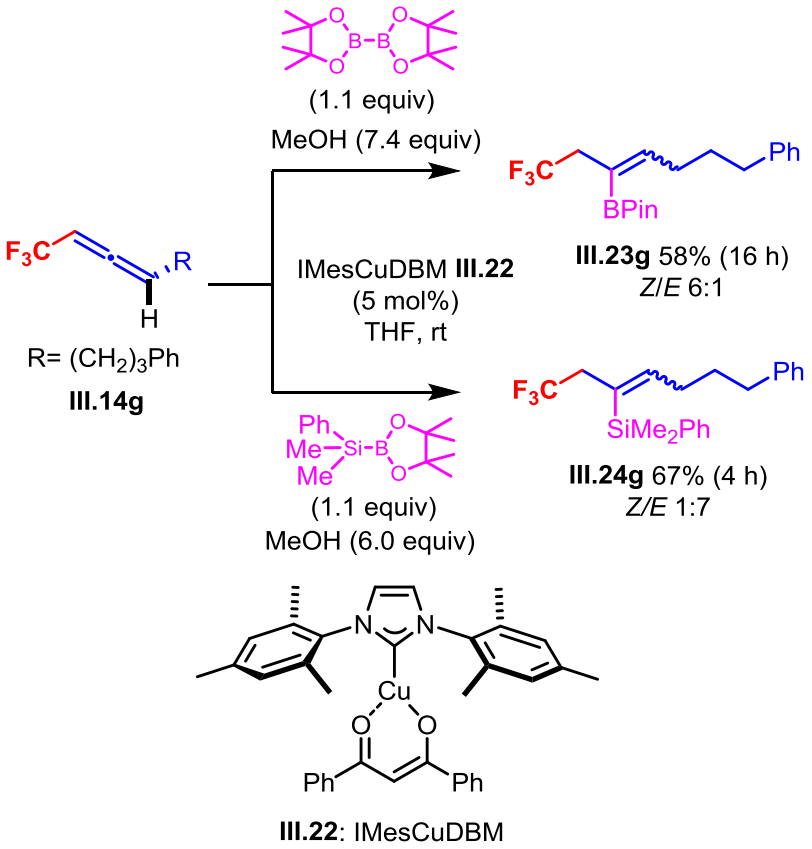
Scheme III-39. Attempt of a gold-catalyzed addition of alcohol on a CF_3-allene

In order to check this point, we moved to another family of intermolecular functionalization: the copper-catalyzed hydrofunctionalization of allenes. This method was already described on non fluorinated allenes[91] and an example had already been carried out on a 1,1-disubstituted CF_3-allene. We were interested in applying this transformation on a 1,3-disubstituted CF_3-allene, for which the regio- and the stereochemistry might be the source of selectivity issues.

The copper-catalyzed hydroboration and hydrosilylation were both carried out and the results are presented in Scheme III-40. Without any further optimization, both transformation worked in acceptable yields and with a complete regioselectivity. Furthermore, the stereoselectivity of the transformation also appeared to be encouraging, as one major product was observed in both cases in a ratio superior to 85:15.

As the next chapter of this manuscript will focus on the boroacylation of allenes, the mechanism of these reactions will be detailled later.

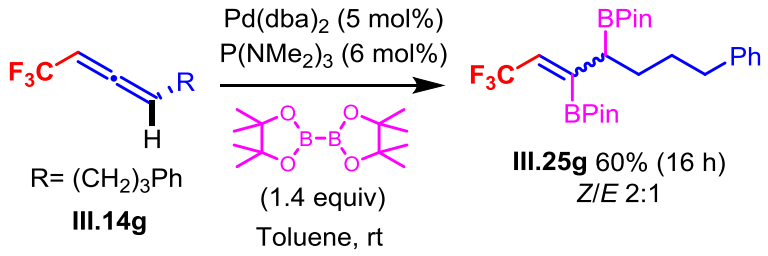
[91] W. Yuan, S. Ma, *Adv. Synth. Catal.* **2012**, *354*, 1867-1872.



Scheme III-40. Copper-catalyzed hydroboration and hydrosilylation of a CF_3-allene

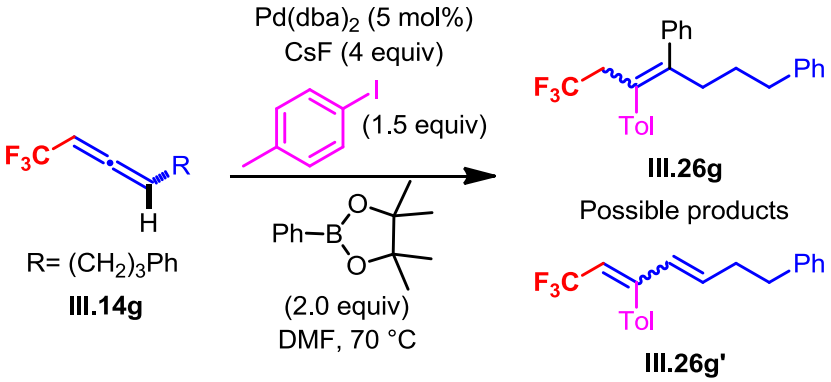
The palladium-catalyzed 1,2-diboration of allenes is also a well-described transformation on classical allenes (Scheme III-41).[92] Once again, the standard conditions for this reaction led to a completely regioselective transformation. The stereoselectivity was a little bit more modest and was opposite to the one observed in the case of the copper-catalyzed transformation.

[92] N. F. Pelz, A. R. Woodward, H. E. Burks, J. D. Sieber, J. P. Morken, *J. Am. Chem. Soc.* **2004**, *126*, 16328-16329.



Scheme III-41. Palladium-catalyzed diboration of a CF_3-allene

Finally, two other attempts with palladium catalysis were carried out. The three-components coupling involving the allene, an aryl iodide and a boronic ester led to a complex mixture of products (Scheme III-42).[93] Some of them might have been identified after a partial purification, and were attributed to the desired coupling product **III.26g** and to the undesired Heck product **III.26g'**. Unfortunately, the complexity of the transformation in this case forced us to stop our investigations in this direction.

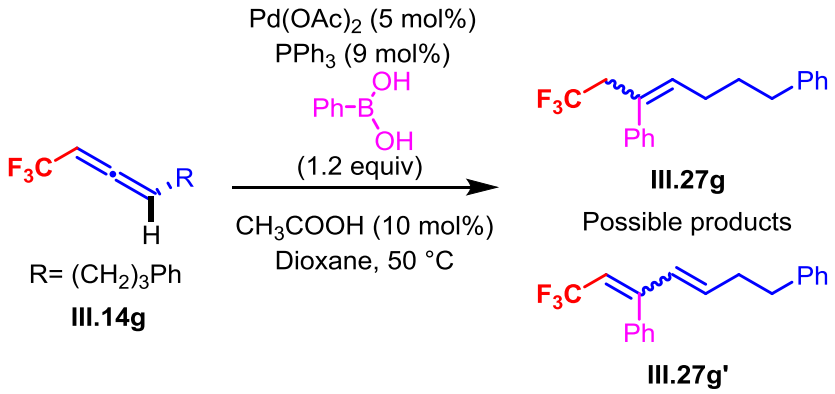


Scheme III-42. Palladium-catalyzed three-component coupling of an aryl iodide, a CF_3-allene and a boronic ester

Finally, a similar coupling of an allene with a boronic ester in the presence of a palladium complex and acetic acid also led to a complex mixture

[93] T.-H. Huang, H.-M. Chang, M.-Y. Wu, C.-H. Cheng, *J. Org. Chem.* **2002**, *67*, 99-105.

(Scheme III-43).[94] Again, some products were supposed to form during the reaction, but we were not able to isolate them in order to confirm this hypothesis.

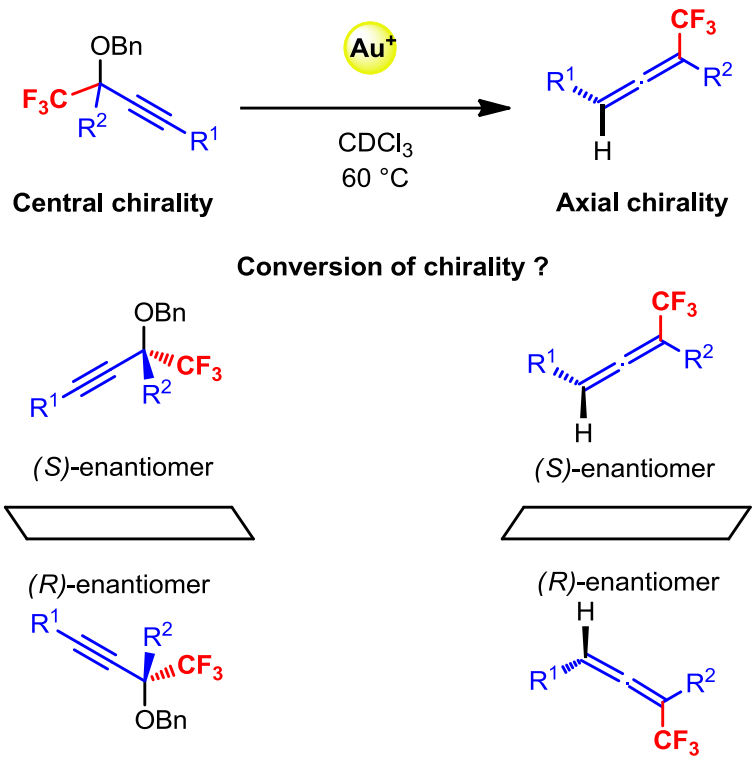


Scheme III-43. Palladium catalyzed coupling of a boronic ester with a CF_3-allene

II.8. Study of the Central-to-Axial Conversion of Chirality

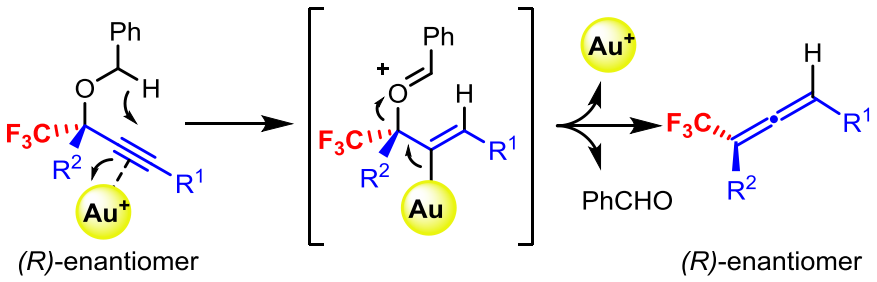
During all the optimization process and the study of the reaction scope, we worked with racemic substrates which were converted into racemic allenes. At this stage, we asked ourselves whether the central chirality of the starting material could be converted into an axial chirality for the CF_3-allene (Scheme III-44).

[94] C. H. Oh, T. W. Ahn, R. Reddy V, *Chem. Commun.* **2003**, 2622-2623.



Scheme III-44. Central-to-axial conversion of chirality during the gold-catalyzed transformation

Mechanistically, the conversion of chirality should happen on the second step of the transformation (Scheme III-45). Starting from the *(R)*-enantiomer, the 1,5-hydride shift generates the vinylgold intermediate which still possesses a chiral centre. The *anti*-elimination of benzaldehyde with the gold species should allow a stereospecific generation of the enantiopure CF_3-allene.

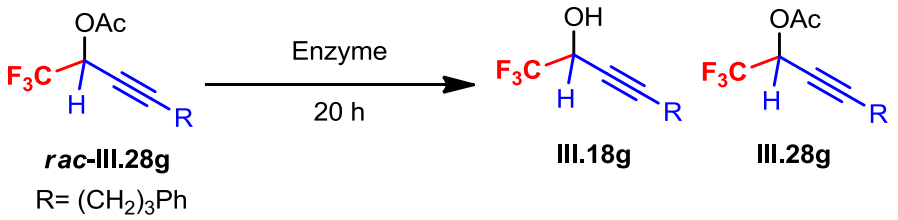


Scheme III-45. Conversion of chirality via a gold-catalyzed 1,5-hydride shift

To verify this hypothesis, it was necessary first to prepare an enantioenriched starting material. The most straightforward method to prepare this compound was the kinetic resolution by the selective acetylation of the propargylic alcohol or the hydrolysis of the propargylic acetate.[95] Enzymatic kinetic resolution methods were performed on the CF_3-acetate ***rac*-III.28g**. A short screening of different reaction conditions allowed to reach a satisfying result (Table III-6). The enzymes Candida Rugosa (C. Rugosa) and Amano Lipase PS (Amano PS) did not lead to good enantiomeric excesses for the alcohol **III.18g** (entries 1-5). Fortunately, the Candida Antartica Lipase B (CALB) was found to promote the selective hydrolysis of one enantiomer of the acetate **III.28g** in water at 40 °C (entry 6). This method allowed the isolation of 0.6 mmol of the alcohol with 80% yield (40% according to the starting material) with 96% *ee*.

[95] T. Yamazaki, H. Iwatsubo, T. Kitazume, *Tetrahedron: Asymmetry* **1994**, *5*, 1823-1830.

Table III-6. Kinetic resolution of the acetate **III.28g** using enzymatic hydrolysis

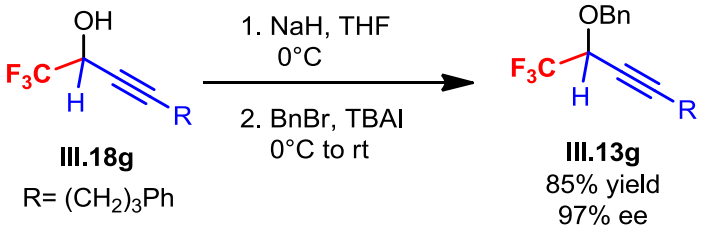


***rac*-III.28g**
R= $(CH_2)_3Ph$

III.18g **III.28g**

Entry	Solvent	T (°C)	Enzyme	Conv	ee	
					18	28
1	Water	40	C. rugosa	26	83	14
2	pH 7 buffer	40	Amano PS	21	78	-8
3	Water	50	C. rugosa	58	67	89
4	pH 7 buffer	50	Amano PS	61	58	nd
5	Water	50	Amano PS	37	63	36
6	Water	40	CALB	53	98	89

The enantioenriched substrate **III.13g** was finally obtained by a classical benzylation of the propargyl alcohol. The chiral information was not lost in the process, and the benzylated product was obtained with an excellent *ee*.



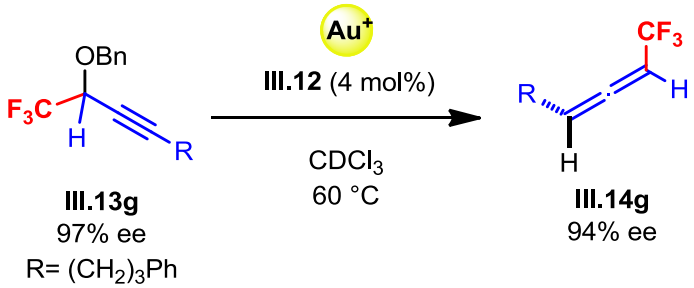
III.18g
R= $(CH_2)_3Ph$

III.13g
85% yield
97% ee

Scheme III-46. Synthesis of the enantioenriched substrate by benzylation of the alcohol

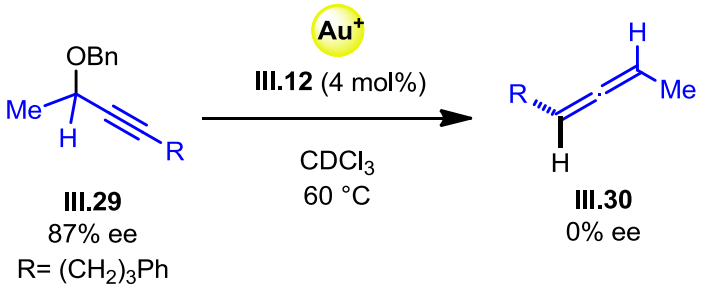
Finally, the conversion of the starting material **III.13g** into the allene **III.14g** was carried out under the standard conditions (Scheme III-47). We were

delighted to see that the chiral information was transfered from a central position to an axial one, as the CF_3-allene was obtained with 94% *ee*.



Scheme III-47. Conversion of chirality from the starting material to the product

Interestingly, the similar transformation on a non fluorinated starting material led to a complete loss of the chiral information (Scheme III-48). The final allene **III.30** was obtained as a racemic mixture in this case.

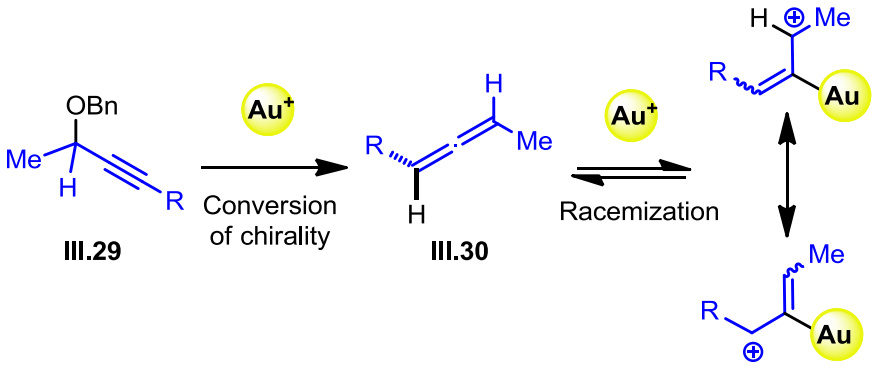


Scheme III-48. Loss of the chiral tranformation during the synthesis of a non fluorinated allene

To explain this conversion of chirality, the following mechanism is proposed (Scheme III-49). The transformation of the enantiopure starting materiel is believed to occur with a conversion of chirality, as in the case of the fluorinated allene. The allene **III.30** could further react with the gold catalyst to generate an allylic carbocation, which is prompt to racemize.[96] This fast

[96] R. J. Harris, K. Nakafuku, R. A. Widenhoefer, *Chem. - Eur. J.* **2014**, *20*, 12245-12254.

equilibrium might be at the origin of the complete loss of the chiral information of the non fluorinated allene.

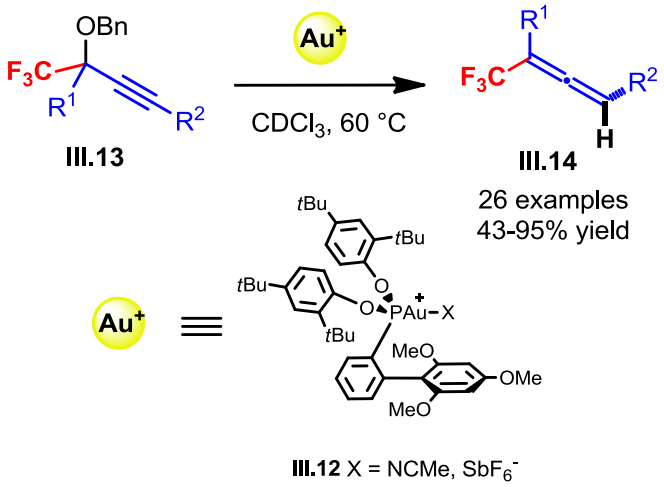


Scheme III-49. Proposed mechanism for the racemization of the allene **III.30**

In the case of the CF_3-allene **III.14g**, the substitution of the allene by an electron-withdrawing group might inhibit the formation of a carbocation, and so prevent the allene from the racemization. This absence of racemization can be correlated with the absence of reactivity of 1,3-disubstituted CF_3-allenes in electrophilic addition reactions, as shown previously.

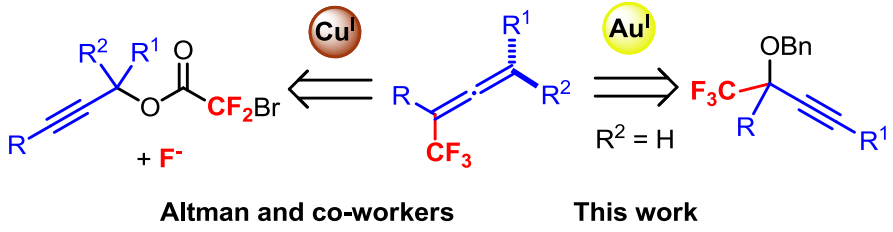
II.9. Conclusions and Perpectives

In this chapter, the previously reported synthesis of allenes was extended to the preparation of more challenging CF_3-allenes. Gold catalysts bearing an electron-deficient ligand turned out to efficiently promote the 1,5-hydride shift involved in the transformation (Scheme III-50).



Scheme III-50. Synthesis of CF_3-allenes by gold-catalyzed hydride shift

In terms of usefulness as synthetic methods, we do believe that the recent report by Altman and co-workers[79] in combination with this work represent complementary tools for the synthesis of trifluoromethylated allenes (Scheme III-51).



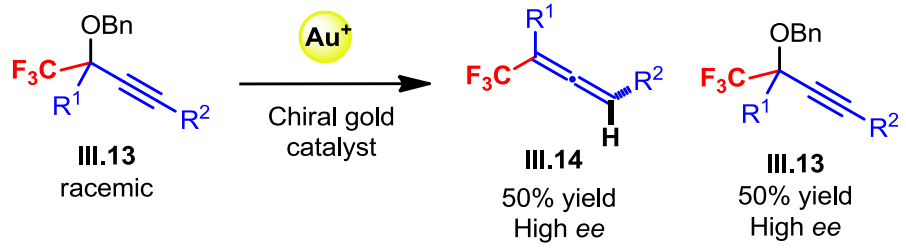
Scheme III-51. Recent methods for the preparation of CF_3-allenes

For instance, we were delighted to discover in a recent publication by Krische and co-workers that the aromatic CF_3-allenes were prepared using these two methods.[97]

[97] M. Holmes, K. D. Nguyen, L. A. Schwartz, T. Luong, M. J. Krische, *J. Am. Chem. Soc.* **2017**, *139*, 8114-8117.

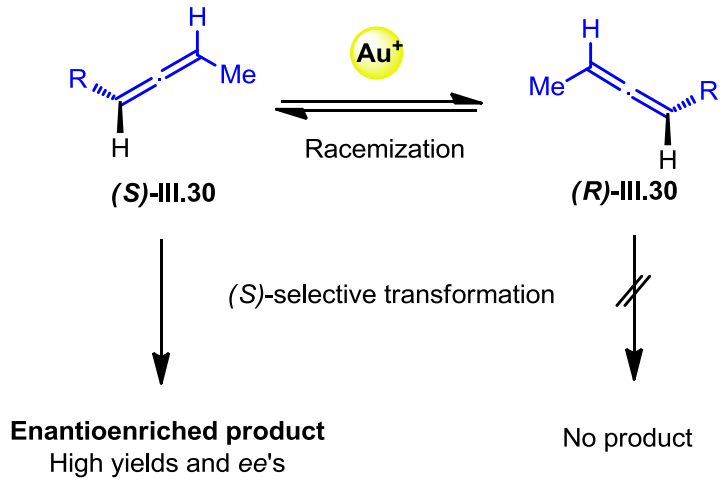
Post-functionalizations of the CF_3-allenes could be carried in an intra- and intermolecular fashion. Indenes, dihydrofurans, boron- and silicon-substituted products could be accessed by the subsequent use of gold, palladium or copper catalysis. These preliminary results inspired us for other projects during this PhD. For instance, the copper-catalyzed functionalization of allenes will be presented in the chapter IV of this manuscript.

Finally, the transfer of chirality during the transformation has been demonstrated, giving a nice opportunity for the synthesis of chiral CF_3-allenes. Beside the complete study of the mechanism of this process and its extension to other examples, a nice perspective would be the development of a kinetic resolution of CF_3-allenes (Scheme III-52).



Scheme III-52. Kinetic resolution of racemic O-benzyl ethers by the selective gold-catalyzed hydride shift

For the non-fluorinated substrates, the presumed racemization could be exploited in dynamic kinetic resolution processes involving the selective reaction on one enantiomer of the allene (Scheme III-53). Associated to a judicious selective transformation, this process would allow the preparation of a functionalized chiral product from a racemic mixture of the allene.



Scheme III-53. Dynamic kinetic resolution of a racemic mixture of the allene **III.30**

Finally, the reaction of a racemic allene with a chiral gold catalyst could also be envisaged. This might allow its deracemization via the formation of a gold-stabilized allylic carbocation.

III. Synthesis of CF_3-Enones by Gold-Catalyzed Acetate Rearrangement

As trifluoromethylated allenes, CF_3-enones are also useful building blocks in organic synthesis. The presence of the trifluoromethyl group on the electrophilic enone moiety allows a versatile conversion of this synthetic intermediate into various interesting structured motifs. Some recent examples of transformations involving CF_3-enones are depicted in Scheme III-54. Most of the developments are related to the Michael acceptor reactivity of the CF_3-enone. The enantioselective addition of alkynylzinc species has been reported by the group of Blay and Pedro (Scheme III-54, (1)).[98] The enantioselective addition of cyanide on this moiety was also shown to be possible using a

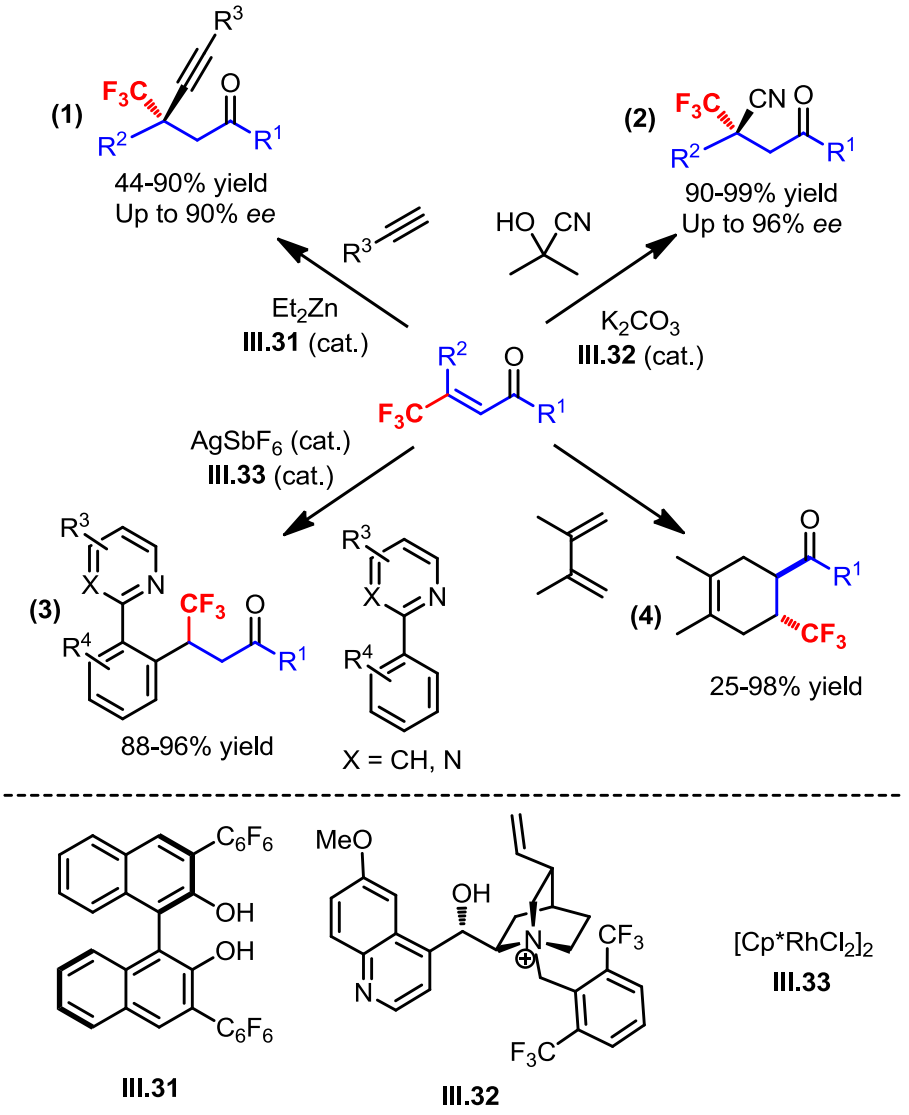
[98] A. Sanz-Marco, G. Blay, C. Vila, J. R. Pedro, *Org. Lett.* **2016**, *18*, 3538-3541.

chiral organocatalyst (Scheme III-54, (2)).[99] Besides, the use of CF_3-enones as electrophilic partners in C-H activation processes was demonstrated by Shibata and co-workers.[100] Rhodium catalysis was employed in order to activate phenylpyridines and make them react with CF_3-enones (Scheme III-54, (3)). Finally, CF_3-enones can also be used in cycloaddition transformations, such as Diels-Alder reactions (Scheme III-54, (4)).[101] Although these examples do not give an exhaustive list of the possible transformations involving CF_3-enones, they give a reasonable idea of the potential of this functional group for the preparation of trifluoromethylated compounds.

[99] H. Kawai, S. Okusu, E. Tokunaga, H. Sato, M. Shiro, N. Shibata, *Angew. Chem., Int. Ed.* **2012**, *51*, 4959-4962.

[100] Q. Jiang, T. Guo, K. Wu, Z. Yu, *Chem. Commun.* **2016**, *52*, 2913-2915.

[101] J. Leuger, G. Blond, R. Froehlich, T. Billard, G. Haufe, B. R. Langlois, *J. Org. Chem.* **2006**, *71*, 2735-2739.



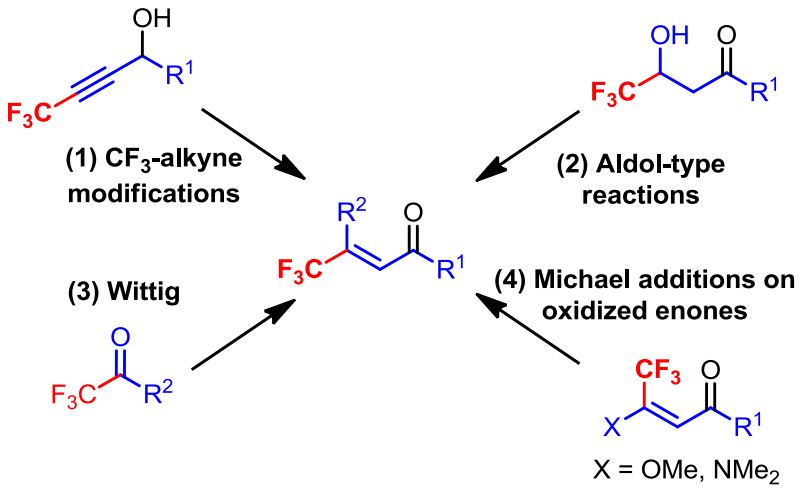
Scheme III-54. Examples of transformations involving CF_3-enones

III.1. Usual Syntheses of CF_3-Enones

While CF_3-enones look like a relatively simple moiety, only a few methods can be used to produce them efficiently. This paragraph will aim at giving a

short overview of the methods described for their preparation, pointing out the ones displaying versatility.

Four categories will be presented (Scheme III-55). At first, like the CF_3-allenes, CF_3-enones can be accessed from the rearrangement of CF_3-alkynes (Scheme III-55, (1)). Then, a large number of methods were developed to prepare aldol-type adducts, which are direct precursors of CF_3-enones (Scheme III-55, (2)). Wittig transformations of CF_3-ketones will be discussed afterwards (Scheme III-55, (3)). Finally, enones bearing a heteroatom (O, N) will be presented as an intermediate for the synthesis of the corresponding enone (Scheme III-55, (4)).

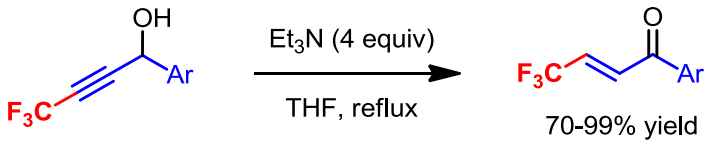


Scheme III-55. Main methods for the preparation of CF_3-enones

CF_3-alkyne modifications

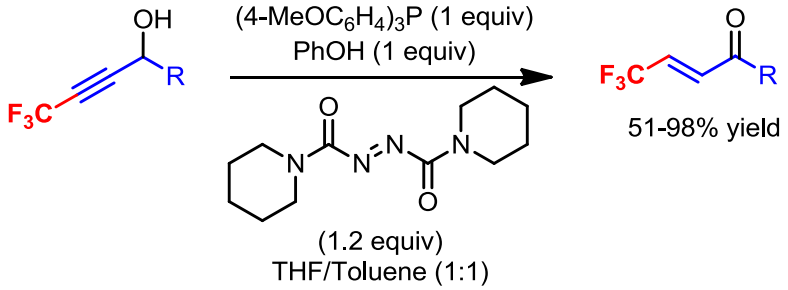
Nucleophilic CF_3-alkyne derivatives allow the preparation of propargylic alcohol bearing a CF_3-group (Scheme III-56). If an aromatic group is also present on the propargylic position, this intermediate can be easily isomer-

ized into the enone in the presence of triethylamine.[102] This method is quite straightforward, but can only be applied for the preparation of aromatic enones.



Scheme III-56. Isomerization of CF_3-alkynes into the corresponding disubstituted CF_3-enones

A more general protocol has also been developed in the presence of a phosphine and a 1,1′-(azodicarbonyl)dipiperidine (Scheme III-57).[103] In this case, some aliphatic enones could also be obtained in good yields.



Scheme III-57. Mitsunobu protocol for the isomerization of CF_3-alkynes

Starting from the same substrates, the CF_3-enones can also result from the hydrogenation of the corresponding alkyne followed by the oxidation of the alcohol.[104] As this transformation formally consists in an isomerization of the starting material, the use of so many reagents makes its atom efficiency relatively poor.

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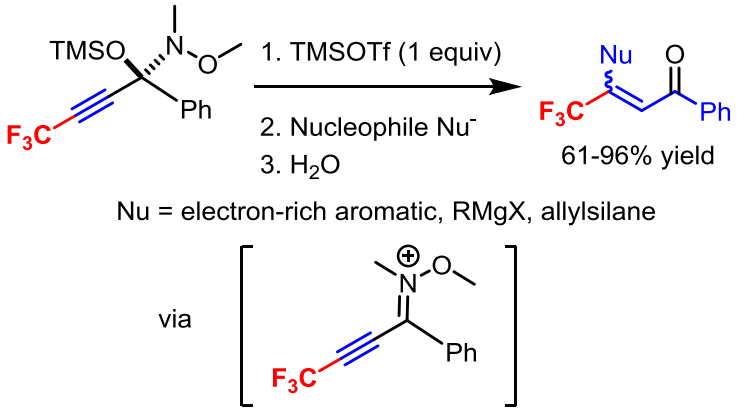
[102] T. Yamazaki, T. Kawasaki-Takasuka, A. Furuta, S. Sakamoto, *Tetrahedron* **2009**, *65*, 5945-5948.

[103] Y. Watanabe, T. Yamazaki, *J. Org. Chem.* **2011**, *76*, 1957-1960.

[104] T. Yamazaki, T. Ichige, T. Kitazume, *Org. Lett.* **2004**, *6*, 4073-4076.

Finally, the same isomerization has also been observed as an unexpected reaction when a substrate was reacted with a palladium catalyst.[105]

The preparation of trisubstituted CF_3-enones was made possible by the SN_2' addition of nucleophiles (aryl, allyl) onto a synthetic equivalent of a CF_3-ynone (Scheme III-58).[106] A Lewis acid activation of the compound allows the addition of a nucleophilic species, which leads after work-up to β,β-disubstituted enones.



Scheme III-58. Preparation of trisubstituted CF_3-enones by functionalization of CF_3-alkynes

The synthesis of perfluorinated enones has also been reported using propargyl-CF_3 alcohols via a Meyer-Schuster rearrangement.[107] Neat heating or reflux in aqueous acetic acid (Scheme III-59) allowed the efficient conversion of the alcohol into the corresponding enone.

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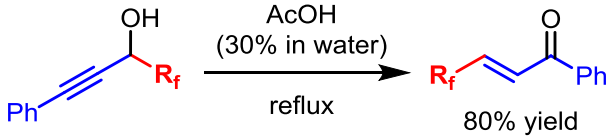
[105] Z.-X. Jiang, F.-L. Qing, *J. Fluorine Chem.* **2003**, *123*, 57-60.

[106] S. L. Jeon, J. K. Kim, J. B. Son, B. T. Kim, I. H. Jeong, *Tetrahedron Lett.* **2006**, *47*, 9107-9111.

[107] V. I. Filyakova, R. R. Latypov, A. L. Kotel'nikova, K. I. Pashkevich, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1987**, *36*, 190-192.

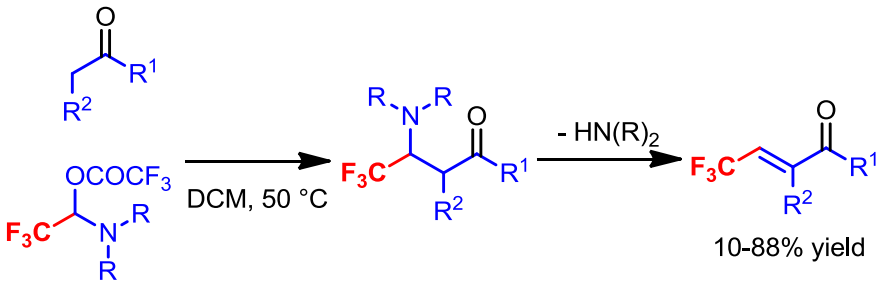


Scheme III-59. Synthesis of a perfluorinated enone via a Meyer-Schuster rearrangement

Aldol-type reactions

The dehydration of aldol-type compounds represents a straightforward access to enone derivatives. However, the direct use of trifluoroacetaldehyde remains rare in the literature because of the difficulties to handle this compound.[108] More stable species can be used instead to generate in situ a reactive equivalent to trifluoroacetaldehyde. This strategy was applied to the synthesis of CF_3-enones in several reports from the literature.

In 1993, the group of Viehe reported the condensation of ketones with activated CF_3-hemiaminals (Scheme III-60).[109] Some di- and trisubstituted CF_3-enones could be prepared following this process.

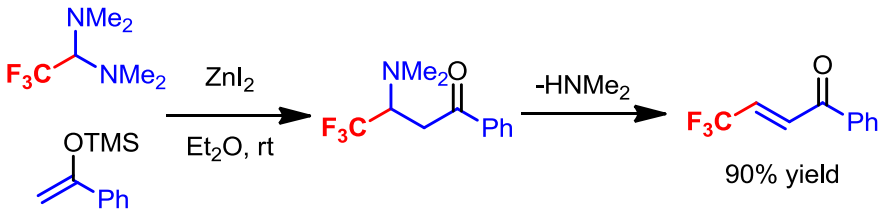


Scheme III-60. Synthesis of CF_3-enones by the condensation of ketones with activated hemiaminals

[108] H. Molines, C. Wakselman, *J. Fluorine Chem.* **1980**, *16*, 97-101.

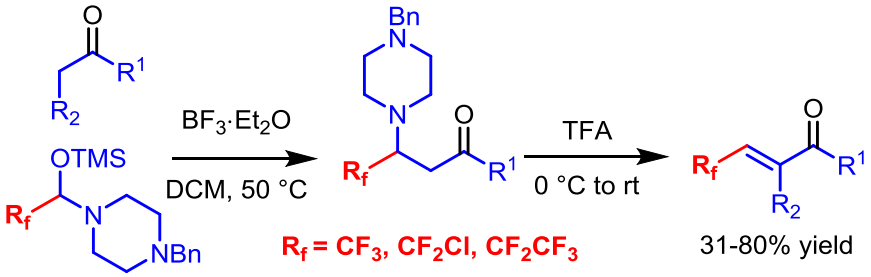
[109] C. Ates, Z. Janousek, H. G. Viehe, *Tetrahedron Lett.* **1993**, *34*, 5711-5714.

The same transformation involving a less activated aminal was reported by the group of Dolbier in 1998 (Scheme III-61).[110] In this case, the system required to be activated by zinc iodide, used as a Lewis acid, to produce the β-amino ketone. The subsequent elimination of dimethylamine gave the CF_3-enone in good yield. However, this method was not applied on other substrates.



Scheme III-61. Synthesis of a CF_3-enone from an aldol-type adduct

A more general version was developed using a protected hemiaminal in the presence of boron trifluoride as a Lewis acid (Scheme III-62).[111] Other perhalogenated chains such as CF_2CF_3 or CF_2Cl groups were also compatible with this method.

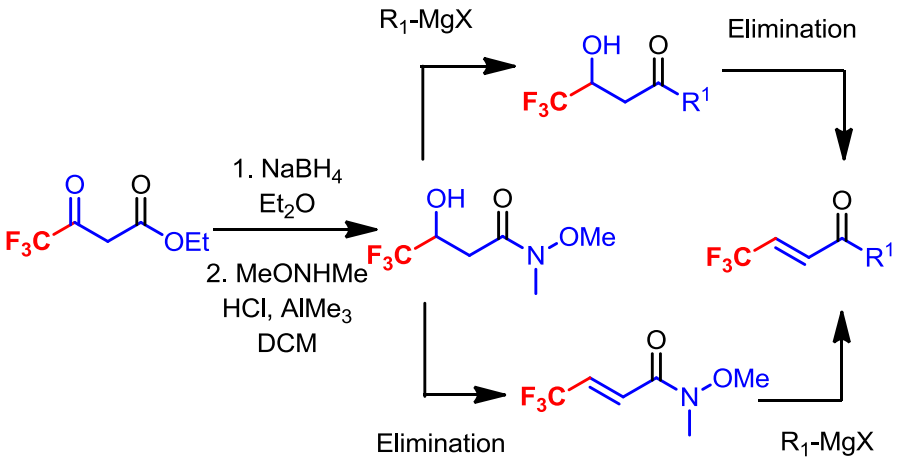


Scheme III-62. Synthesis of CF_3-enones via the condensation of hemiaminals with ketones

[110] Y. Xu, W. R. Dolbier, *Tetrahedron Lett.* **1998**, *39*, 9151-9154.

[111] G. Blond, T. Billard, B. R. Langlois, *J. Org. Chem.* **2001**, *66*, 4826-4830.

Weinreb amides prepared from ethyl trifluoroacetoacetate were also used as intermediates for the preparation of CF_3-enones (Scheme III-63).[112] Starting from the β-hydroxyamide, the addition of the Grignard reagent or the elimination of the alcohol could be carried out in any order to furnish at the end the desired enone. This method was applied to the preparation of β-CF_3-substituted enones lacking other substituents.



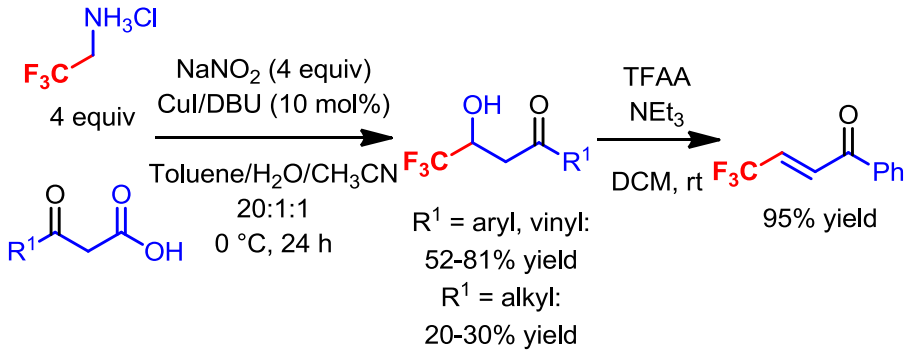
Scheme III-63. Synthesis of CF_3-enones with ethyl trifluoroacetoacetate as the CF_3 source

Last but not least, a trifluoroethylamine salt converted into a diazo compound could be condensed with a α-ketoacid in the presence of a copper catalyst (Scheme III-64).[113] In terms of substitutions, this method turned out to be very efficient to give a rapid access to aldol-type products. On one example, the acylation of the alcohol followed by its elimination yielded the desired enone.

---

[112] O. Marrec, J. Borrini, T. Billard, B. Langlois, *Synlett* **2009**, *8*, 1241-1244.

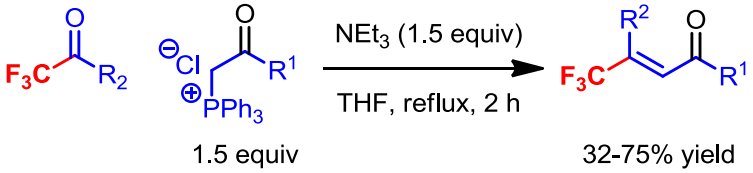
[113] H.-Y. Xiong, Z.-Y. Yang, Z. Chen, J.-L. Zeng, J. Nie, J.-A. Ma, *Chem. - Eur. J.* **2014**, *20*, 8325-8329.



Scheme III-64. Synthesis of a CF_3-enone starting from a trifluorethylamine salt as the CF_3 source

Wittig reactions

The use of trifluoroacetaldehyde as a precursor of disubstituted enones via Wittig reactions has been barely explored.[108] However, Wittig reactions on CF_3-ketones represent a straightforward access to β,β-disubstituted enones, as it was reported by Ishihara and co-workers (Scheme III-65).[114] This method was applied to the preparation of aliphatic and aromatic-substituted CF_3-enones.



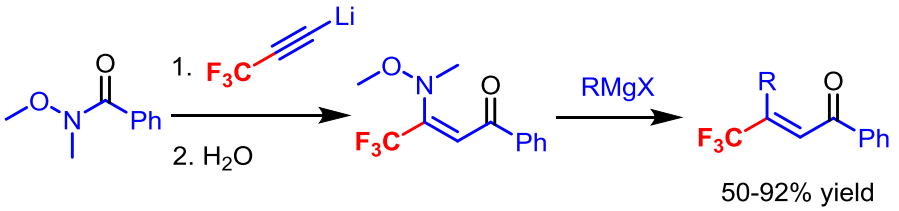
Scheme III-65. Synthesis of CF_3-enones by a Wittig reaction

Michael additions on oxidized enones

Finally, a few strategies involving enones bearing a leaving group such as methoxyamine were reported. The Michael addition of organometallic spe-

[114] T. Konno, T. Takehana, M. Mishima, T. Ishihara, *J. Org. Chem.* **2006**, *71*, 3545-3550.

cies on these compounds allowed the divergent synthesis of trisubstituted CF_3-enones (Scheme III-66).[115] Several aryl- and alkynyl-Grignard reagents were successfully employed to furnish the corresponding enone. The addition of a methyl group proceeded similarly, even if the final amine elimination appeared to be more challenging in this case.



Scheme III-66. Synthesis of CF_3-enones by addition/elimination on a nitrogen-substituted enone

Conclusion

As rapidly shown in the previous paragraphs, several methods already exist for the preparation of CF_3-enones. Although each of them display some advantages, some aspects of these syntheses can still be improved. When the preparation of trisubstituted CF_3-enones is quite easy, a straightforward synthesis of β-CF_3 disubstituted enones remains rare.

Overall, these methods suffer from various drawbacks:

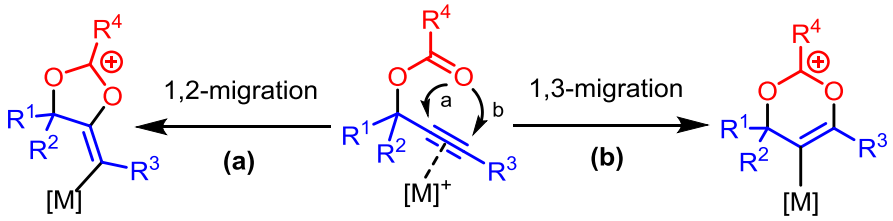
- The use of CF_3-alkynes which are not that easy to prepare.
- The use of a large excess of the CF_3-source (trifluoroethylamine)
- The use of unstable reagents (trifluoroacetaldehyde, triflate protected trifluoroacetaldehyde)
- The overall non-applicability of the method to the preparation of aliphatic enones.

[115] I. H. Jeong, S. L. Jeon, M. S. Kim, B. T. Kim, *J. Fluorine Chem.* **2004**, *125*, 1629-1638.

In this chapter, we will focus on the synthesis of such enones applying a gold-catalyzed [3,3]-rearrangement. The next paragraph will briefly present this rearrangement and give some examples of its application in synthesis.

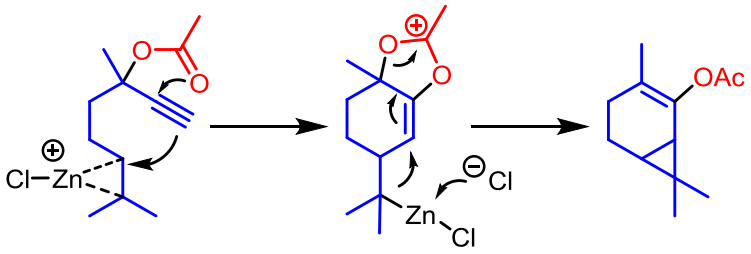
III.2. Gold-Catalyzed [3,3]-Acetate Rearrangement for the Synthesis of Enone Derivatives

The reactivity of propargylic esters has been known for decades in the field of transition metal catalysis. Two types of rearrangement have been observed and studied, based on the 1,2- or the 1,3-migration of acetate groups.



Scheme III-67. 1,.2- and 1,.3-migration of propargylic esters

The 1,2-migration has been proposed for the first time in 1976 by Ohloff and co-workers using a zinc(II) salt as the catalyst.[116] Their proposed mechanism is depicted in Scheme III-68.

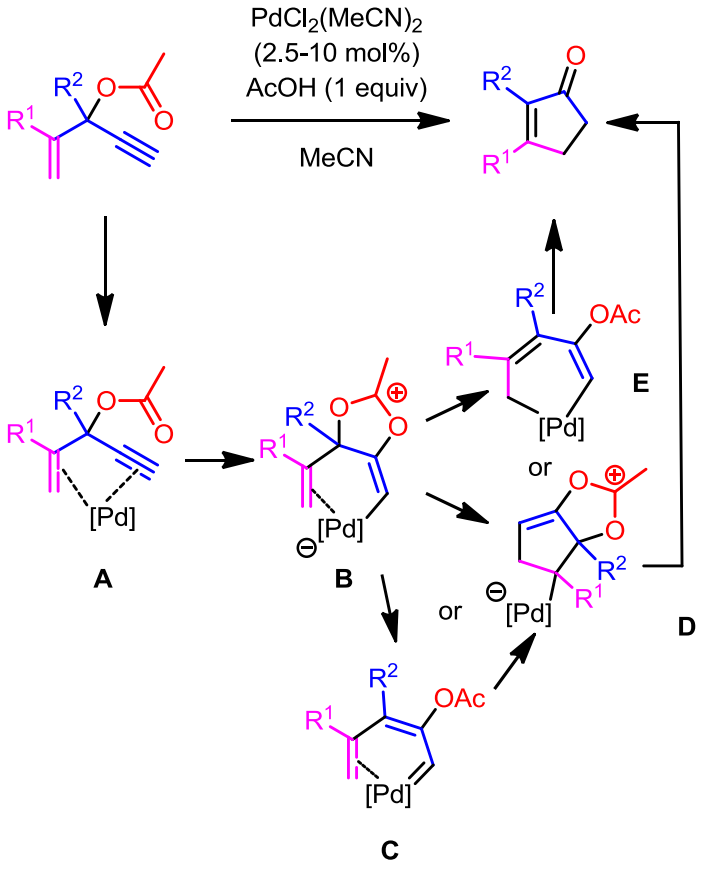


Scheme III-68. Zinc(II)-catalyzed acetate rearrangement: postulated mechanism

The reaction was also investigated by Rautenstrauch in 1984 with a more efficient palladium-mediated catalytic system.[117] The proposed mechanisms

[116] H. Strickler, J. B. Davis, G. Ohloff, *Helv. Chim. Acta* **1976**, *59*, 1328-1332.

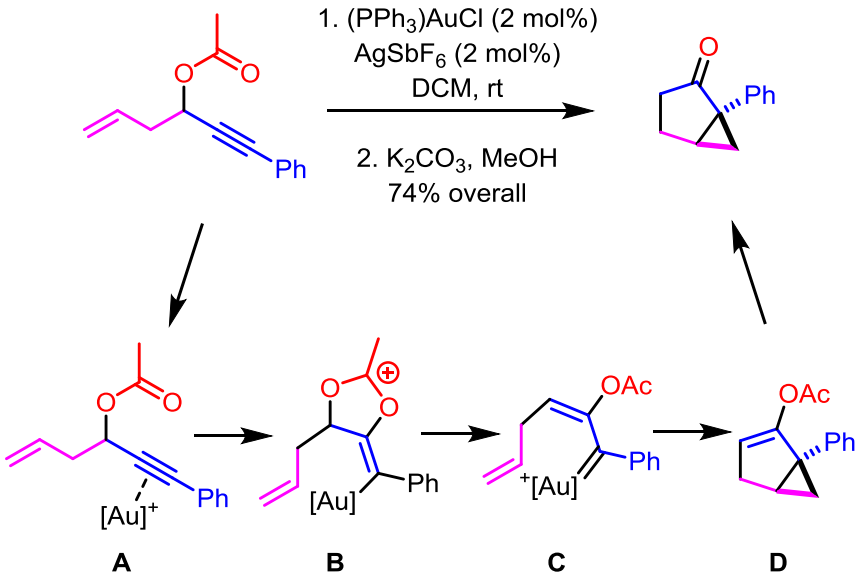
in the publication are presented on Scheme III-69. The first one assumes a redox-neutral process where palladium is only used as a Lewis acid (via intermediate **D**). In this sequence, the involvement of a carbenic species **C** is also speculated. The second one relies on the involvement of a redox process, presumably based on a Pd^{II}/Pd^{IV} cycle (via intermediate **E**). Nowadays, the redox-neutral mechanism in commonly accepted, as well as the involvement of a metal carbene as an intermediate.



Scheme III-69. Proposed mechanism for the palladium-catalyzed 1,2-acetate migration (palladium formal charges are written as depicted in the publication)

[117] V. Rautenstrauch, *J. Org. Chem.* **1984**, *49*, 950-952.

This method was applied to the synthesis of cyclopentenones in moderate to good yields. Fürstner and co-workers then involved this transformation into a domino sequence acetate rearrangement/cyclopropanation catalyzed by a platinum salt.[118] They showed afterwards that gold complexes were very efficient to catalyze this transformation, and several [3,1,0]-bicycles were prepared following this method (Scheme III-70). The proposed mechanism involves a carbenic species, which could react with the alkene in an intramolecular fashion to furnish the cyclopropyl ring. This mechanism is still used nowadays to explain the reactivity of these species.



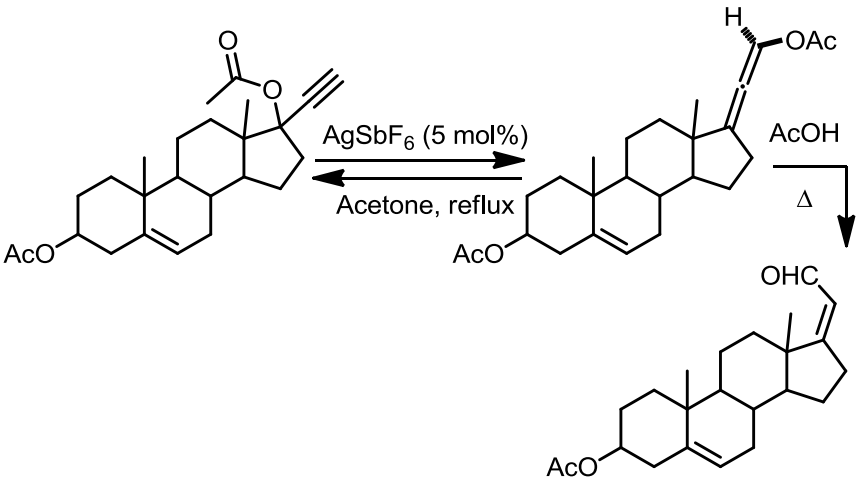
Scheme III-70. Gold-catalyzed acetate 1,2-migration/cyclopropanation

In the case of the 1,3-migration of acetates, zinc[119] and then silver (Scheme III-71)[120] were initially used to catalyze the formation of an allenoate from a

[118] V. Mamane, T. Gress, H. Krause, A. Fürstner, *J. Am. Chem. Soc.* **2004**, *126*, 8654-8655.

[119] P. D. Landor, S. R. Landor, *J. Chem. Soc.* **1956**, 1015-1019.

propargylic ester. This step has been described as an equilibrium, which has to be pushed forward by the irreversible transformation of the allenoate into an enal.



Scheme III-71. Example of [3,3]-acetate rearrangement catalyzed by silver (ref. 120d)

This transformation is mediated by the Lewis acidity of the metal complex, and can potentially be catalyzed by a wide range of transition metal complexes. Gold was added to this list in 2003, when the group of Ohe and Uemura described that gold(III) chloride could act as a promoter in this transformation.[121] In a more general manner, a report of Zhang in 2005 exploited the gold-catalyzed rearrangement in a domino process for the synthesis of fused indolines/cyclobutanes (Scheme III-72).[122]

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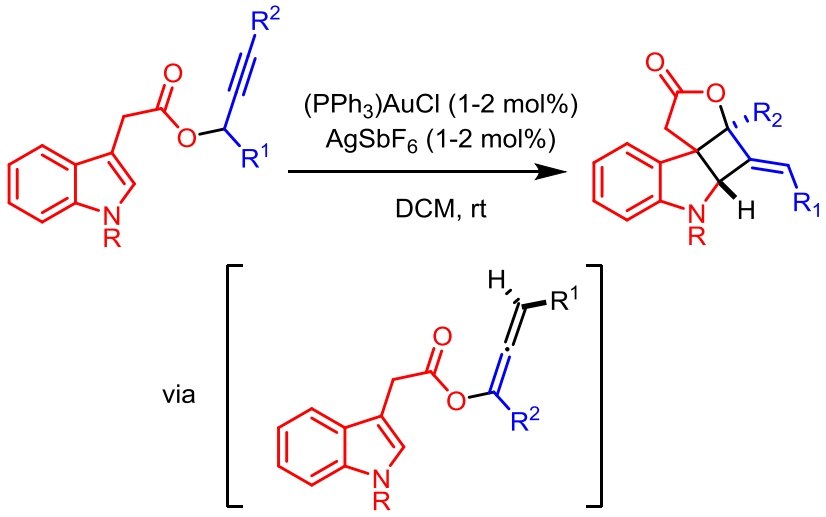
[120] (a) G. Saucy, R. Marbet, H. Lindlar, O. Isler, *Helv. Chim. Acta* **1959**, *42*, 1945-1955; (b) H. Schlossarczyk, W. Sieber, M. Hesse, H.-J. Hansen, H. Schmid, *Helv. Chim. Acta* **1973**, *56*, 875-944; (c) W. R. Benn, *J. Org. Chem.* **1968**, *33*, 3113-3118; (d) D. G. Oelberg, M. D. Schiavelli, *J. Org. Chem.* **1977**, *42*, 1804-1806.

[121] K. Miki, K. Ohe, S. Uemura, *J. Org. Chem.* **2003**, *68*, 8505-8513.

[122] L. Zhang, *J. Am. Chem. Soc.* **2005**, *127*, 16804-16805.



Scheme III-72. Gold-catalyzed synthesis of indoline/cyclobutane bicycles via a [3,3]-acetate rearrangement

Since these seminal reports, the propargylic ester rearrangement is known as a benchmark reaction in the field of gold catalysis. This transformation has been applied on various substrates exploiting the different intermediates that are formed in valuable synthetic methods.[123] A non-exhaustive list is presented in Scheme III-73. In the case of [1,2]-migration, the generated gold carbene can react or be trapped in several ways. The group of Nevado reported the preparation of 7-membered rings by its reaction with several dienes (eq 1).[124] The trapping with an oxidizing agent such as diphen-

[123] For reviews, see: (a) G. Henrion, F. Gagosz, *Chemistry of Organogold Compounds* (Wiley), **2014**, p. 149-234; (b) R. Kazem Shiroodi, V. Gevorgyan, *Chem. Soc. Rev.* **2013**, *42*, 4991-5001; (c) P. Maulron, F. D. Toste, *Modern Gold Catalyzed Synthesis* (Wiley), **2012**, p. 75-134.

[124] D. Garayalde, K. Krüger, C. Nevado, *Angew. Chem. Int. Ed.* **2011**, *50*, 911-915.

ylsulfoxide led to the preparation of carbonyl moieties (eq 2).[125] The group of Toste also reported the intermolecular cyclopropanation of the gold carbene with various olefins (eq 3).[126]

For the [3,3]-rearrangements, the generated allenoate is generally involved in domino processes in which the gold catalyst initiates a second catalytic cycle. If no other reactive functionality is present, the allenoate can rearrange in the presence of gold to furnish α,β-unsaturated 1,3-diones (eq 4).[127] Otherwise, a nucleophilic alkene[128] or a neighbouring cyclobutane[129] are reactive enough to initiate a rearrangement mediated by gold and can give access to quite sophisticated moieties (eq 5 and 6).

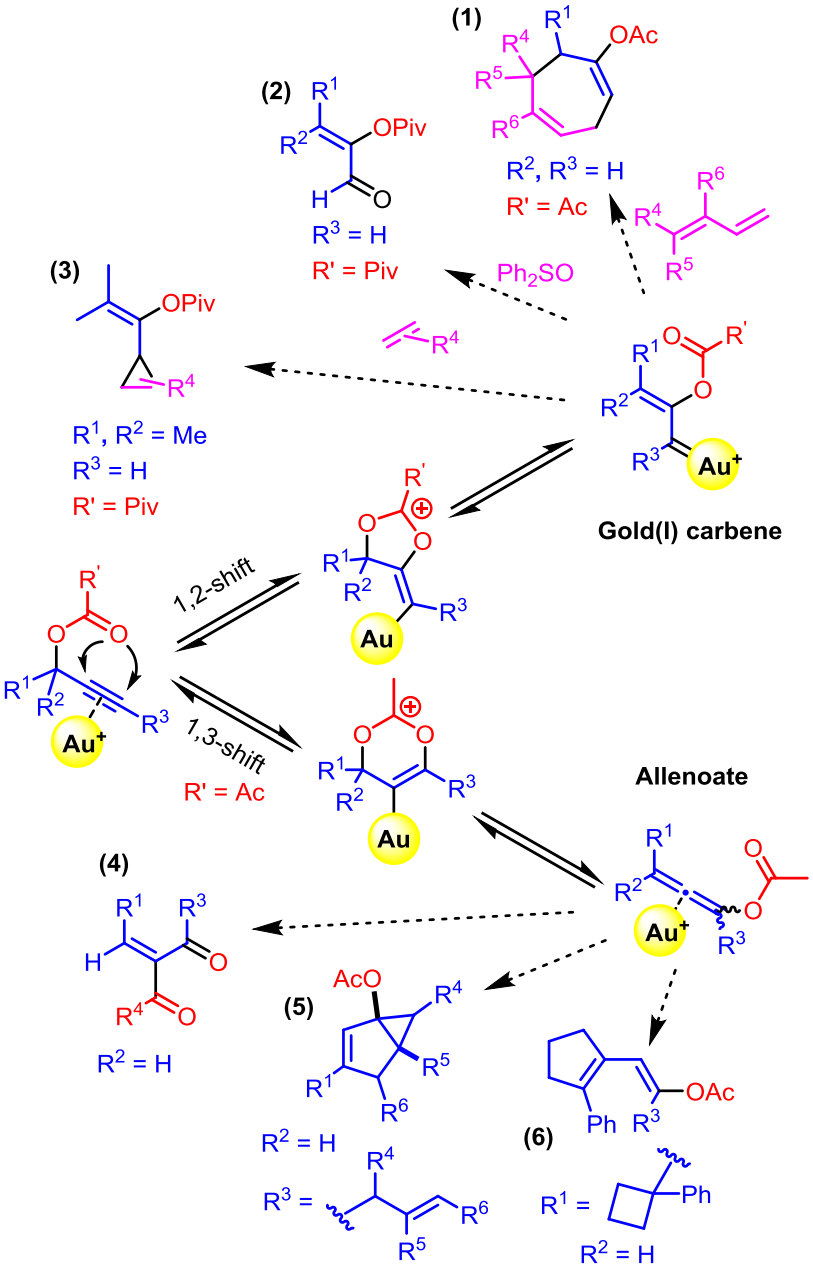
[125] C. A. Witham, P. Mauleón, N. D. Shapiro, B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 5838-5839.

[126] M. J. Johansson, D. J. Gorin, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 18002-18003.

[127] S. Wang, L. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 8414-8415.

[128] A. Buzas, F. Gagosz, *J. Am. Chem. Soc.* **2006**, *128*, 12614-12615.

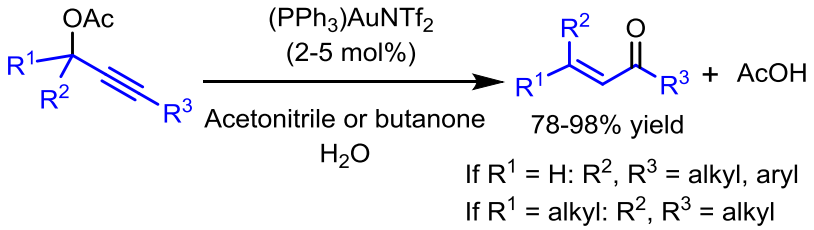
[129] A. S. Dudnik, T. Schwier, V. Gevorgyan, *Org. Lett.* **2008**, *10*, 1465-1468.



Scheme III-73. Applications of gold-catalyzed rearrangements of propargyl esters

Among its other applications, the [3,3]-acetate rearrangement has been applied in the synthesis of α,β-unsaturated aldehydes and ketones.

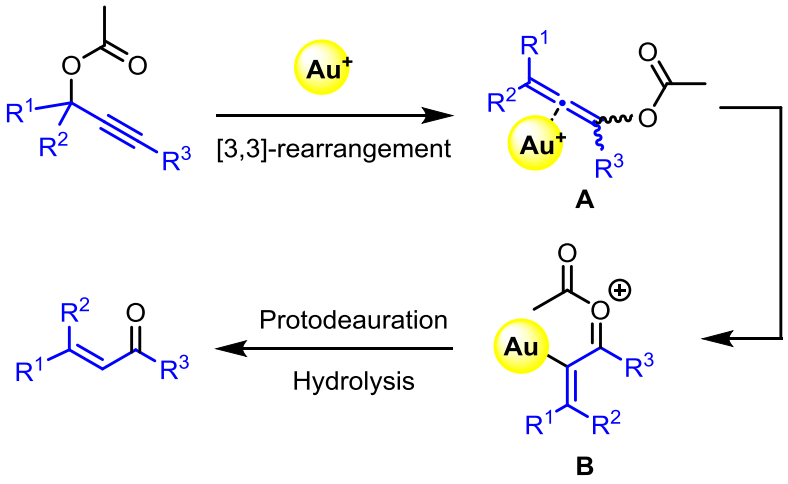
The group of Zhang reported the synthesis of enones by the gold-catalyzed [3,3]-rearrangement of propargyl acetates followed by the hydrolysis of the allenoate (Scheme III-74).[130] Good yields were obtained and in most cases, the *(E)*-isomer of the enone was exclusively formed.



Scheme III-74. Gold-catalyzed rearrangement of propargyl acetates into enones

The proposed mechanism is depicted in Scheme III-75. After a first [3,3]-rearrangement, the allenoate **A** is activated again by the gold catalyst to generate the intermediate **B**. After hydrolysis and protodeauration of this intermediate, the desired enone is obtained, generally with a good *(E)*-selectivity.

[130] M. Yu, G. Li, S. Wang, L. Zhang, *Adv. Synth. Catal.* **2007**, *349*, 871-875.



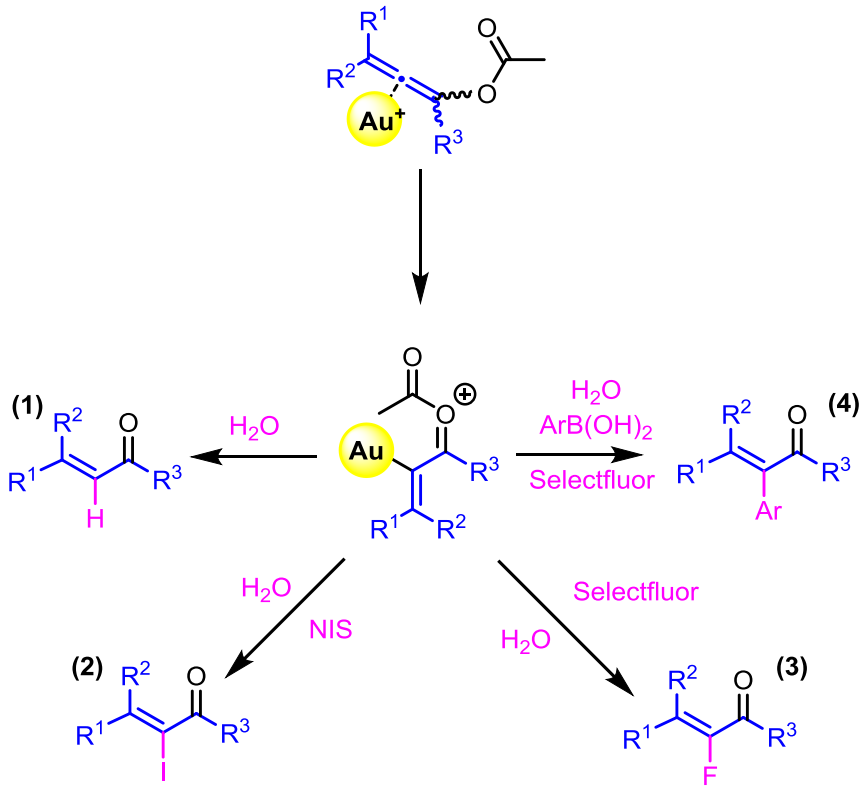
Scheme III-75. Proposed mechanism for the synthesis of enones from porpagyl acetates

The quenching of intermediate **B** by a protic nucleophile is the first example that has been developed (Scheme III-76, eq 1). Then, extensions to the use of more sophisticated electrophiles were carried out. The use of electrophilic sources of halides allowed the preparation of iodo- and fluoro-enones, by the use of *N*-iodosuccinimide (eq 2)[131] and Selectfluor (eq 3)[132], respectively. Finally, the application of this intermediate in an oxidative cross-coupling reaction with boronic acids was reported by the group of Zhang in the presence of Selectfluor (eq 4).[133]

[131] M. Yu, G. Zhang, L. Zhang, *Org. Lett.* **2007**, *9*, 2147-2150.

[132] T. de Haro, C. Nevado, *Chem. Commun.* **2011**, *47*, 248-249.

[133] G. Zhang, Y. Peng, L. Cui, L. Zhang, *Angew. Chem. Int. Ed.* **2009**, *48*, 3112-3115.

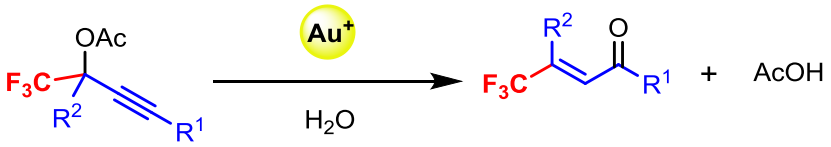


Scheme III-76. Extension of the [3,3]-acetate rearrangement to various functionalizations

The work described in the following paragraphs is a contribution to the extension of this method scope. The application of the [3,3]-propargyl acetates rearrangement to fluorinated substrates would allow the synthesis of trifluoromethylated enones. The optimization, the scope and the incorporation of this method into a one-pot procedure will be presented in the next paragraphs.

III.3. Objectives of the Project

Using the strategy described above, we were interested by the possibility to synthetize trifluoromethylated enones via a gold-catalyzed [3,3]-acetate rearrangement (Scheme III-77).



Scheme III-77. Gold-catalyzed [3,3]-acetate rearrangement for the synthesis of CF_3-enones

This strategy would provide a straightforward and modular preparation of CF_3-enones from very simple starting materials. Especially, this method would be efficient for the preparation of disubstituted CF_3-enones, for which the previously described methods are found to be efficient in the literature.

The stereoselectivity of the reaction would allow the double bond to adopt selectively a *(E)*-configuration, which also constitutes an advantage compared to other described methods.

Finally, the mild nature of the reagent (gold catalyst) and the side-product (acetic acid) would allow use of this process in a one-pot sequence where the obtained enone could be involved in a second transformation.

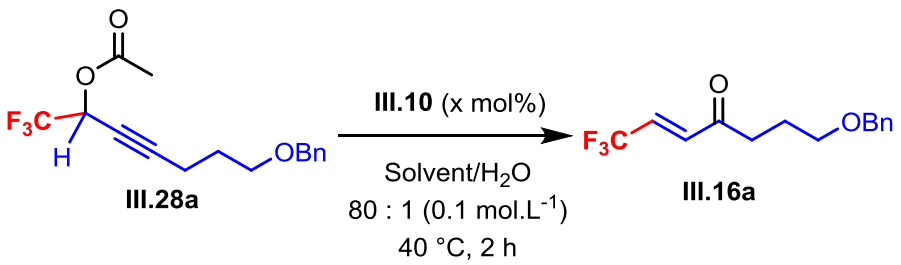
With these goals in mind, we started to study the potential of this transformation.

III.4. Optimization of the Reaction Conditions

We started our investigations with compound **III.28a** chosen as a model substrate. We selected a few experimental conditions used in the literature for a related transformation for which polar solvents, miscible with water, are usually employed (Table III-7).[130] We started by evaluating acetone (en-

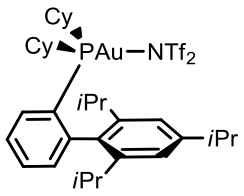
try 1) and dioxane (entry 2) in the presence of 4 mol% of a standard gold catalyst **III.10**. It turned out that the reaction worked better in acetone as the solvent with this catalyst. In order to be able to compare the yields obtained in the presence of gold complexes bearing different ligands, we decreased the catalyst loading to reach a partial conversion of the substrate. With 2 mol% of catalyst in acetone, a 55% yield was obtained (entry 3). Using butanone instead of acetone led to a lower yield (entry 4), and acetone was therefore chosen as the solvent for the reaction.

Table III-7. Preliminary screening for the gold-catalyzed synthesis of CF_3-enones



Entry	Solvent	Cat. Loading (mol%)	Yield[a] **16a** (%)	Yield[a] **28a** (%)
1	Acetone	4	89	< 5
2	Dioxane	4	29	66
3	Acetone	2	55	34
4	Butanone	2	26	78

[a] NMR yield estimated using 1,3,5-trimethoxybenzene as an internal standard

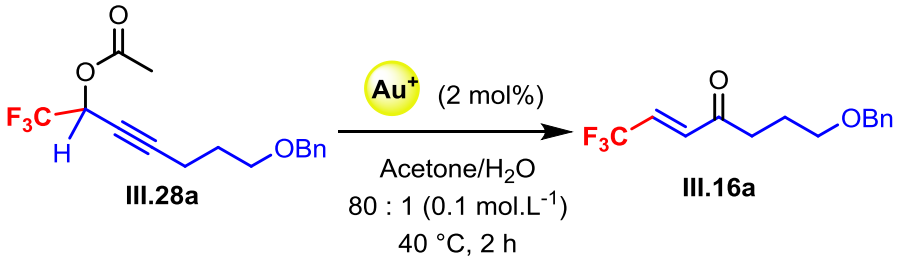


III.10 XPhosAuNTf$_2$

After this first screening, we tested different gold complexes in order to find an optimum catalyst for this transformation (Table III-8). We started by using different phosphine-based gold catalysts (entries 1-3). Using the *t*BuXPhos-based catalyst **III.31** or the PPh$_3$AuNTf$_2$ **III.32** had a detrimential effect on the yield of the reaction.

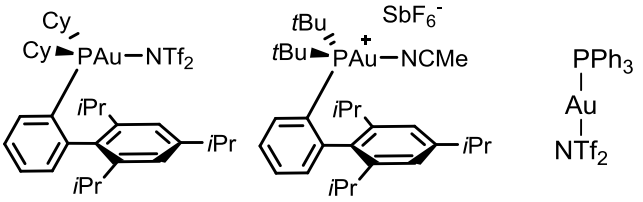
Switching to an NHC-based catalyst was more effective as the conversion was complete in this case and the assessed NMR yield almost quantitative (entry 4). Gold complexes **III.11** and **III.12** bearing a phosphonite ligand as well as the phosphite-based catalyst **III.34** led to a very poor conversion of the starting material (entries 5-7). Finally, the gold(III) salt AuCl$_3$ and (Pyridinecarboxylatio)AuCl$_2$ complex **III.35** also led to disappointing yields (entries 8-9). IPrAuNTf$_2$ **III.33** catalyst proved to be the most efficient among the catalysts tested. It was therefore used in the next steps of the optimization.

Table III-8. Screening of gold complexes for the synthesis of CF_3-enones

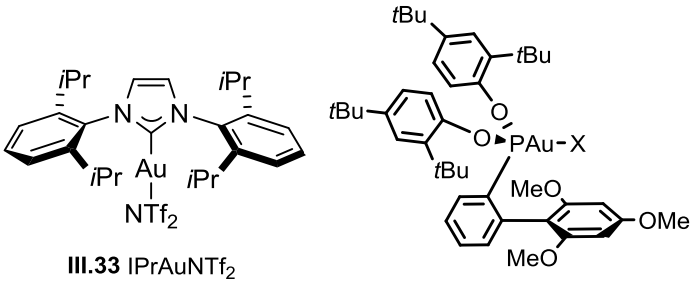


Entry	Catalyst	Yield[a] **16a** (%)	Yield[a] **28a** (%)
1	$XPhosAuNTf_2$ **III.10**	55	34
2	*t*$BuXPhosAuSbF_6$ **III.31**	30	70
3	PPh_3AuNTf_2 **III.32**	< 5	93
4	$IPrAuNTf_2$ **III.33**	> 95	< 5
5	$PhosphoniteAuNTf_2$ **III.11**	< 5	83
6	$PhosphoniteAuSbF_6$ **III.12**	9	92
7	$PhosphiteAuNTf_2$ **III.34**	< 5	> 95
8	$AuCl_3$	20	81
9	(Pyridinecarboxylato)$AuCl_2$ **III.35**	< 5	> 95

[a]NMR yield estimated using 1,3,5-trimethoxybenzene as an internal standard

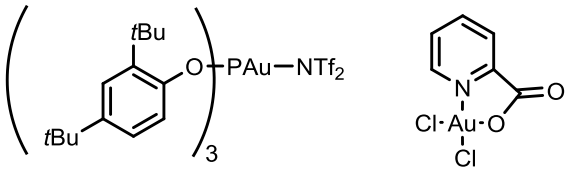


III.10 **III.31** **III.32** PPh_3AuNTf_2



III.33 $IPrAuNTf_2$

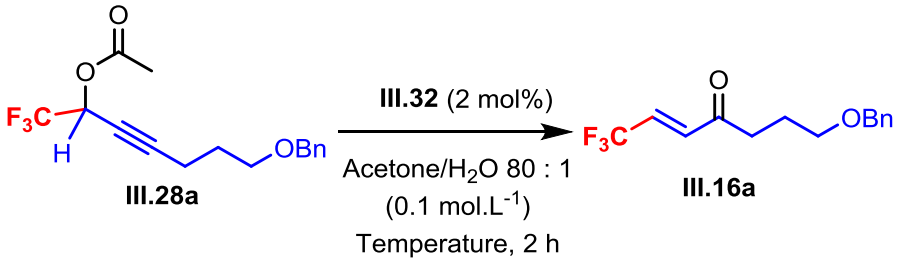
III.11 X = NTf_2^-
III.12 X = NCMe, SbF_6^-



III.34 $PhosphiteAuNTf_2$ **III.35** $PyridinecarboxylatoAuCl_2$

A few tests on the influence of the reaction temperature were then carried out (Table III-9). When the reaction was performed at room temperature or at 40 °C, no significant change was observed (entries 1-2). On the contrary, a decrease of the temperature down to 0 °C led to a drop of the reaction yield (entry 3).

Table III-9. Effect of the temperature on the gold-catalyzed rearrangement

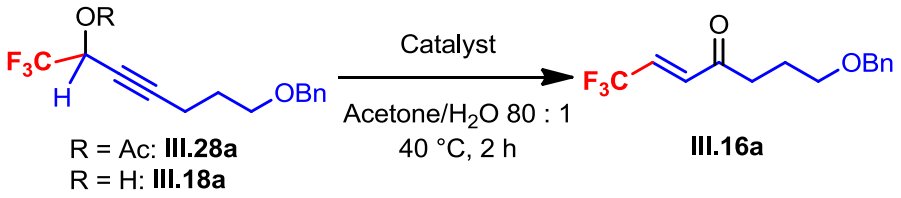


Entry	Temperature (°C)	Yield[a] **16a** (%)	Yield[a] **28a** (%)
1	40 °C	> 95	< 5
2	rt	> 95	< 5
3	0 °C	64	36

[a]NMR yield estimated using 1,3,5-trimethoxybenzene as an internal standard

Finally, it was checked that silver salts could not be used as substitutes for the gold complex in this transformation (Table III-10, entries 1-2). A Brønsted acid like HCl could not catalyzed the transformation neither, even in superstoichiometric amounts (entry 3). Alcohol **III.16a** was then subjected to the optimal catalysis conditions and the desired product was detected by ^{1}H NMR spectroscopy (entry 4). The conversion was however very low and the product was drowned in a mixture of products. In this case, the intermolecular gold-catalyzed hydration of the alkyne might have occurred non selectively, and subsequent side reactions led to several decomposition products. Finally, $AgNTf_2$ was inefficient to promote any reaction starting from this alcohol (entry 5).

Table III-10. Blank tests for the preparation of trifluoromethylated enones



R = Ac: **III.28a**
R = H: **III.18a**

III.16a

Entry	Catalyst	R	Result
1	AgOTf 4 mol%	Ac	No reaction
2	$AgNTf_2$ 4 mol%	Ac	No reaction
3	HCl_{aq} 2 equiv	Ac	No reaction
4	**III.33** 4 mol%	H	Complex mixture
5	$AgNTf_2$ 4 mol%	H	No reaction

With these optimized reaction conditions in hand, we then focused on the synthesis of a library of representative trifluoromethylated *O*-acyl propargylic esters.

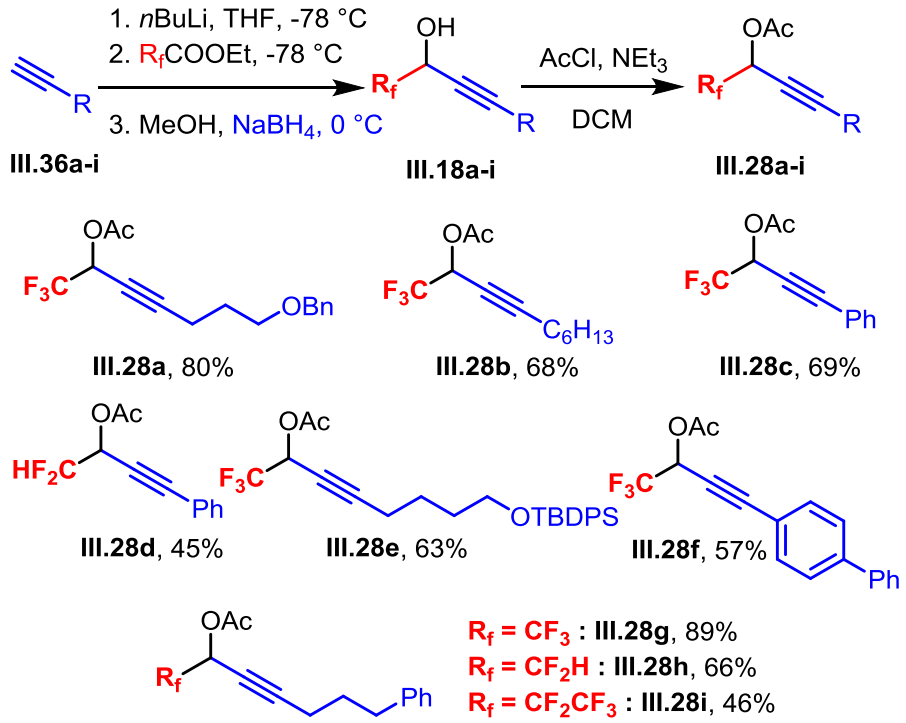
III.5 Substrates Syntheses

The same general strategy than for the preparation of *O*-benzyl propargylic ethers was employed. Again, ethyl trifluoroacetate was used as the trifluoromethyl source in most cases. These syntheses are depicted in the next sections.

Secondary substrates

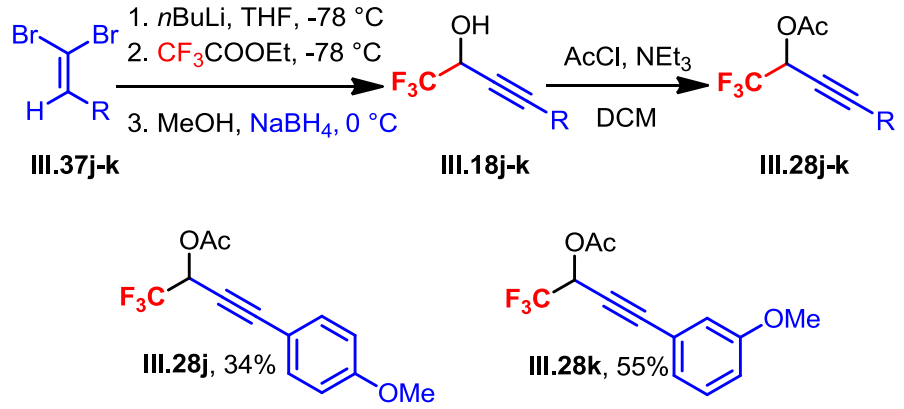
The synthesis starts with the deprotonation of an alkyne **III.36** with *n*-butyllithium. The resulting organolithium species was then trapped by

ethyl trifluoroacetate at low temperature. Reduction of the intermediate using sodium borohydride in the presence of methanol at 0 °C was subsequently performed. This led to the formation of a CF_3-propargylic alcohol **III.18a-i**, which could be acetylated using a standard procedure to furnish the desired products **III.28**. This method was applied to aliphatic, aromatic substrates as well as on several fluorinated moieties. Overall yields for the synthesis of compounds **III.28a-i** are presented in Scheme III-78.



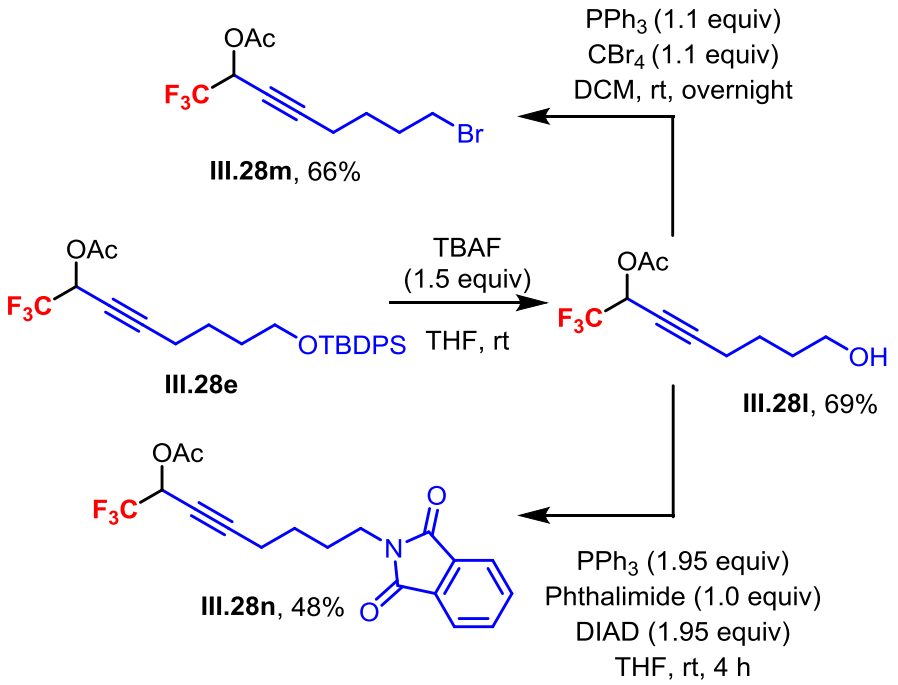
Scheme III-78. Synthesis of secondary substrates

The two compounds **III.28j** and **III.28k** were obtained using a similar strategy (Scheme III-79). The alkynyl-lithium species was generated from the vinyldibromo **III.37j-k** via a Corey-Fuchs reaction. The same protocol was then followed to obtain these two substrates.



Scheme III-79. Synthesis of substrates **III.28j** and **III.28k**

Compound **III.28e** was itself a precursor for three other substrates (Scheme III-80). The deprotection of the TBDPS group with TBAF afforded the alcohol **III.28l** in 69% yield. Substitution of the alcohol by a bromide atom or a phthalimide using phosphorus-based chemistry led to the obtention of the acetates **III.28m-n**.

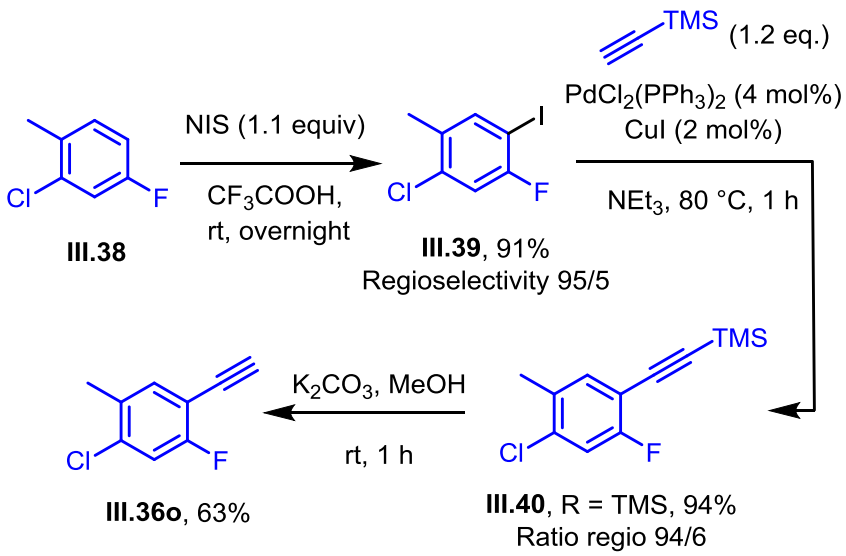


Scheme III-80. Synthesis of substrates **III.28l-n** starting from substrate **III.28e**

We were interested in compound **III.28o** possessing a polyfunctionalized aromatic group because of the known bioactivity of this moiety.[134] As described below, its synthesis was a little bit more challenging.

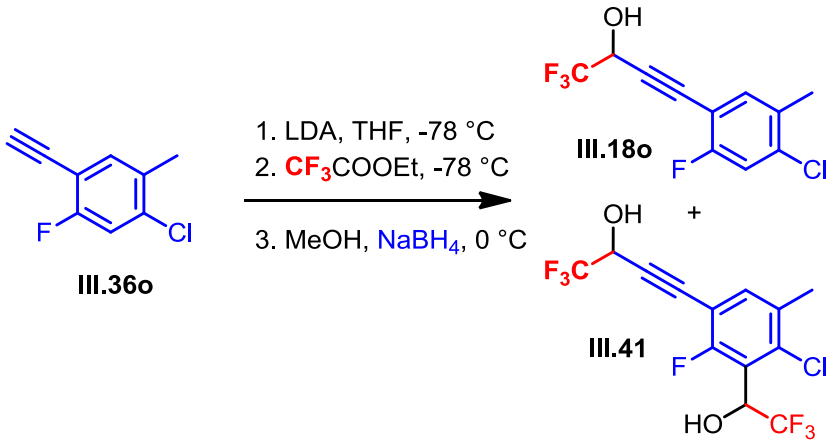
The sequence started with the iodination of 2-chloro-4-fluorotoluene in trifluoroacetic acid. The iodinated compound was obtained in excellent yield and with good regioselectivity. The resulting compound **III.39** was subjected to a Sonogashira coupling to obtain the intermediate **III.40**. Deprotection of the TMS group furnished the alkyne **III.36o**.

[134] M.-T. Hsieh, H.-C. Lin, S.-C. Kuo, *Tetrahedron*, **2016**, *72*, 5880-5885.



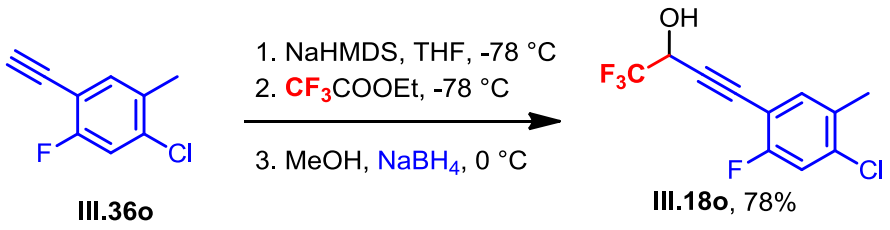
Scheme III-81. Synthesis of the alkyne **III.36o** starting from 2-chloro-4-fluorotoluene **III.38**

Alkyne **III.36o** was then put in the presence of a base to generate the corresponding alkynyl lithium species. Because of the presence of other acidic positions on the aromatic ring, we decided to use LDA instead of *n*BuLi to selectively deprotonate the acetylenic proton. After trapping the acetylide with ethyl trifluoroacetate and reduction with sodium borohydride, it turned out that at least two products were formed (Scheme III-82). The desired compound **III.18o** was present in the crude mixture, as well as a by-product which was identified as the compound **III.41**. The formation of the latter is probably due to the double deprotonation of the substrate oriented by the fluorine and chlorine atoms on the aromatic ring. The resulting intermediate is then trapped by two equivalents of ehyl trifluoroacetate. As these compounds were hardly separable using classical chromatography techniques, we decided to perform the reaction in the presence of a weaker base than LDA.



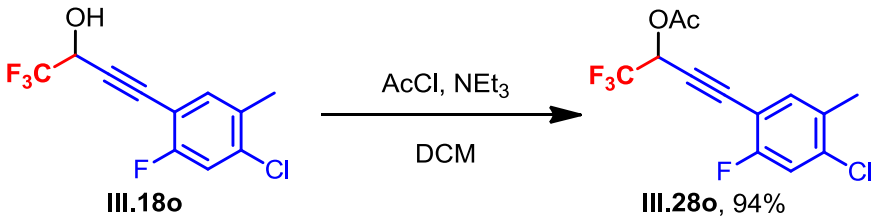
Scheme III-82. Reactivity of the alkyne **III.36o** with the standard procedure

When LDA was replaced by NaHMDS, only the desired alcohol **III.18o** was obtained (Scheme III-83). The selectivity of this transformation can obviously be attributed to the lower basicity and the higher steric demand of NaHMDS, and so to its unability to deprotonate the aromatic ring.



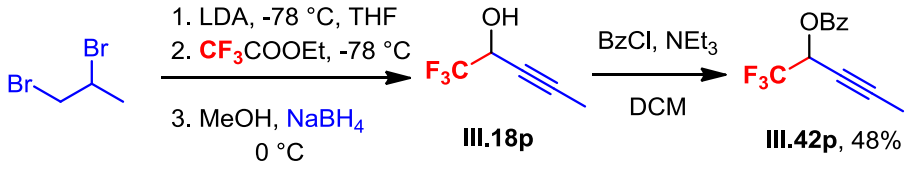
Scheme III-83. Preparation of the alcohol **III.18o** with using NaHMDS as a base

The acetylation proceeded smoothly on alcohol **III.18o** to provide acetate **III.28o** in excellent yield (Scheme III-84).



Scheme III-84. Acetylation of the alcohol **III.18o**

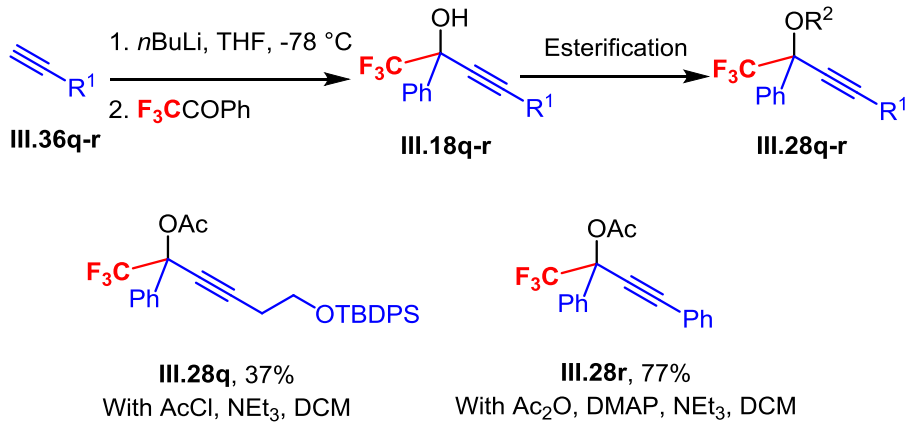
Finally, acetate **III.42p** was prepared in a few steps from 1,2-dibromopropane. An excess of LDA was used to promote the double elimination from the starting material and generate the propynyllithium species at low temperature. Its trapping by ethyl trifluoroacetate and subsequent reduction produced the alcohol **III.18p**. This intermediate was not purified and directly subjected to a standard benzoylation protocol. A benzoate was preferred to an acetate in this case to decrease the volatility of the final product.



Scheme III-85. Synthesis of substrate **III.42** from 1,2-dibromopropane

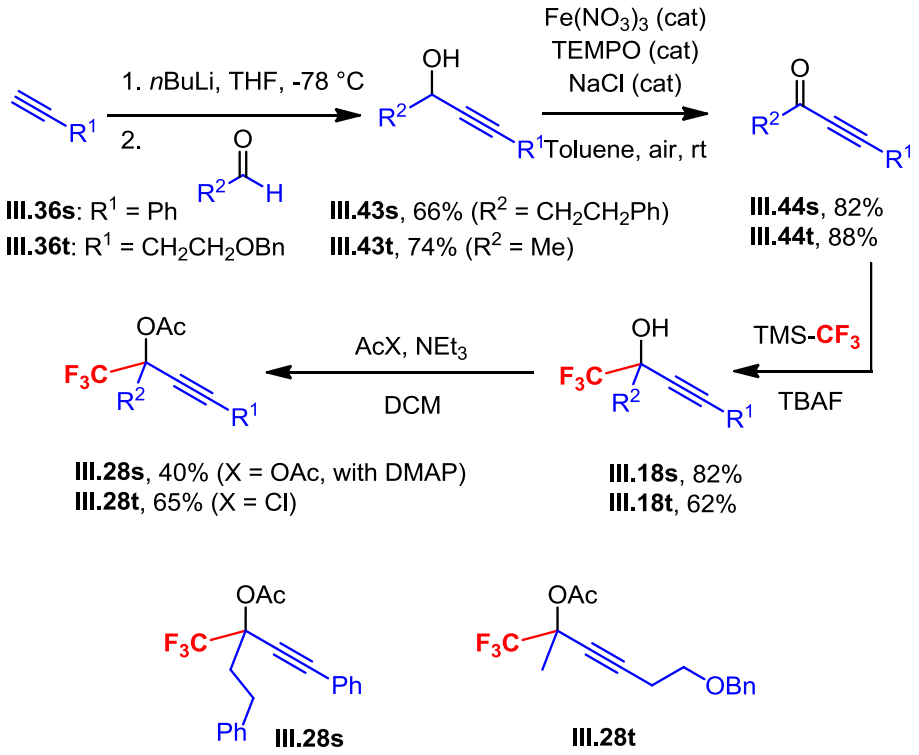
Tertiary substrates

Globaly, tertiary substrates were more difficult to obtain due to the difficulty of the acetylation step in some cases. The deprotonation of an alkyne followed by its quenching with trifluoroacetophenone directly led to the formation of the corresponding alcohol (Scheme III-86). The esterification procedure had to be adapted in some cases, but the two desired acetates **III.28q-r** were obtained in moderate to good yields from alcohols **III.18q-r**.



Scheme III-86. Synthesis of acetates **III.28q-r** from trifluoroacetophenone

Finally, acetates **III.28s-t** were obtained in a few steps from the corresponsding alkynes as well (Scheme III-87). Deprotonation of alkynes **III.36s-t** with *n*-butyllithium followed by their trapping with an aldehyde furnished alcohols **III.43s-t**. Oxidation of these secondary alcohols led to the formation of ketones **III.44s-t**. Then, addition of a trifluoromethyl anion generated from $TMSCF_3$ yielded the corresponding tertiary alcohols **III.18s-t**, which could be acetylated to fursnish the acetates **III.28s-t**.



Scheme III-87. Synthetic sequence for the preparation of substrates **III.28s-t**

With all these substrates in hands, we could start our investigations on the scope of the transformation.

III.6. Scope of the Method

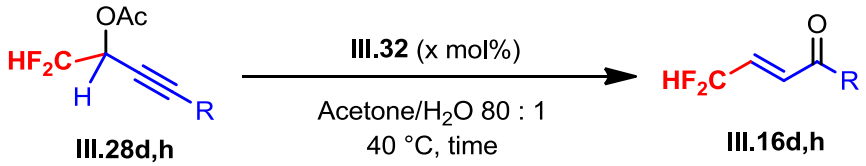
Secondary substrates

Difluoromethyl group-containing substrates (**III.28d** and **III.28h)** were the first ones to be tested (Table III-11). These substrates appeared to be particularly difficult to convert into the corresponding enones. Substrate **III.28h** which possesses an alkyl chain was converted at 63% into the corresponding enone after 19 h reaction (entry 1). Increasing the concentration to 0.4

mol.L^{-1} seemed to speed up the process, and enone **III.16h** was obtained in 88% yield after 6 h of reaction. The aromatic substrate **III.28d** was even more difficult to convert. Only 21% of conversion was observed after 19 h under the standard conditions at 0.1 mol.L^{-1} (entry 3). Increasing the concentration to 0.4 mol.L^{-1} allowed the conversion to reach a maximum of 50%, but some improvement was still required. As the gold catalyst was supposed to be deactivated after a few hours, 4 mol% of the gold catalyst were used in this case and an 89% yield was obtained after 18 h of reaction. Due to the difficulty to obtain these first CF_3-enones at 0.1 mol.L^{-1}, it was decided to carry out all the examples at a concentration of 0.4 mol.L^{-1}.

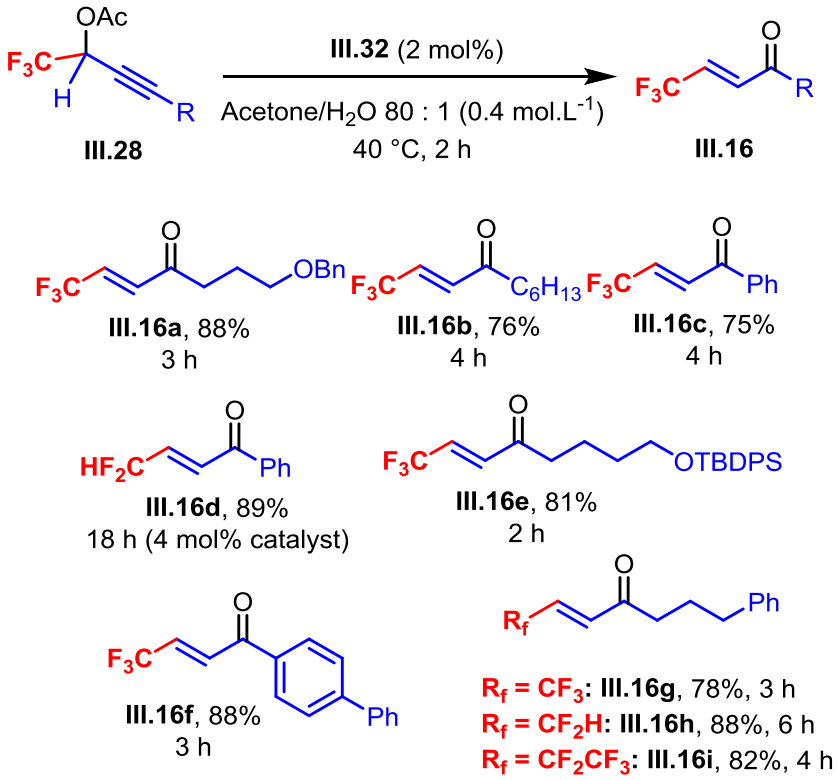
It appeared *a posteriori* that these two secondary substrates were especially non reactive and that this higher concentration can be seen as an extra security measure.

Table III-11. Modified concentration for the difluoromethylated substrates



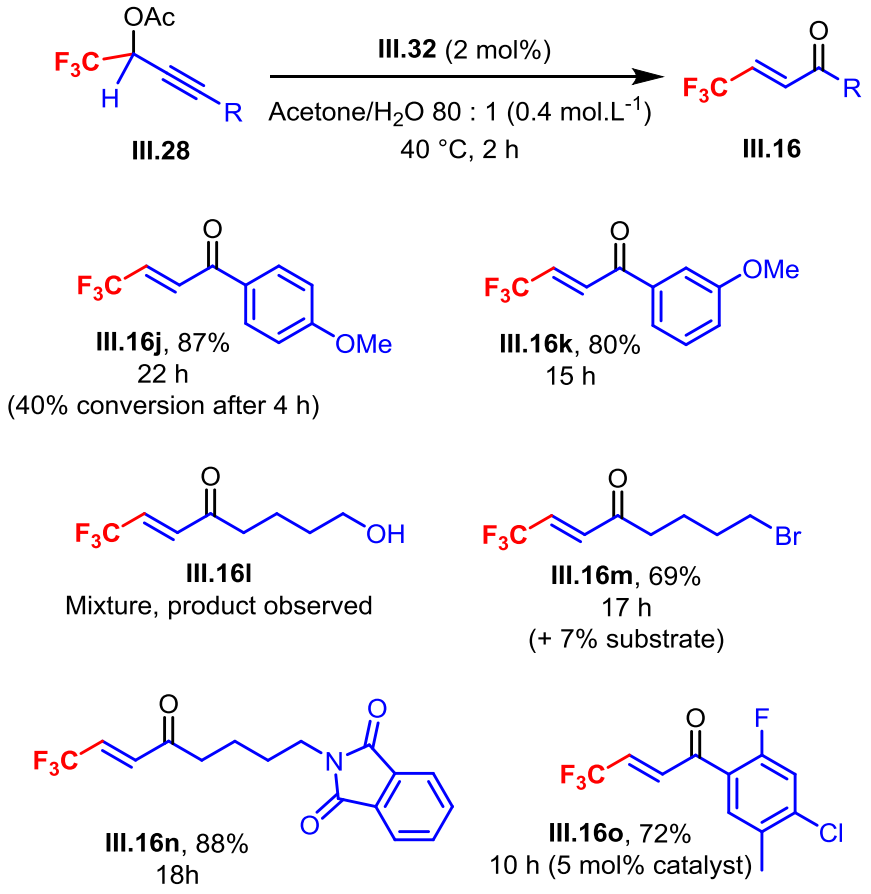
Entry	x	R	C (mol.L^{-1})	Time (h)	(Conversion) Yield [%]
1	2	CH_2CH_2Ph	0.1	19	(63)
2	2	CH_2CH_2Ph	0.4	6	88
3	2	Ph	0.1	19	(21)
4	2	Ph	0.4	14	(50)
5	4	Ph	0.4	18	89

Thus, the scope of the first secondary substrates was studied with these new optimal conditions (Scheme III-88). The reaction of substrate **III.28a** was tested at 0.4 mol.L^{-1} and the corresponding enone **III.16a** was obtained in 88% isolated yield. Other aliphatic substrates **III.25b,e,g** were converted with the same efficiency. Enones prepared from the rearrangement of aromatic substrates **III.28c,f** were isolated in 75% and 88% yield, respectively. As described above, this method was also extended to difluoromethylated substrates **III.28d,h** and good yields were obtained in such cases. Finally, the perfluorinated compound **III.28j** was also a good substrate, as the corresponding enone could be produced in 82% yield.



Scheme III-88. Scope of substrates **III.28a-i**

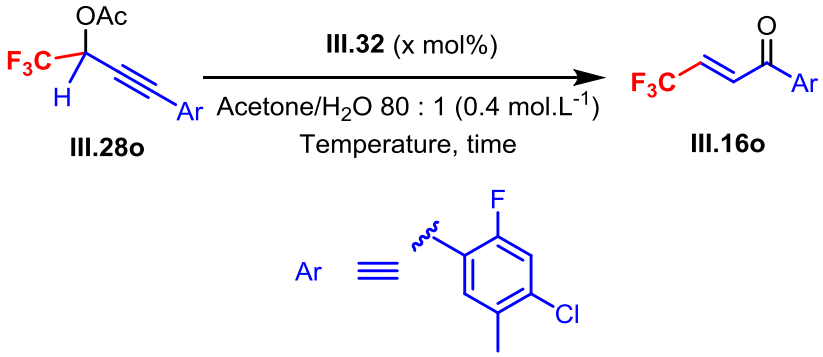
We then moved to the second generation of substrates (Scheme III-89). Electron-rich aromatic starting materials **III.28j-k** could be converted in good yields after longer reaction times. Due to the presence of a free alcohol, substrate **III.28l** was, as expected, not cleanly converted into the enone. A complex mixture was obtained in this case, and the investigations were not pushed further. On the contrary, the brominated and phthalimide analogs were selectively transformed into the corresponding enones **III.16m-n** in good yields. Finally, substrate **III.28o** could be turned into enone **III.16o** in 72% yield in the presence of 5 mol% catalyst.



Scheme III-89. Scope of the substrates **III.16l-o**

This last substrate was the subject of a few tests (Table III-12). In a reaction carried out at 40 °C for 6 h, the product was obtained with small amounts of a side product (entry 1). When the reaction was carried out in the presence of 3 mol% of the catalyst at room temperature, only a poor conversion of the starting material was observed (entry 2). In order to favour the hydrolysis of the reaction intermediate, a higher concentration in water was used (entry 3). Unfortunately, this led to a decrease in the conversion. Finally, it was chosen to carry out the transformation with a higher catalyst loading in a shorter reaction time in order to minimize product decomposition (entry 4).

Table III-12. Conversion of the substrate **III.28o** in the optimized conditions



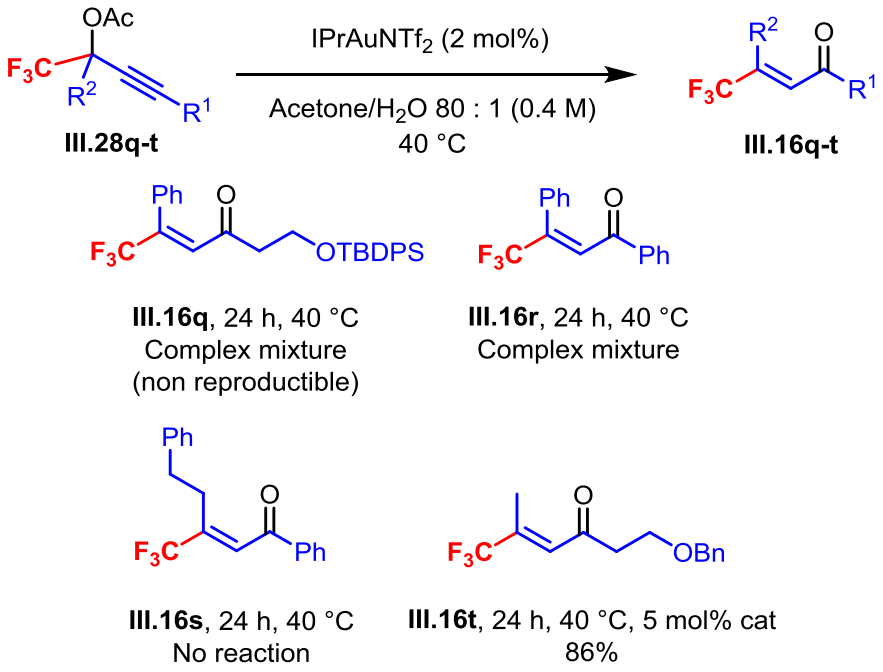
Entry	x	Temperature (°C)	Time (h)	Result
1	2	40	6	75% conversion but presence of a side product
2	3	rt	Over-night	30% conversion
3[a]	4	40	6	Almost no con-version
4[b]	5	40	4	72% yield (side product in the crude)

[a] Solvent used: acetone/H_2O 10 : 1; [b] Carried out at a concentration of 0.5 mol.L^{-1}

Some side products were still present, but the conversion was complete, which allowed us to isolate the product in 72% yield. However, it would be useful to perform this reaction on a higher scale and to monitor it in order to understand its mechanism and indentify the side products.

Tertiary substrates

The tertiary substrates did not display a reactivity similar to the secondary ones (Scheme III-90). Acetate **III.28q** led to a mixture of two products: the starting material and probably the allenoate intermediate. Acetate **III.28r** did not allow the selective formation of the enone product, but a mixture of at least 4 products according to ^{19}F NMR. Substrate **III.28s** was not converted at all under the reaction conditions. Finally, acetate **III.28t** was selectively converted into the enone **III.16t** and isolated in 86% yield. These results suggest that the steric hindrance around the acetate moiety plays a determining role in the formation of the intermediates and the final product.



Scheme III-90. Scope of the tertiary substrates

In the case of the substrate **III.28q**, some experimental data are provided in Figure III-1. The crude spectrum clearly shows the appearance of a new product with a similar proton pattern than the starting material. Besides, the ^{13}C NMR of this crude showed a signal at 198.5 ppm, which is characteristic of the central carbon atom of an allene function. Finally, other reports in the literature showed the formation of this type of products with other transition metal catalysts (Pt, Rh).[135]

[135] (a) K. Cariou, E. Mainetti, L. Fensterbank, M. Malacria, *Tetrahedron* **2004**, *60*, 9745-9755; (b) Y. Shibata, K. Noguchi, K. Tanaka, *J. Am. Chem. Soc.* **2010**, *132*, 7896-7898.

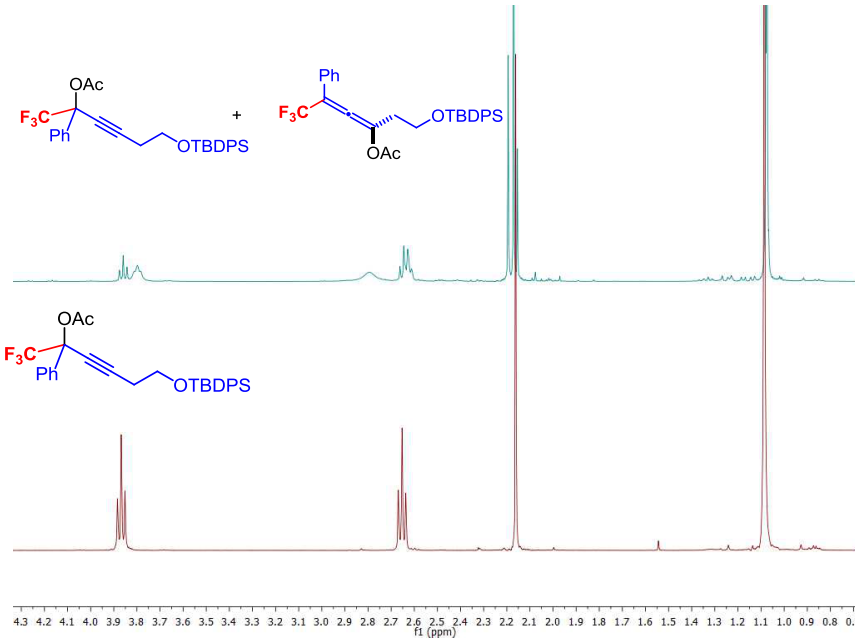


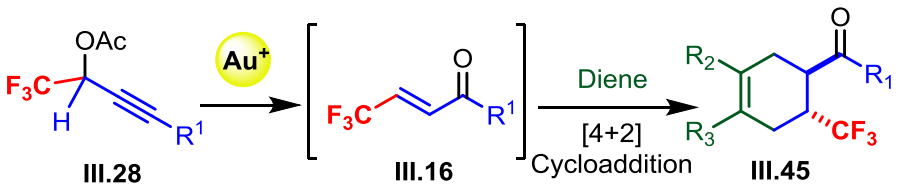
Figure III-1. ^{1}H NMR spectra of the transformation of substrate **III.28q** ($CDCl_3$, 400 MHz; above: crude mixture; below: reference).

With these pieces of information brought together, we are confident about the nature of this generated product. Further work on the reactivity of the tertiary substrates is still in progress.

III.7. Application to One-Pot Rearrangement/Diels-Alder Sequences

After exploiting the [3,3]-acetate rearrangement in the synthesis of CF_3-enones, we were wondering whether this transformation could be involved in one-pot processes by transforming the generated enone. Compared to the other methods used to generate CF_3-enones, this process is relatively mild and only releases not very reactive by-products (acetic acid). With this idea in mind, we wanted to perform a Diels-Alder reaction at the end of the se-

quence in order to incorporate the trifluoromethyl intermediate in the formation of a cycloadduct (Scheme III-91).[101]

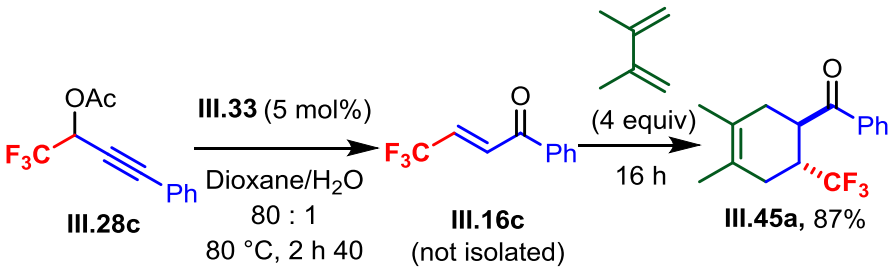


Scheme III-91. Idea of the one pot rearrangement/Diels-Alder process

Performing both reactions in a one-pot fashion led us to slightly modify the reaction conditions:

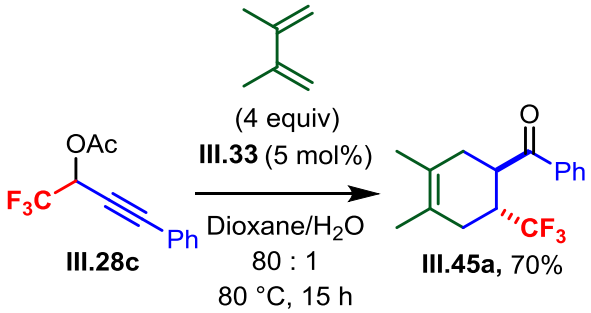
- Dioxane was used instead of acetone, in order to be able to heat the reaction mixture up to 80 °C without reaching the boiling point of the solvent, as this temperature was used in the literature to promote the [4+2] cycloaddition.[101]
- 5 mol% catalyst were used. As we were not studying anymore the gold-catalyzed rearrangement but the subsequent reaction, this increase in catalyst loading was applied to make sure that all the starting material was consumed efficiently.

In first instance, we decided to run the gold-catalyzed rearrangement for a few hours at 80 °C, followed by the addition of 4 equivalents of 2,3-dimethylbutadiene to the reaction mixture (Scheme III-92). To our delight, the cycloadduct **III.45a** could be isolated in 87% yield.



Scheme III-92. First test of the one-pot sequence: delayed addition of the diene

Then, the same reaction was run with the introduction of all reagents from the initial reaction start. With the 4 equivalents of diene added at the beginning of the transformation, the Diels-Alder adduct could still be obtained in 70% yield (Scheme III-93).

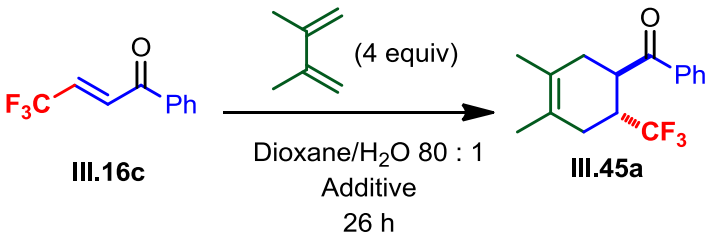


Scheme III-93. One-pot sequence with the simultaneous addition of all substrates

In both cases, characteristic peaks of saturated hydrocarbons were observed by ^{1}H NMR spectroscopy. This made us suspect some oligomerization of the diene under the reaction conditions. Besides, we were wondering whether the Lewis acidity of the gold complex was playing a role in the activation of the dienophile in the Diels-Alder reaction. To obtain some clues about these questions, we ran three test reactions directly on enone **III.16c** (Scheme III-94). The simple mixing of the enone and the diene under the reaction conditions led to the very selective formation of cycloadduct **III.45a**. The addition of one equivalent of acetic acid did not affect the reaction and the

product was obtained with full conversion of the diene. Finally, when the gold catalyst was added, the result was similar to that obtained with the one-pot procedure. These tests led to two conclusions:

- The gold complex is not enhancing the reactivity of the dienophile.
- The degradation of the diene is due to the gold complex, presumably via a cationic mechanism.



Additive	Conversion (^{1}H NMR)
/	Complete
AcOH (1 eq)	Complete
IPrAuNTf$_2$ (5 mol%)	Complete + saturated hydrocarbons

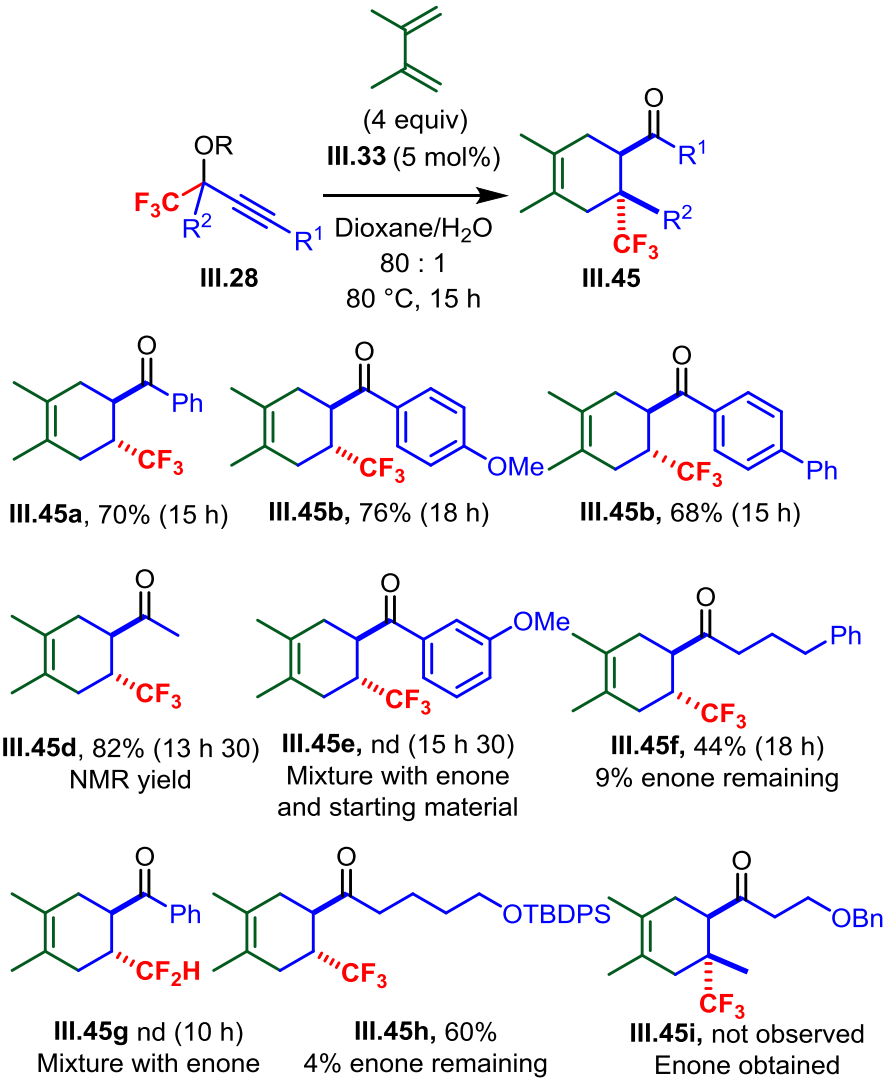
Scheme III-94. Investigations on the degradation of the diene

With these pieces of information, we decided to test this transformation on a few other enones with 2,3-dimethylbutadiene as the Diels-Alder partner (Scheme III-95). Cycloadducts **III.45a-c** bearing an aromatic ring were obtained in good yields.

Benzoate **III.42p** was used to prepare the cyclohexenyl moiety **III.45d** in 82% NMR yield. In this case, the gold-catalyzed rearrangement was particularly useful to generate in situ the volatile CF_3-enone which would be difficult to isolate. The one-pot sequence allowed the direct synthesis of the cycloadduct without the isolation of the reaction intermediate.

Using substrate **III.28k** which possesses a methoxy group at the *meta* position of the aromatic ring led to a mixture of enone **III.16k** and the desired cycloadduct **III.45e**. The same issue was observed for the cycloadduct

III.45f. In this case, a purification was attempted and the product could be isolated in 44% yield along with 9% of enone. The same problem was encountered with products **III.45g** and **III.45h**. For the latter, the purification

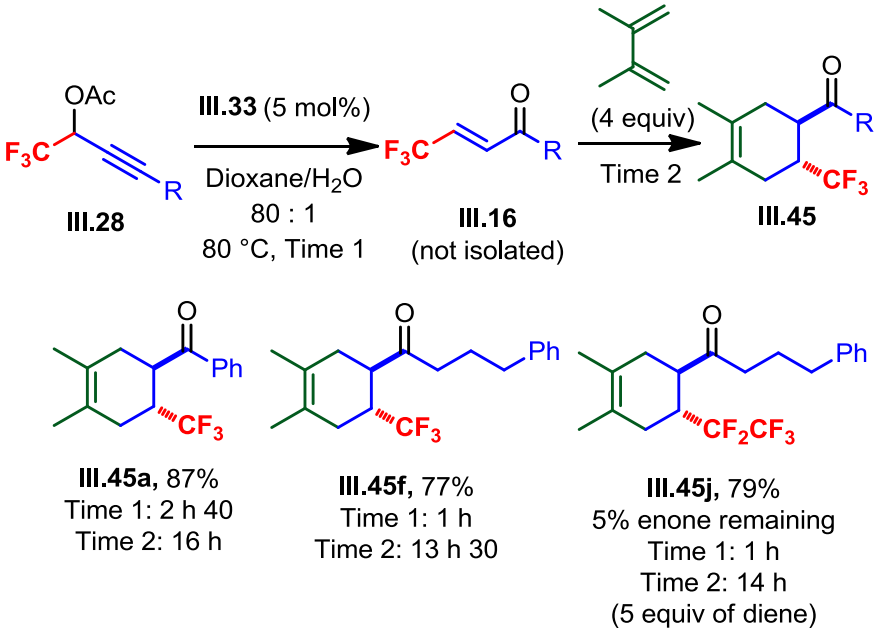


Scheme III-95. Scope for the one-pot gold-catalyzed rearrangement/Diels-Alder reaction

afforded 60% of compound **III.45h** with 4% of the enone.

Finally, the Diels-Alder reaction did not proceed with a tertiary enone and only the corresponding enone was recovered.

For some of these reactions, during which a partial conversion was observed, a sequential protocol was adopted (Scheme III-96). Under these conditions, the Diels-Alder adducts **III.45a,f,j** were isolated in good yields.



Scheme III-96. Preparation of CF_3-cycloadducts via a sequential protocol

Then, other dienes were tested in this procedure to generate cyclohexene moieties with a different carbon skeleton (Scheme III-97).

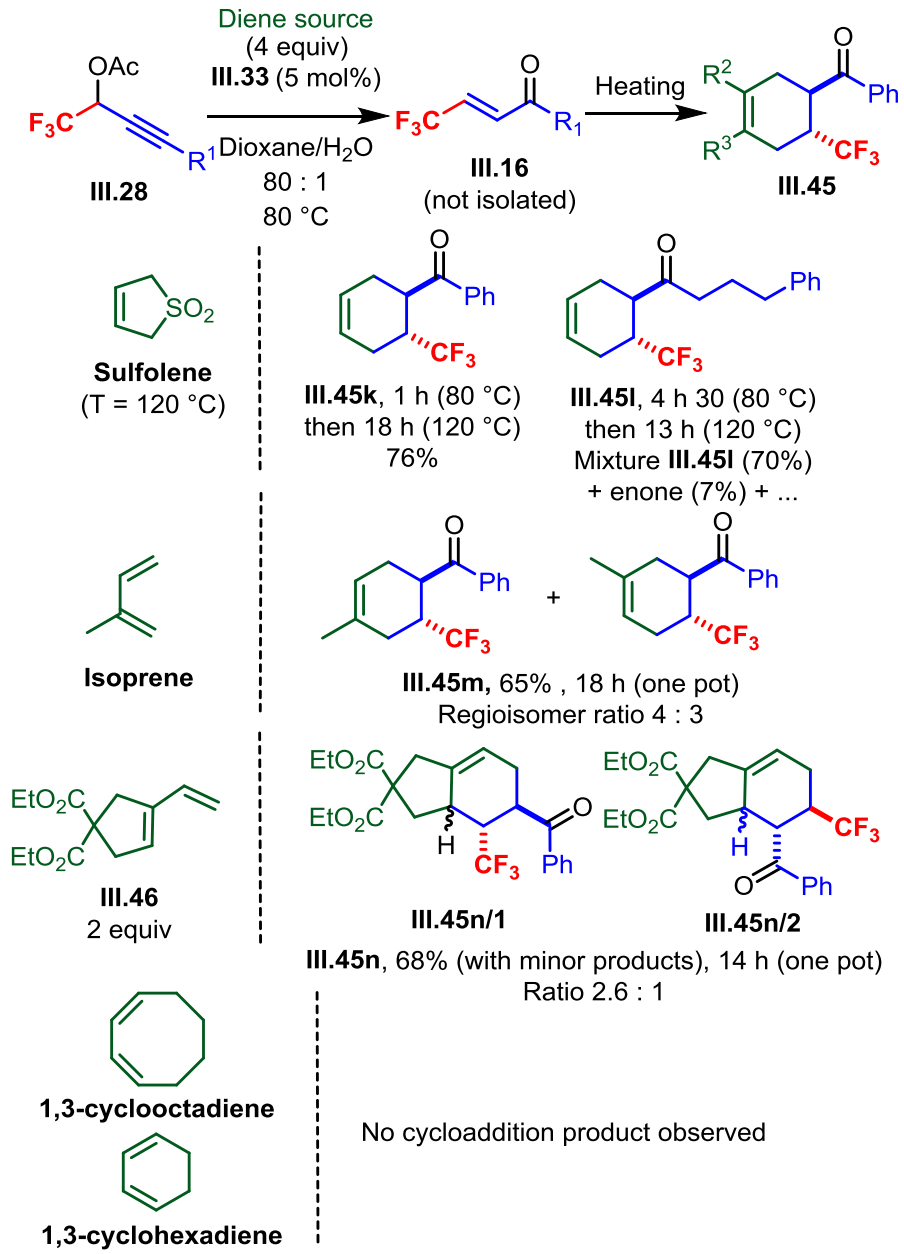
Sulfolene is a stable solid reagent that generates under heating butadiene and sulfur dioxide via a cycloreversion. This compound allows an easy release of the diene and has been considered in our transformation. Propargyl acetate **III.28c**, the gold catalyst and sulfolene were mixed together at 80 °C in order to promote the gold-catalyzed rearrangement. Then the mixture was heated to 120 °C to promote the release of butadiene, and so initiate the

Diels-Alder cycloaddition. Cycloadduct **III.45k** was obtained in 76% yield following this procedure. Unfortunately, cycloadduct **III.45l** was obtained in mixture with several minor compounds, including the corresponding CF_3-enone.

The use of isoprene led to the formation of two regioisomers of **III.45m** in similar ratios. Diene **III.46**, prepared via a gold-catalyzed enyne cycloisomerization,[136] was engaged into this transformation. As it might be expected, several regioisomers were formed. A global isolated yield of 68% was determined, assuming that all the minor products were also isomers. The two major isomers were formed in a 2.6 : 1 ratio. Unfortunately, attempts to generate in situ both partners for the Diels-Alder reaction did not lead to any satisfactory result.

Finally, using 1,3-cyclooctadiene or 1,3-cyclohexadiene in the Diels-Alder reaction did not lead to any conversion into the cycloadduct.

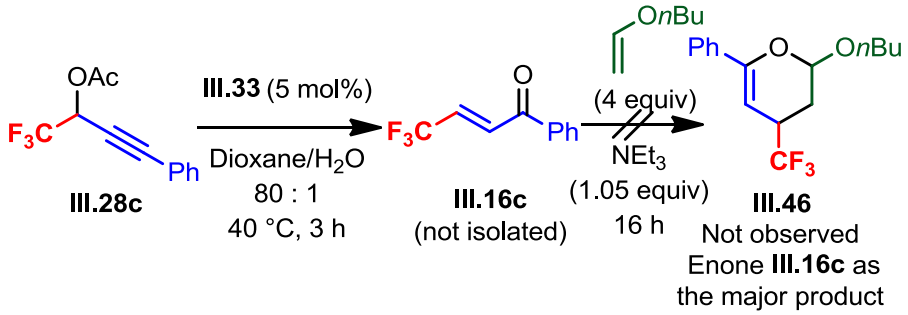
[136] For a procedure to prepare this diene, see: « Développement de nouveaux complexes d'or et leur application en catalyse homogène » by P. Faudot dit Bel (2015, supervisor: F. Gagosz).



Scheme III-97. Preparation of the CF_3-cycloadducts with several dienes

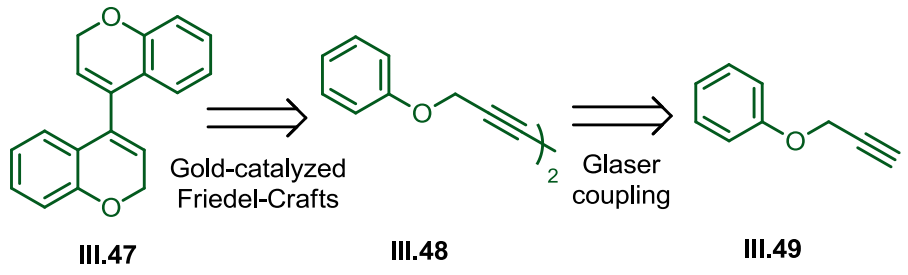
Less fruitful results were obtained in a reverse electron demand Diels-Alder reaction. We were wondering if the trifluoromethylated enone could be used

a diene for a Diels-Alder reaction in the presence of an electron-rich dienophile (Scheme III-98). When an enol ether was introduced in the reaction medium, only its presumable decomposition happened, as the enone was recovered at the end of the process.



Scheme III-98. Reaction of the CF_3-enone as a diene in the Diels-Alder reaction

Diene **III.47** was also envisaged as a coupling partner for a Diels-Alder reaction (Scheme III-99). To prepare it, a simple retrosynthesis was proposed. The two bicyclic moieties could be formed via a gold-catalyzed cyclization from the symmetrical diyne **III.48**. This intermediate directly comes from the corresponding alkyne **III.49** using a Glaser coupling.[137]

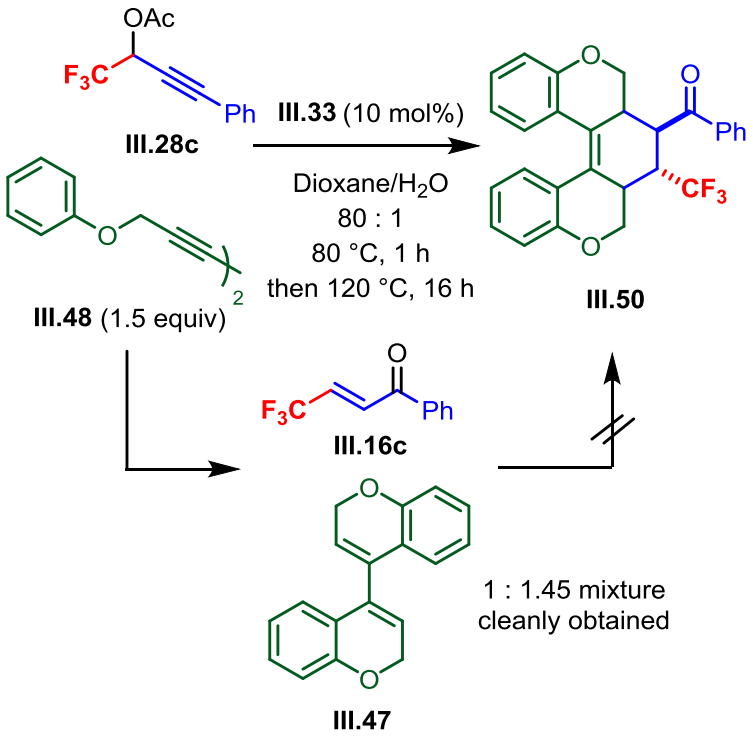


Scheme III-99. Retrosynthesis of the diene **III.47**

After checking that the double cyclization could be carried out using our catalytic system, we envisioned to introduce both precursors in the same reaction to generate the corresponding Diels-Alder partners in situ (Scheme

[137] J. Mo, D. Eom, E. Lee, P. H. Lee, *Org. Lett.* **2012**, *14*, 3684-3687.

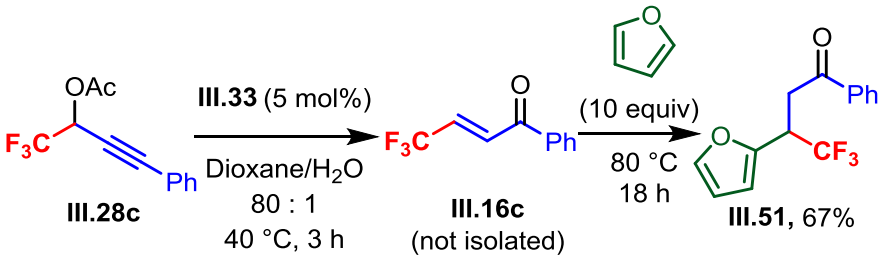
III-100). The reaction mixture was heated to 80 °C for one hour and then to 120 °C overnight. We obtained a clean mixture of CF_3-enone **III.16c** with the cyclic compounds, showing that both generation methods were compatible with each other, but the final Diels-Alder reaction might be too difficult to perform due to the non-planarity of the diene and its preferential transoid conformation.



Scheme III-100. Generation of both Diels-Alder partners in situ

Finally, a Diels-Alder reaction with furan as the diene was attempted (Scheme III-101). Instead of the cycloadduct, the Michael addition product

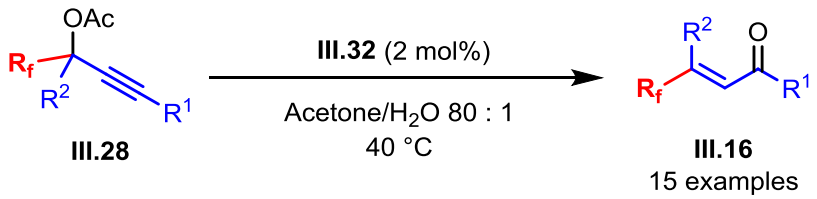
was obtained in 67% yield. This transformation has actually been reported and is known to proceed in a 1,4-addition manner.[138]



Scheme III-101. Attempt for the Diels-Alder reaction between **III.16c** and furan

III.8. Conclusions and Perspectives

During this project, we were able to extend the gold-catalyzed [3,3]-acetate rearrangement to the synthesis of fluorinated analogs. This method was applied successfully on 15 examples (Scheme III-102). Further investigations for the preparation of tertiary substrates are ongoing.



Scheme III-102. Synthesis of CF_3-enones from the corresponding propargyl acetates

The involvement of this transformation in a one-pot process with a Diels-Alder reaction was also developed (Scheme III-103). This method was applied on 10 examples, using several enone precursors as well a several dienes.

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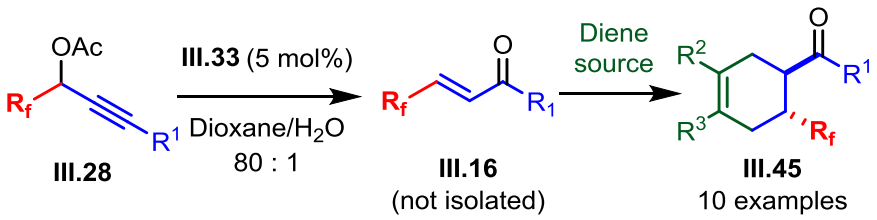
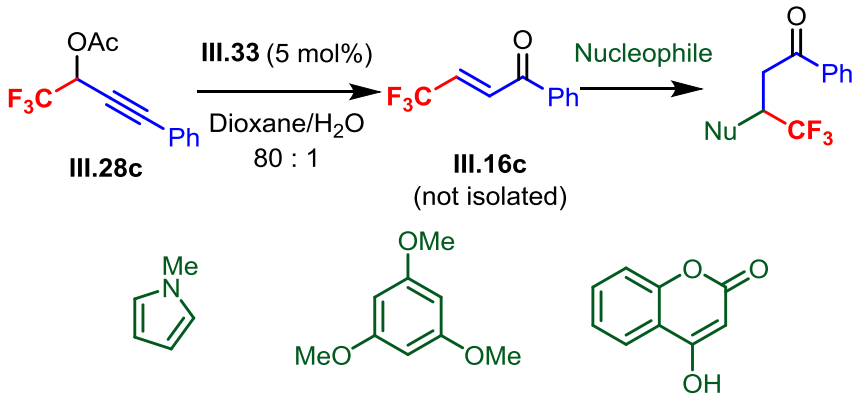
[138] J. Leuger, G. Blond, T. Billard, G. Haufe, B. R. Langlois, *J. Fluorine Chem.* **2011**, *132*, 799-803.



Scheme III-103. One-pot sequence for the syntehsis of CF_3-Diels-Alder cycloadducts

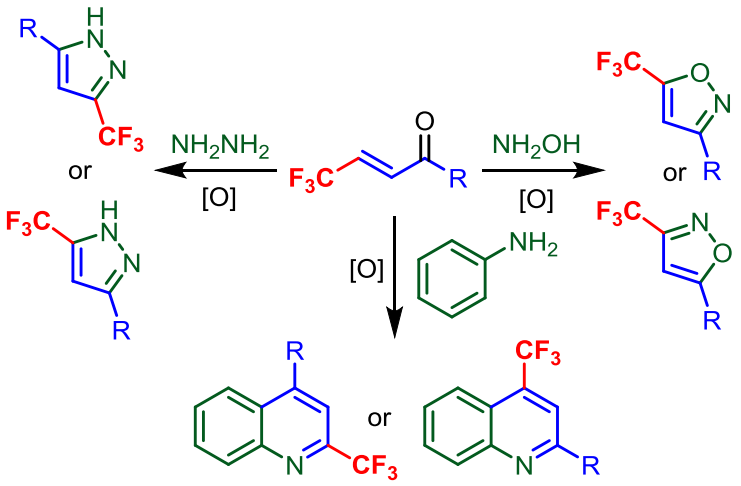
The one-pot rearrangement/1,4-addition transformation was also observed when a furan ring was used as a reacting partner. Extension to the use of other electron-rich (hetero)aromatic compounds could be envisaged to check whether furan constitutes a particular case or if it is generally applicable to other nucleophiles (Scheme III-104).



Scheme III-104. Possibility to investigate the 1,4-addition of heterocycles

Finally, a more applicable perspective would consist in using the CF_3-enones as building blocks for the elaboration of heterocycles, which are interesting moieties in the field of medicinal chemistry (Scheme III-105). The condensation of an enone with a hydrazine/hydroxylamine derivative in oxidizing conditions would furnish the corresponding pyrazole/oxazole. However, the preparation of CF_3-pyrazoles and CF_3-oxazoles directly from CF_3-ketones

has been reported, which lowers the interest of such a method.[139] The synthesis of CF_3-quinolines using a modified Skraup reaction would remain interesting in this context.



Scheme III-105. Synthesis of CF_3-heterocycles from the corresponding CF_3-enone

[139] R. J. Linderman, K. S. Kirollos, *Tetrahedron Lett.* **1989**, *30*, 2049-2052.

Chapter IV: Copper-Catalyzed Borofunctionalization of Allenes

The work described in this chapter has been made in collaboration with Dr. Kiran Indukuri (post-doc researcher in the laboratory of Prof. Riant, UCL).

I. Introduction: Copper(I)-Catalyzed BorylCupration of Unactivated Carbon-Carbon Bonds

Copper-catalyzed functionalization of unsaturations has followed the developments of organocuprates in the last decades. Although the development of copper-mediated borylations remains recent compared to the related silylations or reductions, this topic has gained an increasing interest during the last years.[140] This section will describe the recent developments in the field of borocupration. Mechanistic investigations will be presented and representative examples involving alkenes, alkynes, enynes and 1,3-dienes given.

I.1. Mechanistic aspects: stoichiometric borocupration

The first investigations on borocupration reactions were made in 2000 on enones, terminal alkynes and allylic chlorides independentely by the group of Ito and Hosomi[141] and by the group of Miyaura.[142]

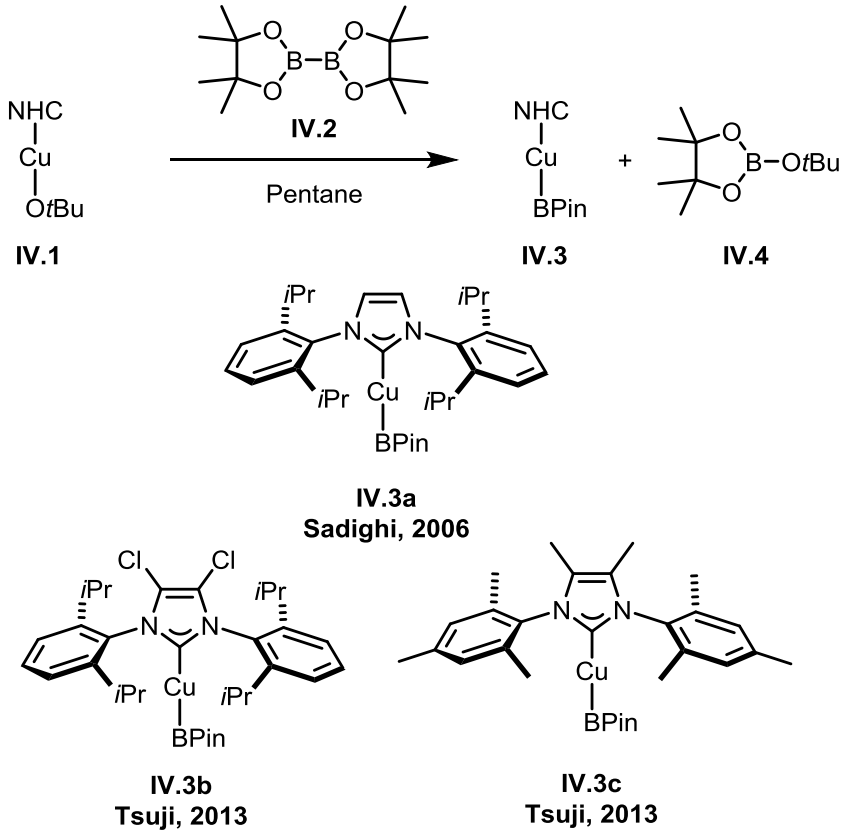
This work led to the determination of the elementary steps of the reaction mechanism. Several groups studied the stoichiometric generation of copper-boron species stabilized by NHC ligands (Scheme IV-1). The σ-metathesis

[140] For recent reviews, see: (a) K. Semba, T. Fujihara, J. Terao, Y. Tsuji, *Tetrahedron* **2015**, *71*, 2183-2197; (b) H. Yoshida, *ACS Catal.* **2016**, *6*, 1799-1811; (c) H. Yoshida, *Chem. Rec.* **2016**, *16*, 419-434.

[141] H. Ito, H. Yamanaka, J.-i. Tateiwa, A. Hosomi, *Tetrahedron Lett.* **2000**, *41*, 6821-6825.

[142] (a) K. Takahashi, T. Ishiyama, N. Miyaura, *Chem. Lett.* **2000**, *29*, 982-983; (b) K. Takahashi, T. Ishiyama, N. Miyaura, *J. Organomet. Chem.* **2001**, *625*, 47-53.

between the *tert*-butoxide precursor **IV.1** and B_2Pin_2 **IV.2** can be employed for the preparation of NHC-Cu-Bpin complexes **IV.3** which can be characterized. Three examples are presented below: the IPr derivative **IV.3a** was reported by Sadighi and co-workers[143] while the complexes **IV.3b** and **IV.3c** were described by the group of Tsuji.[144]



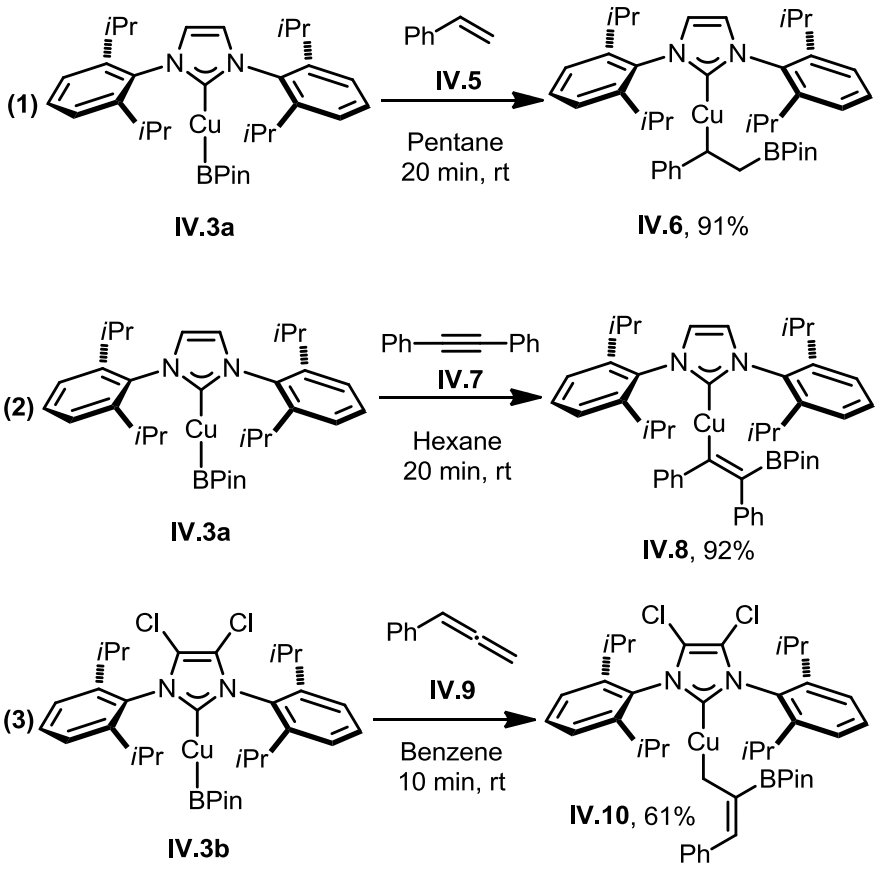
Scheme IV-1. Preparation of Cu-B species stabilized by NHC ligands

The isolation of these complexes allowed the study of the borocupration step in the presence of several carbon-carbon unsaturations (Scheme IV-2). The

[143] D. S. Laitar, P. Müller, J. P. Sadighi, *J. Am. Chem. Soc.* **2005**, *127*, 17196-17197.

[144] K. Semba, M. Shinomiya, T. Fujihara, J. Terao, Y. Tsuji, *Chem. - Eur. J.* **2013**, *19*, 7125-7132.

stoichiometric addition of nucleophilic boron species could be carried out on an alkene (eq 1), an alkyne (eq 2) or an allene (eq 3) to generate respectively alkyl-,[145] vinyl-[146] and allylcopper[144] intermediates.



Scheme IV-2. Examples of the stoichiometric borocupration of unsaturated carbon-carbon bonds

To achieve a catalytic double functionalization of the substrate, the organo-copper species must then be quenched by an electrophilic source. Protons

[145] D. S. Laitar, E. Y. Tsui, J. P. Sadighi, *Organometallics* **2006**, *25*, 2405-2408.

[146] L. Zhang, J. Cheng, B. Carry, Z. Hou, *J. Am. Chem. Soc.* **2012**, *134*, 14314-14317.

from water or alcohols remain the most simple reagents to perform this step, even if various other electrophiles have also been tested. Selected examples of various trapping agents will be presented in the following sections.

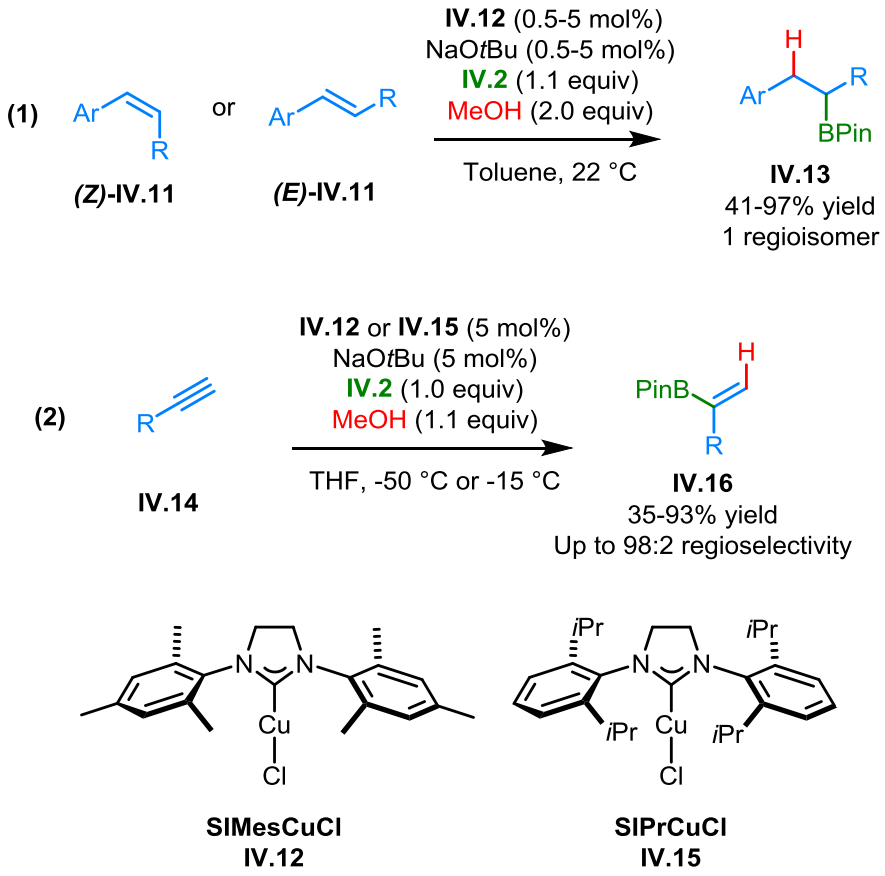
I.2. Alkenes and alkynes in catalytic borocupration

Due to their ease of access, alkenes and alkynes were naturally the first substrates on which catalytic borocupration methods were developed (Scheme IV-3).

By using B_2Pin_2 in the presence of a proton source and a copper catalyst, efficient hydroboration systems were elaborated. The first catalytic hydroboration of alkenes was reported in 2009 by the group of Hoveyda (Scheme IV-3, eq 1)[147] and the first analogous transformation on alkynes was described by the same group in 2011 (Scheme IV-3, eq 2).[148]

[147] Y. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 3160-3161.

[148] H. Jang, A. R. Zhugralin, Y. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2011**, *133*, 7859-7871.

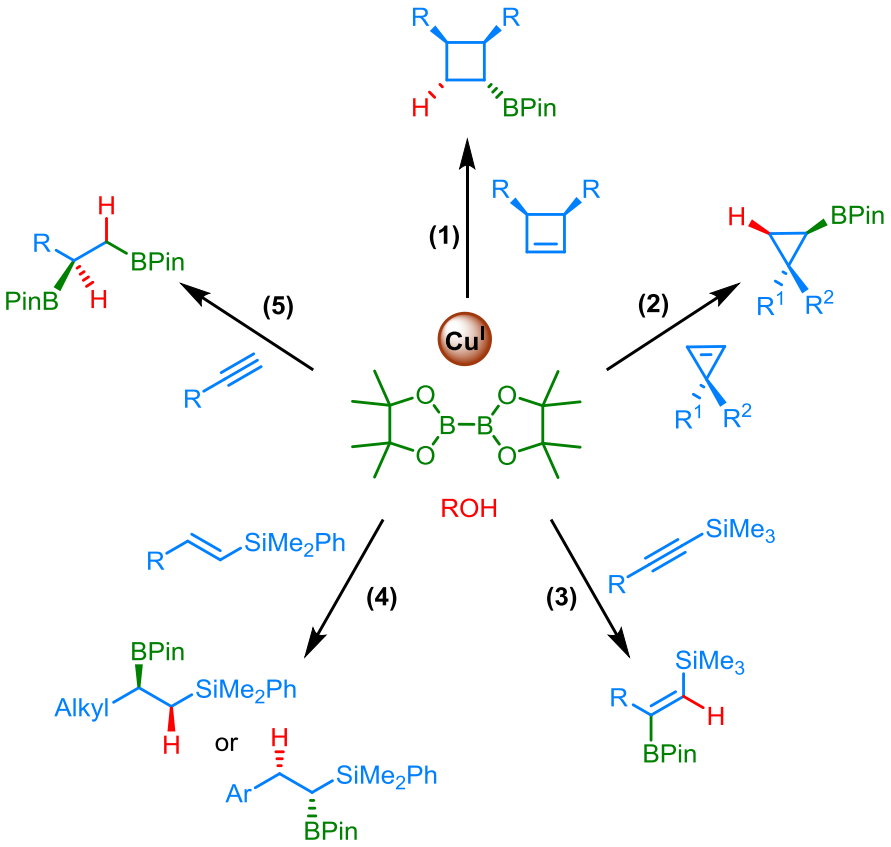


Scheme IV-3. Copper-catalyzed hydroboration of alkenes and alkynes

Since the publication of these first reports, the method has been exploited on several families of alkenes and alkynes possessing various substituents. Selected original examples are presented in Scheme IV-4. The group of Tortosa applied the hydroboration of alkenes to unsaturated small rings such as cyclobutenes (eq 1)[39c] and cyclopropenes (eq 2).[149] In both cases, the use of chiral ligands on copper allowed the desymmetrization of the meso or prochiral cycle. The hydroboration of alkynylsilanes was developed by the

[149] A. Parra, L. Amenós, M. Guisán-Ceinos, A. López, J. L. García Ruano, M. Tortosa, *J. Am. Chem. Soc.* **2014**, *136*, 15833-15836.

group of Lee and Yun in 2014 (eq 3).[150] Vinylsilane and –borane moieties were easily obtained by this method in a very regioselective manner.



Scheme IV-4. Copper-catalyzed hydroboration of various alkenes and alkynes

An analogous transformation was applied to vinylsilanes to stereoselectively generate compounds containing both an alkylborane and an alkylsilane moieties (eq 4).[151] Depending on the nature of the substituent on the vinylsilane (aromatic or aliphatic), a reversed regioselectiviy was observed on

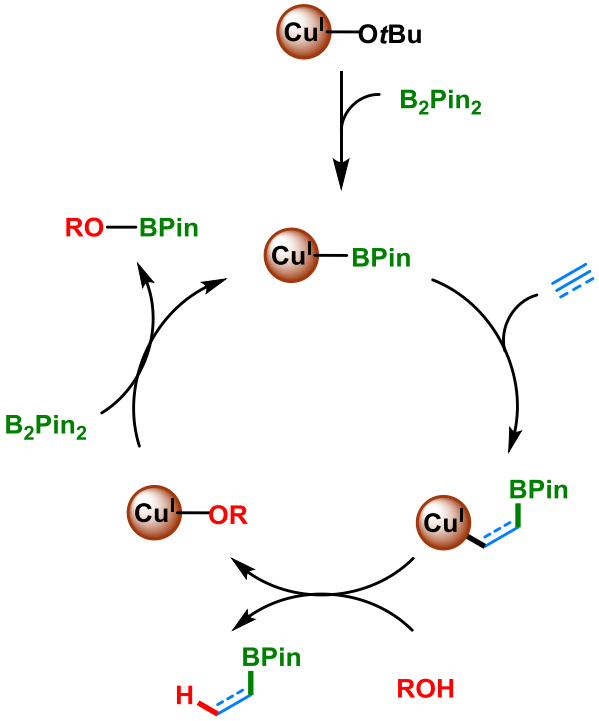
[150] Y. M. Chae, J. S. Bae, J. H. Moon, J. Y. Lee, J. Yun, *Adv. Synth. Catal.* **2014**, *356*, 843-849.

[151] F. Meng, H. Jang, A. H. Hoveyda, *Chem. - Eur. J.* **2013**, *19*, 3204-3214.

the final product. Last but not least, the double hydroboration of alkynes in the presence of a chiral ligand was applied to the generation of 1,2-diborylated products as presented in equation 5.[152]

For all these transformations, a common mechanism has been proposed as depicted in Scheme IV-5. Starting from an active precatalyst, such as a copper *tert*-butoxide complex, a σ-metathesis with B_2Pin_2 generates a copper-boron species. The *syn*-borocupration of the unsaturation carbon-carbon bond generates an organocopper intermediate (alkyl- or vinylcopper), which can then react with a proton source. This last step delivers the hydroboration product and regenerates the copper alkoxide which is able to reinitiate the catalytic cycle.

[152] Y. Lee, H. Jang, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 18234-18235.



Scheme IV-5. General mechanism for the copper-catalyzed hydroboration of alkenes and alkynes

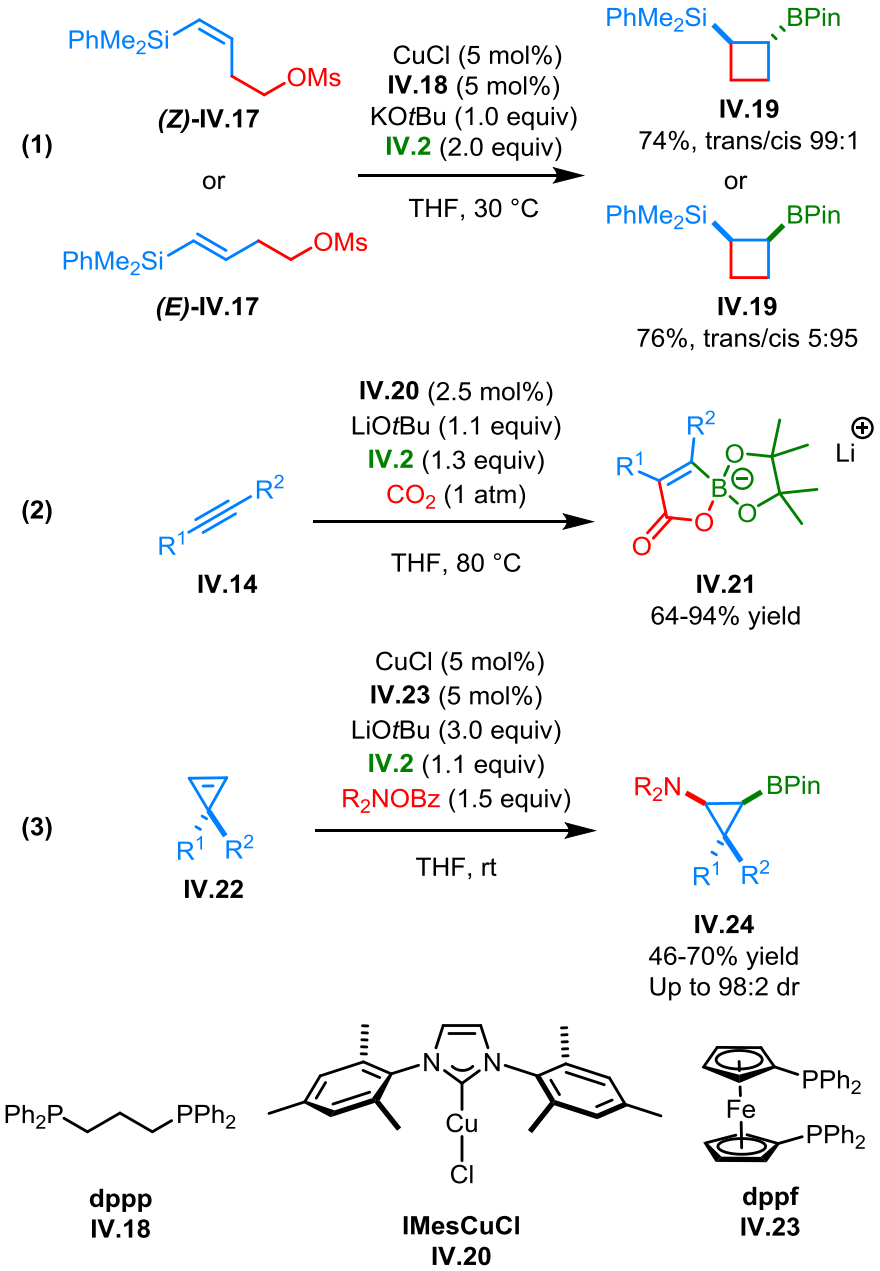
Although the first examples of borocupration strategies employed proton sources as electrophilic reagents, more recent developments involved the use of other electrophiles in order to perform the difunctionalization of the unsaturations. Various electrophiles have been tested, and several articles discuss the last contributions in this area.[140] Three selected examples are presented in Scheme IV-6.

The use of alkyl electrophiles allows the straightforward formation of a C-C(sp^3) bond. The group of Ito and Sawamura applied this new transformation in an intramolecular fashion to prepare boron- and silicon-substituted cyclobutanes (Scheme IV-6, eq 1).[153] The regioselective borocupration of a

[153] H. Ito, T. Toyoda, M. Sawamura, *J. Am. Chem. Soc.* **2010**, *132*, 5990-5992.

vinylsilane followed by the attack on the electrophilic sp^3 carbon led to the formation of the cyclobutane skeleton. The stereospecificity of this transformation has been demonstrated by the conversion of the *(E)* and *(Z)* vinylsilanes into the *syn*- and *anti*-cyclobutanes, respectively.

Carbon dioxide has also been demonstrated to be a useful electrophile allowing the facile introduction of carboxylic acid moieties (Scheme IV-6, eq 2).[146] In the case of alkynes, the copper-catalyzed borocarboxylation led to the formation of spirocyclic compounds isolated as lithium salts. *O*-benzyl-substituted amines have also be used as efficient electrophiles to trap organocopper species by the group of Tortosa (Scheme IV-6, eq 3).[149] In line with the enantioselective hydroboration they described, they were able to react the cyclopropylcopper intermediate with an electrophilic nitrogen moiety. This led to the formation of boron- and amino-substituted cyclopropanes with a good *syn* diastereoselectivity.



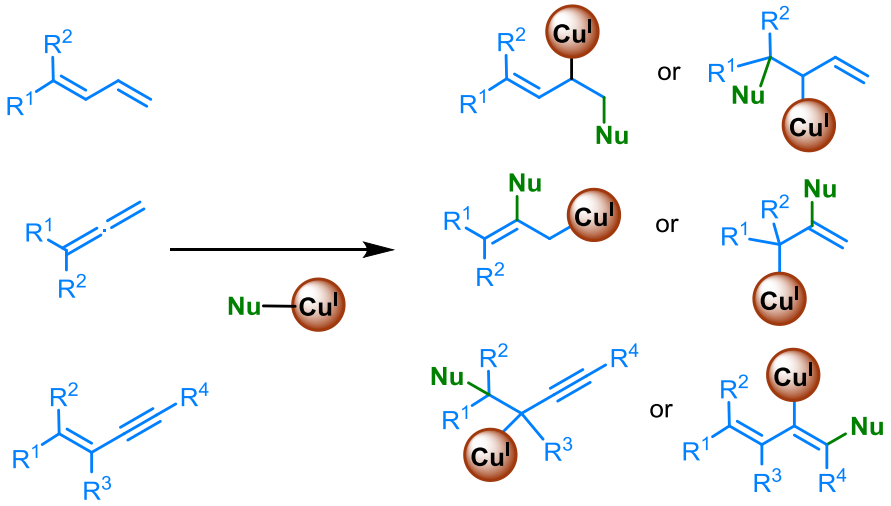
Scheme IV-6. Copper-catalyzed borofunctionalization of alkenes and alkynes

II. Copper-Catalyzed Functionalization of Allenes in the Literature

Beside alkenes and alkynes that have been the subject of intensive research for decades, other carbon-carbon bond unsaturations such as allenes, 1,3-dienes[154] and enynes[155] have been the subject of recent research interests. These functional groups are sharing a common feature: the potential generation of allylcopper or propargylcopper intermediates by addition of an organocopper nucleophile (Scheme IV-7). For a long period of time, these transformations hadn't been envisaged due to potential regio- and stereoselectivity issues that they could create. However, once these being fixed, a reaction involving one of these moieties possesses a high potential for the synthesis of complex carbon skeletons.

[154] For a review, see ref.140a. For selected examples, see: (a) Y. Sasaki, C. Zhong, M. Sawamura, H. Ito, *J. Am. Chem. Soc.* **2010**, *132*, 1226-1227; (b) ref. 144.

[155] (a) Y. Sasaki, Y. Horita, C. Zhong, M. Sawamura, H. Ito, *Angew. Chem. Int. Ed.* **2011**, *50*, 2778-2782; (b) Y. Yang, I. B. Perry, G. Lu, P. Liu, S. L. Buchwald, *Science* **2016**, 353, 144-150.



Scheme IV-7. Allylcopper species generation by the cupration of 1,3-dienes or allenes

In the context of this project, we wanted to focus on the copper-catalyzed and regioselective borofunctionalization of allenes. The next paragraph aims to describe the existing literature reports when the project was initiated on the copper-mediated addition of nucleophiles onto allenes, with a special emphasis on the boryl-, silyl- and hydrocupration processes.[156] The scope of electrophiles, as well as mechanistic considerations will be presented.

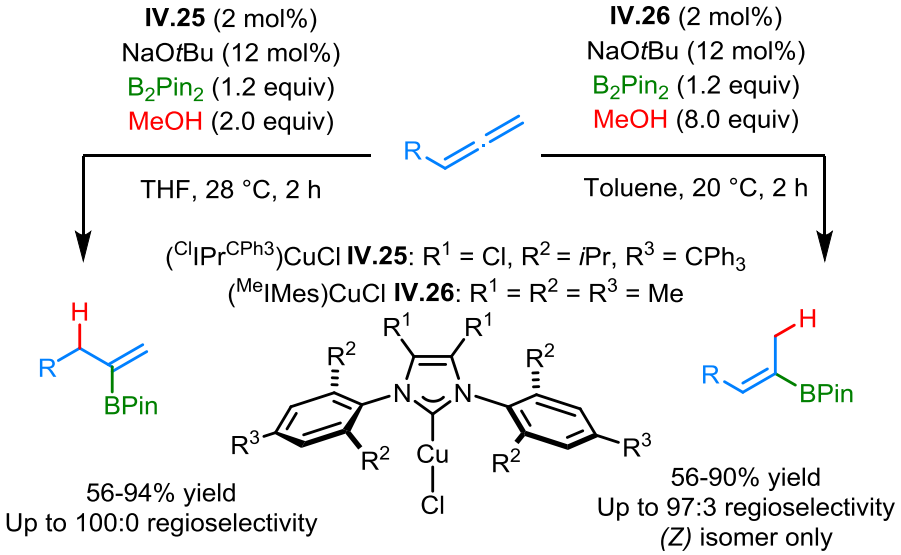
II.1. Borocupration of Allenes

The first example of copper-catalyzed hydroboration of activated allenes using B_2Pin_2 as the boron source was reported in 2011 by the group of Santos.[157] Then, several groups went interested in extending such a strategy to unactivated allenes, with the aim to control the regioselectivity of the trans-

[156] For a recent review on the enantioselective copper-catalyzed functionalization of allenes, see: A. P. Pulis, C. Yeung, D. J. Procter, *Chem. Sci.* **2017**, 8, 5240-5247.

[157] S. B. Thorpe, X. Guo, W. L. Santos, *Chem. Commun.* **2011**, *47*, 424-426.

formation. The groups of Ma,[91,158] Tsuji[144] and Hoveyda[49] proposed several catalytic systems in order to prepare vinylboron derivatives with controlled regio- and/or stereoselectivities (Scheme IV-8). Hoveyda and co-workers also developed an enantioselective version of this transformation starting from 1,1-disubstituted allenes.[159] It is important to note that in all the cases, this transformation appeared to be perfectly regioselective towards the formation of the vinylboron product *versus* the allylboron one. This suggests that the reaction mechanism involves a selective formation of an allylcopper intermediate.



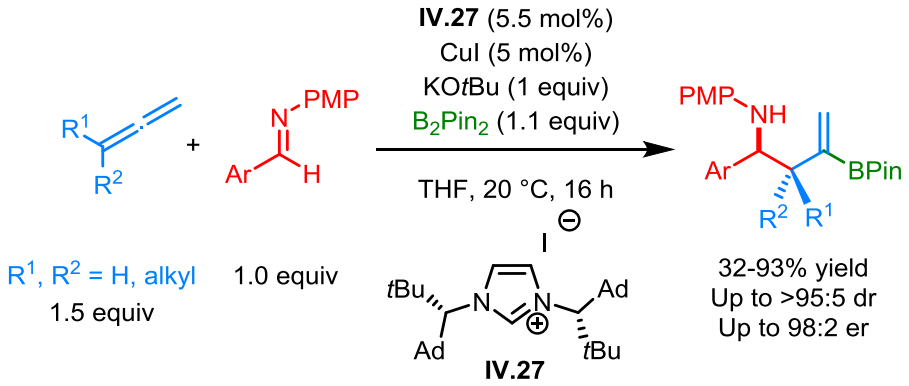
Scheme IV-8. Copper-catalyzed hydroboration of allenes developed by Tsuji

With the aim to develop more sophisticated functionalization tools, several groups started to test other electrophiles than a simple proton. For example, carbonyl derivatives turned out to be efficient reagents in this transformation. Hoveyda and co-workers initiated the work in 2013 using several

[158] W. Yuan, X. Zhang, Y. Yu, S. Ma, *Chem. - Eur. J.* **2013**, *19*, 7193-7202.

[159] H. Jang, B. Jung, A. H. Hoveyda, *Org. Lett.* **2014**, *16*, 4658-4661.

aldehydes and ketones which allowed then to obtain terminal vinylboron compounds with good regio-, diastereo- and enantioselectivities.[160] An analogous transformation employing aldimines was developed by the group of Procter in 2016 (Scheme IV-9).[161] By using the chiral NHC salt **IV.27**, they could carry out an enantioselective three-component coupling of terminal allenes, aromatic aldimines and bispinacolatodiboron.



Scheme IV-9. Copper-catalyzed borofunctionalization of allenes with imines

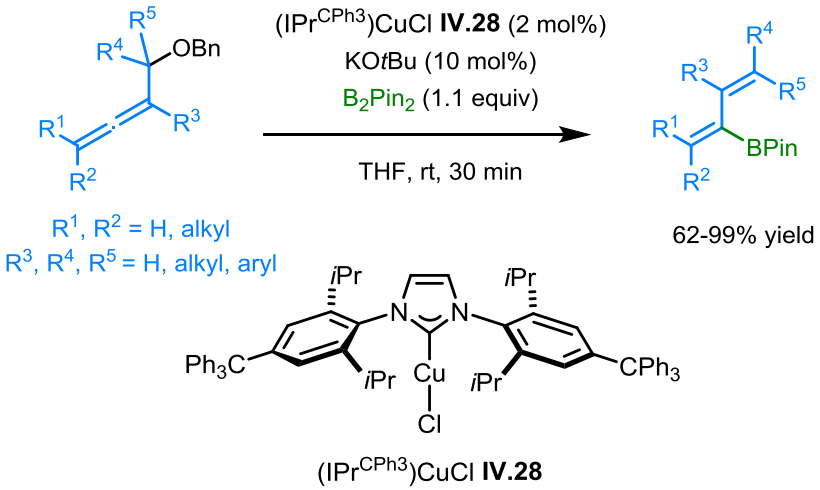
Other variants involving a related mechanistic pathway were reported using similar conditions. An intramolecular version with 1,3-diones as the electrophiles was reported by the group of Tao and Tian in 2016.[162] The borocyanation of allenes was described by Montgomery and co-workers and was

[160] F. Meng, H. Jang, B. Jung, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2013**, *52*, 5046-5051.

[161] (a) J. Rae, K. Yeung, J. J. W. McDouall, D. J. Procter, *Angew. Chem. Int. Ed.* **2016**, *55*, 1102-1107; (b) K. Yeung, R. E. Ruscoe, J. Rae, A. P. Pulis, D. J. Procter, *Angew. Chem. Int. Ed.* **2016**, *55*, 11912-11916.

[162] Y.-S. Zhao, X.-Q. Tang, J.-C. Tao, P. Tian, G.-Q. Lin, *Org. Biomol. Chem.* **2016**, *14*, 4400-4404.

employed in a one-pot sequencial double functionalization of allenes.[163] Hoveyda and co-workers also carried out the regio-, stereo- and enantioselective borocupration/1,6-addition with α,β-γ,δ-diunsaturated malonates as the electrophiles.[164] Finally, the synthesis of 1,3-dienes via borocupration/elimination sequence applied to allenes was reported by the group of Tsuji in 2013 (Scheme IV-10).[165]



Scheme IV-10. Copper-catalyzed boration/elimination of allenes

For all these examples, a general catalytic cycle could be proposed. Literature reports seem to agree on the mechanistic pathway, but some controversial steps can be pointed out. A general mechanism is presented on Scheme IV-11 and the detailed steps are discussed afterwards.

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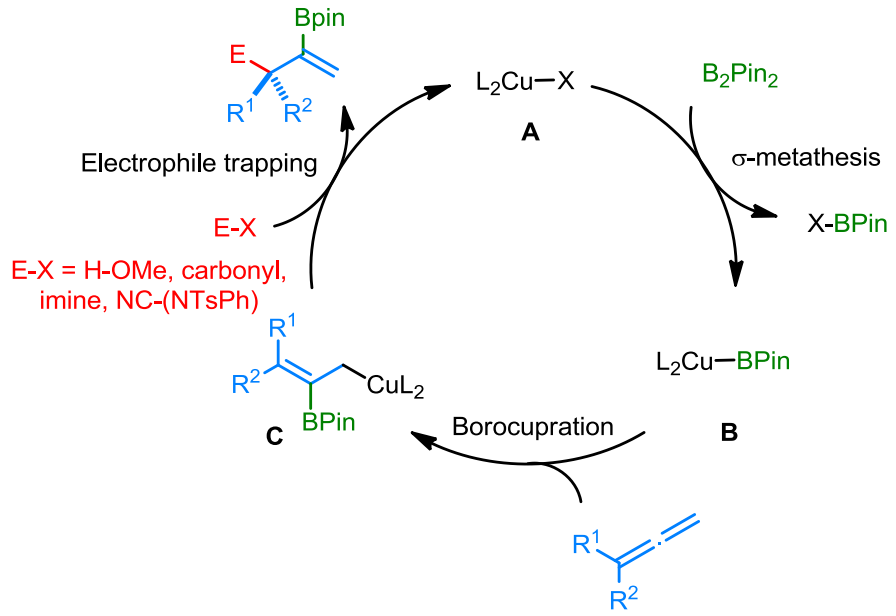
[163] W. Zhao, J. Montgomery, *J. Am. Chem. Soc.* **2016**, *138*, 9763-9766.

[164] F. Meng, X. Li, S. Torker, Y. Shi, X. Shen, A. H. Hoveyda, *Nature* **2016**, *537*, 387-393.

[165] K. Semba, T. Fujihara, J. Terao, Y. Tsuji, *Angew. Chem. Int. Ed.* **2013**, *52*, 12400-12403.

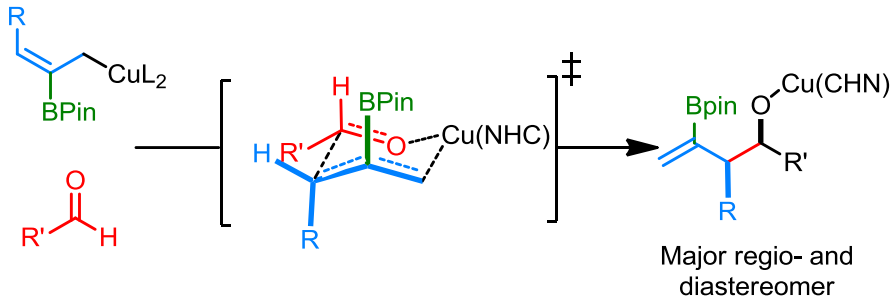
The copper(I) active species **A** is formed from a copper precatalyst and initiates the catalytic cyle by a σ-metathesis with bispinacolatodiboron. This generates an active Cu-B species **B** which is engaged in the 1,2-borocupration of the allene to produce an allylcopper intermediate **C**. The allylcopper **C** is then captured by the electrophile (MeOH, aldehyde, ketone, imine, electrophilic cyano group) to release the borofunctionalized product and regenerate the copper catalyst **A**. While the initial step dealing with the generation of the active Cu-B species remains similar to these described in other copper-catalyzed processes, several mechanistic pathways were envisioned for the rest of the catalytic cycle to explain the regioselectivity observed. When terminal allenes were used, terminal vinylboron compounds were most of the time obtained[158-163] and the mechanism depicted in Scheme IV-11 perfectly explains the regioselectivity.



Scheme IV-11. General mechanism of the copper-catalyzed borofunctionalization of allenes

Both key steps have to happen selectively to allow the formation of a unique regioisomer:

- The addition of the Cu-B species occurs regioselectively on the terminal carbon of the allene to generate the terminal allylcopper species.
- The capture of the electrophile by the allylcopper intermediate happens regiospecifically on the γ-position. Most of the reports involve a Zimmerman-Traxler transition state to explain the diastereoselectivity obtained in several processes (Scheme IV-12).[166]



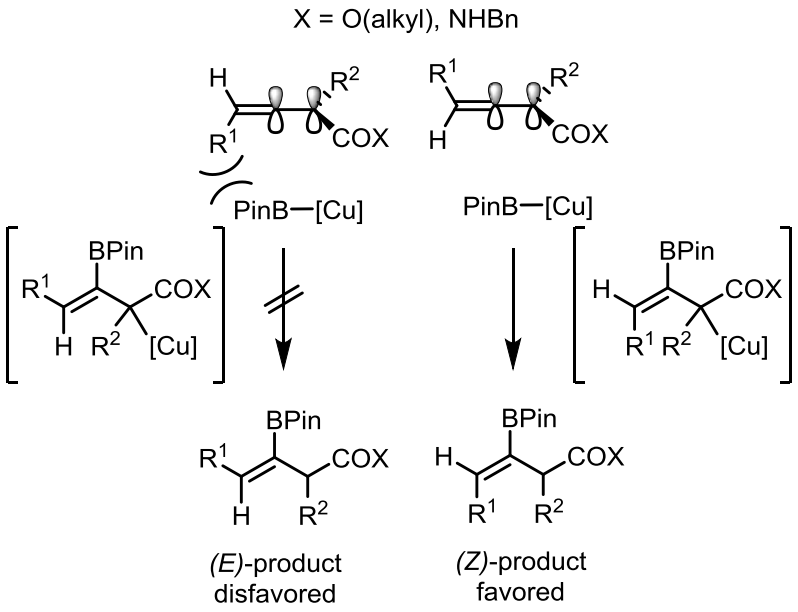
Scheme IV-12. Example of catalytic step involving a Zimmerman-Traxler transition state (from ref. 160)

However, several groups succeeded in reversing the regioselectivity to obtain the internal vinylboron as the major product.

When an allenoate[157] or a 2,3-allenamide[158] was employed, the conjugated addition of the Cu-B species was proposed to be the main borocupration pathway (Scheme IV-13). Beside this particular regioselectivity, the stereoselectivity for the formation of the *(Z)*-product could be explained by the involvement of the steric effects between the conjugated allene and the Cu-B species. In this case, a copper enolate is generated and the exact structure of the organocopper intermediate is particularly complex to determine, due to

[166] H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.* **1957**, *79*, 1920-1923

all the potential copper migrations that can take place.[167] The hydroboration products were in both cases isolated with the indicated regio- and stereoselectivity.



Scheme IV-13. Reversed regioselectivity for the Cu-catalyzed hydroboration of allenoates and allenamides (adapted from ref 157)

On the other side, several groups were able to reverse the regioselectivity by playing on the composition of the catalytic system, in particular on the nature of the ligand (Scheme IV-8). [49,144,158a] They were able to obtain the internal vinylboron compound with a good regioselectivity. In all cases, it was highlighted that a less bulky ligand (phosphine or NHC, depending on the case) was required to furnish the internal double bond product. However, the proposed mechanistic reason is different in the three publications.

[167] A more detailed mechanistic proposal was made in ref 158 based on DFT calculations.

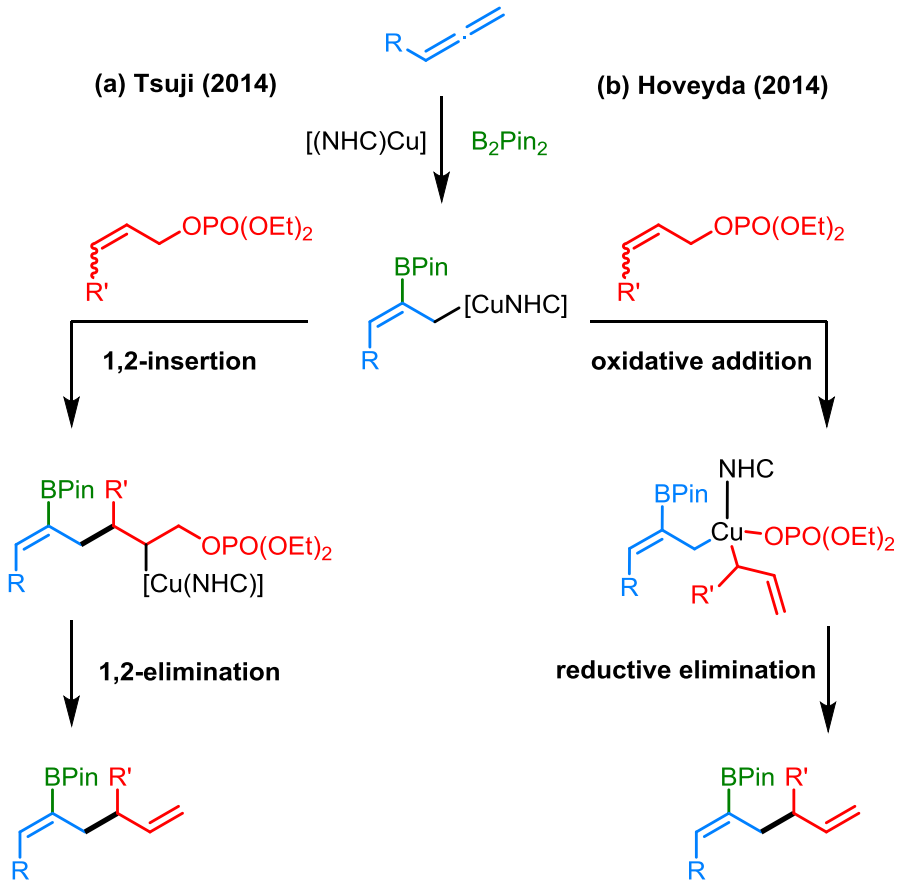
1) Yuan and Ma attributed the change to the different regioselectivity of the Cu-B addition onto the allene.[158a] Larger ligands would favour the attack on the terminal carbon atom of the allene, whereas smaller ligands would lead to the cupration of the internal carbon of the allene. This mechanisitic pathway involves two different allylcopper species, which lead to the two regioisomers by the same regiospecific γ-protonation.
2) Tsuji and co-workers explained the difference by the regioselectivity of the protonation of the allylcopper species.[144] The same terminal allylcopper intermediate would be involved in both cases, and the γ- or the α-protonation directed by the ligand will lead to the terminal or the internal alkene, respectively. This mechanism is supported by the characterization of intermediates such as the copper-boryl complex and the allylcopper species.
3) Finally, Hoveyda and co-workers proposed that an equilibrium between the regioisomers of the allylcopper species exists.[49] Whatever the bulkiness of the ligand, the faster cupration of the terminal carbon of the allene is proposed. Large copper complexes would not be able to undergo the 1,3-migration and would lead to the terminal alkene by γ-protonation of the allylcopper. At the opposite, smaller ligands would favour the isomerization of the allylcopper towards the formation of the internal allylcopper. The same regiospecific γ-protonation pathway would lead to the internal vinylboron product.

Depending on the nature of the electrophile being used, a mechanistic pathway involving the α-functionalization of the allylcopper species can also be proposed. The use of allylic electrophiles such as allyl phosphonates was

also reported concomitantly by the groups of Tsuji[168] and Hoveyda.[169] If both agree on the involvement of an α-functionalization of the allylcopper species, the mechanistics insights turned out to be very different (Scheme IV-14). Tsuji proposed the 1,2-insertion of the allyl phosphonate in the allylcopper intermediate, which would be followed by an elimination step to generate the double bond. In contrast, Hoveyda assumed the implication of a copper(III) intermediate through the oxidative addition of the allylic electrophile. The final product would then be released by a reductive elimination.

[168] K. Semba, N. Bessho, T. Fujihara, J. Terao, Y. Tsuji, *Angew. Chem. Int. Ed.* **2014**, *53*, 9007-9011.

[169] F. Meng, K. P. McGrath, A. H. Hoveyda, *Nature* **2014**, *513*, 367-374.



Scheme IV-14. Copper-catalyzed boroallylation of allenes: mechanistic proposal of (a) Tsuji and (b) Hoveyda

Prior to these reports, a mechanistically similar α-quenching of the allylcopper species with an aryl iodide was described by the group of Brown.[170] Even if the authors did not discuss in details the coupling between the iodide and the nucleophile, a mechanism similar to those proposed by Hoveyda and co-workers on Scheme IV-14 is highly likely, even if a radical-based mechanism can not completely be ruled out. The copper-catalyzed

[170] Y. Zhou, W. You, K. B. Smith, M. K. Brown, *Angew. Chem. Int. Ed.* **2014**, *53*, 3475-3479.

borostannation of allenes reported by Yoshida and co-workers in 2014 is also believed to occur via an α-quenching of the allylcopper intermediate by the stannyl electrophile.[171]

Finally, a reversed regioselective borocupration of 1,1-disubstituted allenylsilanes was reported by the group of Ma in 2016.[172] In this case, the selective formation of the allylboron/*(Z)*-vinylsilane product was observed, suggesting the involvement of a vinylcopper intermediate. Control experiments showed that the unusual regio- and stereoselectivity of this transformation essentially came from the sterics of the starting material.

II.2. Silylcupration of Allenes

Whereas the stoichiometric silylcupration of allenes using silylcopper or silylcuprate species has been the subject of several studies since the 80's,[173] most of the developments made on the corresponding catalytic version were carried out in the past 5 years. Surprisingly, the original report on copper-catalyzed silylfunctionalization of allenes was released in 1984 by Oshima and co-workers (Scheme IV-15).[174] In this case, the authors suggested that the copper allows the regioselective transfer of the silicon group onto the central atom of the allene thus generating an allylmagnesium species. This intermediate was then trapped by an appropriate electrophile, such as a proton, an aldehyde, TMSCl, allyl bromide or methyl iodide. Even if this process involves the stoichiometric generation of an allymagnesium intermedi-

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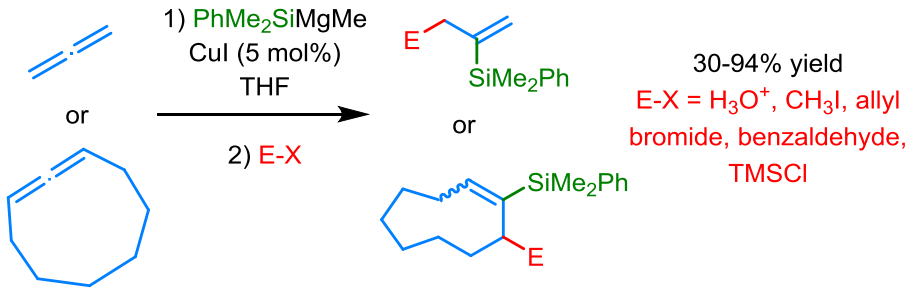
[171] Y. Takemoto, H. Yoshida, K. Takaki, *Synthesis* **2014**, *46*, 3024-3032

[172] W. Yuan, L. Song, S. Ma, *Angew. Chem. Int. Ed.* **2016**, *55*, 3140-3143.

[173] For a review, see: A. Barbero, F. J. Pulido, *Acc. Chem. Res.* **2004**, *37*, 817-825

[174] Y. Morizawa, H. Oda, K. Oshima, H. Nozaki, *Tetrahedron Lett.* **1984**, *25*, 1163-1166.

ate, it remains the first example of an allene silylfunctionalization using a catalytic amount of copper(I).



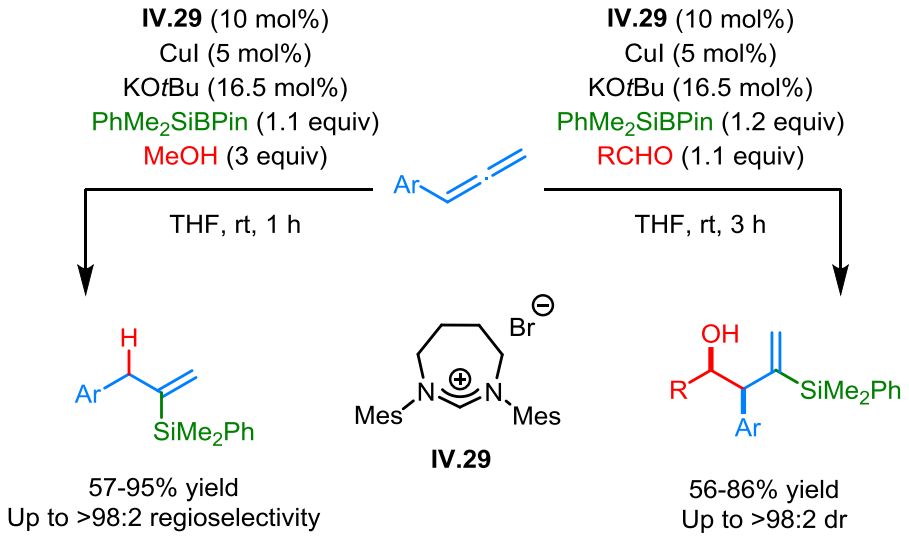
Scheme IV-15. Copper-catalyzed silylmagnesation of allenes

The extension of this strategy to a domino process involving a catalytic amount of an allylcopper intermediate was reported in 2014. This transformation is based on the use of the Suginome's reagent[46] ($PhMe_2SiBPin$) as the silicon source. The group of Xu and Loh reported a synthesis of vinylsilanes involving a copper-catalyzed hydrosilylation of electron-poor allenes.[175] The same year, Procter and co-workers developed a regioselective silylfunctionalization of aromatic allenes using a Cu-NHC complex as the catalyst (Scheme IV-16).[176] In this case, protons and aldehydes were used as the electrophiles to trap the allylcopper intermediate. Another regioselective hydrosilylation of allenoates was reported in 2016 by the group of Santos.[177]

[175] Y.-H. Xu, L.-H. Wu, J. Wang, T.-P. Loh, *Chem. Commun.* **2014**, *50*, 7195-7197

[176] J. Rae, Y. C. Hu, D. J. Procter, *Chem. - Eur. J.* **2014**, *20*, 13143-13145

[177] S. Pashikanti, J. A. Calderone, M. K. Nguyen, C. D. Sibley, W. L. Santos, *Org. Lett.* **2016**, *18*, 2443-2446.



Scheme IV-16. Copper-catalyzed silylfunctionalization of aromatic allenes

A similar transformation with $Et_3SiBPin$ and aldehydes and ketones in the presence of a phosphine ligand was developed by the group of Tsuji and Fujihara in 2015.[178] In this case, the internal vinylsilane was obtained regioselectively.

The quenching of the organocopper intermediate by CO_2 was also carried out by the group of Tsuji and Fujihara in 2014 (Scheme IV-17).[179] Using different copper sources and ligands, they were able to control the selectivity of the addition towards the formation of an allyl- or vinylcopper intermediate. In the case of aliphatic 1,1-disubstituted allenes, they were able to develop a regiodivergent method allowing the obtention of either vinyl- or allylsilanes.

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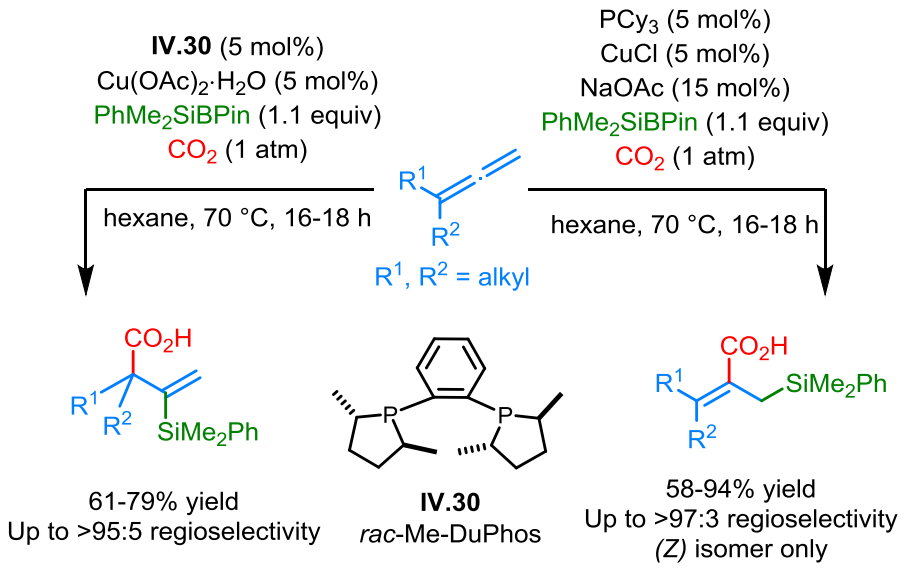
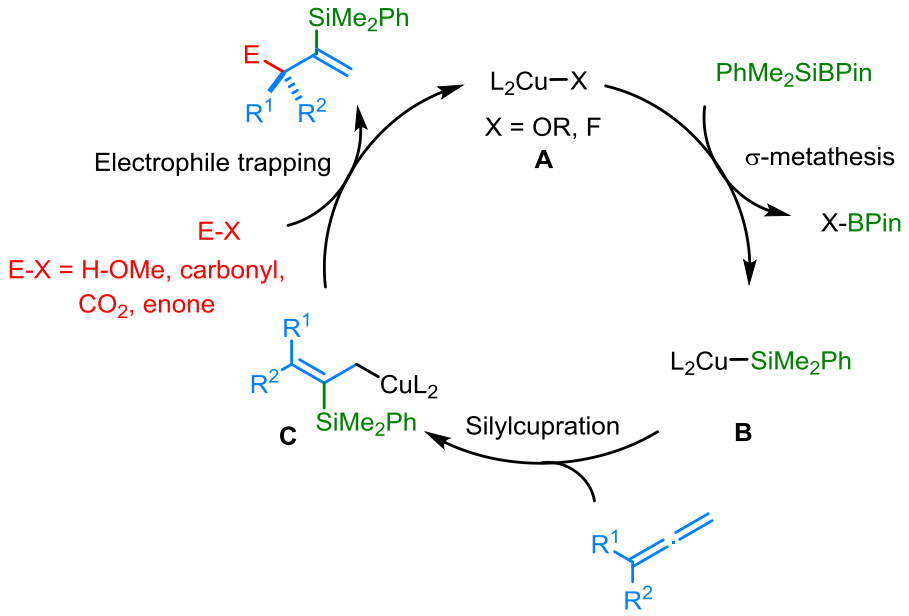
[178] Y. Tani, T. Yamaguchi, T. Fujihara, J. Terao, Y. Tsuji, *Chem. Lett.* **2015**, *44*, 271-273.

[179] Y. Tani, T. Fujihara, J. Terao, Y. Tsuji, *J. Am. Chem. Soc.* **2014**, *136*, 17706-17709.



Scheme IV-17. Cu-catalyzed difunctionalization of allenes with silylborane and CO_2

For all these transformations, a mechanism close to the boron-based cupration can be proposed (Scheme IV-18). Starting from a copper precatalyst, the copper(I) active species **A** is generated and undergoes a σ-metathesis with the Suginome's reagent to give the active Cu-Si species **B**. The silylcupration then occurs on the less hindered position of the allene to give the primary allylcopper species **C**. In the majority of the reports, this step is regioselective and does not lead to the formation of the vinylcopper species. In their report on the silylcarboxylation of allenes, Tsuji and Fujihara highlighted the influence of the steric bulk of both the ligand and the substrate, but the involvement of electronic effects cannot be excluded.[179] The allylcopper **C** finally reacts with the electrophilic partner (proton source, aldehyde, ketone, CO_2…) through a six-membered transition state to furnish the terminal alkene and generate a secondary/tertiary sp^3 centre. This leads to the regeneration of a Cu-X species, which needs in some cases to react with a hard Lewis base (alcoholate, carboxylate…) to regenerate the active species **A**.



Scheme IV-18. Mechanism of the copper-catalyzed silylfunctionalisation of allenes

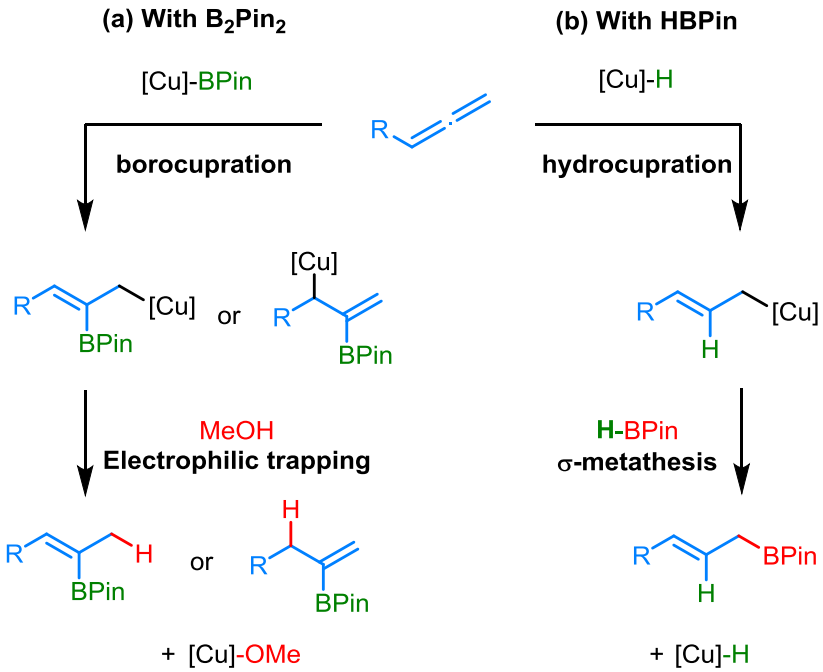
Such as in the case of borocupration, the obtention of the allylsilane regioisomer remains rare in the field copper-catalyzed silylfunctionalization of allenes. Following the example of silylcarboxylation by the group of Tsuji which was discussed above,[179] Yoshida and co-workers reported in 2015 another case of reverse regioselectivity in the copper-catalyzed silylstannation of allenes for the production of allylsilane/vinylstannane products.[180]

[180] H. Yoshida, Y. Hayashi, Y. Ito, K. Takaki, *Chem. Commun.* **2015**, *51*, 9440-9442.

II.3. Hydrocupration of Allenes

Examples of copper-catalyzed hydrofunctionalization of unactivated allenes[181] involving a copper hydride species remain more rare than their boron and silicon analogs. In 2013, in their article on the catalytic borocupration/protonation of allenes using bispinacolatodiboron,[144] the group of Tsuji reported the regioselectively-reversed hydroboration of allenes with the pinacolborane (Scheme IV-19). As described previously, the borocupration of allenes followed by the reaction with methanol afforded the vinylboron product (Scheme IV-19a). The use of a borane instead of the bispinacolatodiboron led to the formation of an allylborane (Scheme IV-19b). Mechanistically, this new process involves the formation of a copper hydride species. This [Cu-H] reacts with the allene with the same standard regioselectivity than the [Cu-B] and [Cu-Si] related species. The allylcopper intermediate subsequently undergoes a σ-metathesis with the borane to release the allylborane and regenerate the copper hydride.

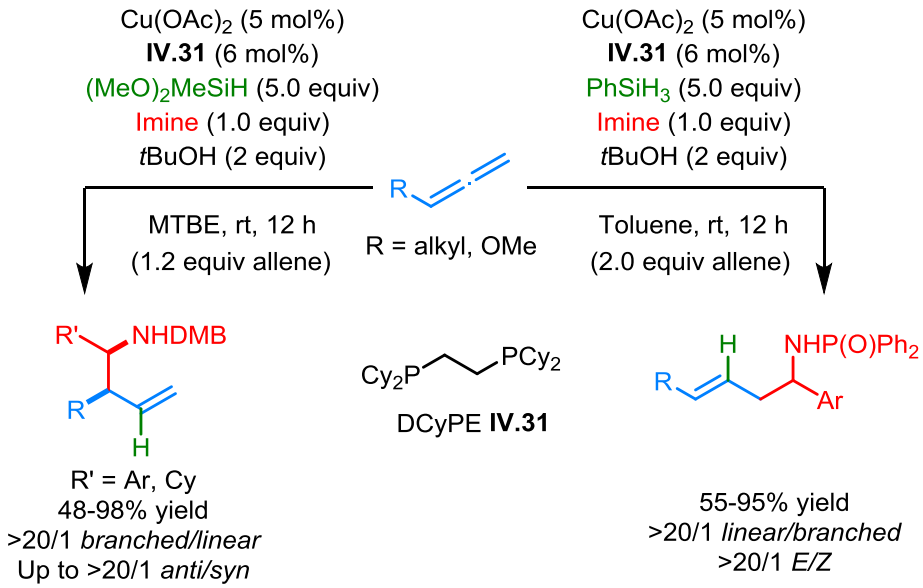
[181] For a report on a domino process involving the Cu-H addition onto allenoates, see: D. Zhao, K. Oisaki, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2006**, *47*, 1403-1407.



Scheme IV-19. Copper-catalyzed hydroboration of allenes with (a) a diboron reagent (b) a borane reagent

In 2016, Buchwald and co-workers reported the copper-catalyzed regioselective hydroamination of allenes (Scheme IV-20).[182] Mechanistically, the reaction is believed to involve the same terminal allylcopper species. The γ- or α-trapping of this allylic nucleophile with an imine leads to the formation of the branched or the linear products, respectively. This regio- and stereoselective functionalization was obtained by changing the nature of the silane and the nature of the group of the imine.

[182] R. Y. Liu, Y. Yang, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 14077-14080.



Scheme IV-20. Copper-catalyzed hydroamination of allenes

Finally, the group of Tsuji and Fujihara recently described the copper-catalyzed hydroallylation of allenes using allyl chlorides as electrophiles.[183] This report is reminiscent to the publication by the same group on the boro-allylation of allenes with allyl phosphates (Scheme IV-14a).[168]

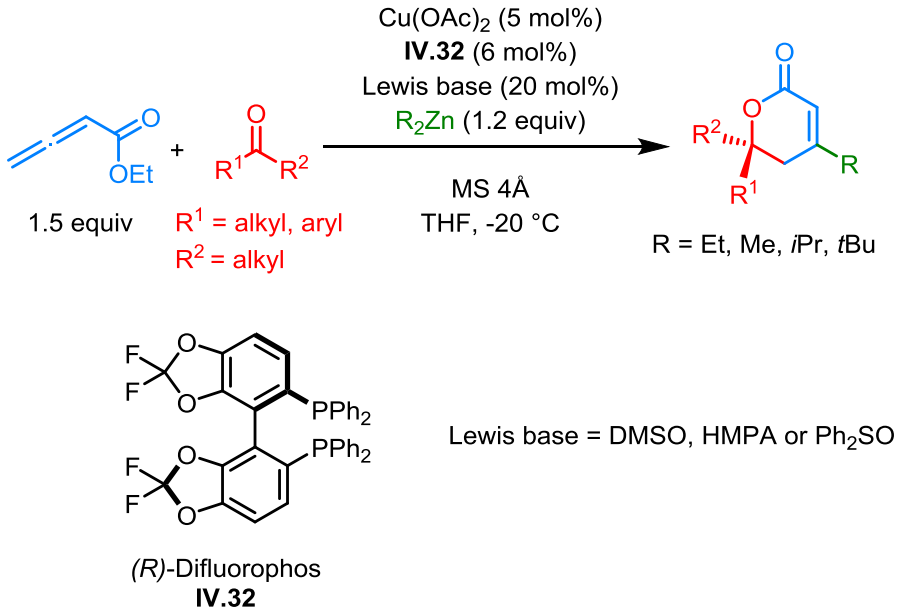
II.4. Nitrogen-, Oxygen- and Carbon-Based Copper-Catalyzed Functionalization of Allenes

Hydrides, silicon- and boron-based groups are the most common nucleophiles employed in copper-catalyzed functionalizations of allenes. However, a few reports involving other species were recently published by the group of Kanai.

This group reported a catalytic carbocupration of allenoates, leading to the generation of allylcopper species. The enantioselective quenching of the

[183] T. Fujihara, K. Yokota, J. Terao, Y. Tsuji, *Chem. Commun.* **2017**, *53*, 7898–7900.

allylcopper species by a carbonyl followed by a cyclization led to the formation of α,β-unsaturated lactones (Scheme IV-21).[184]



Scheme IV-21. Copper-catalyzed allenoate functionalization for the enantioselective synthesis of unsaturated lactones

The same group described the first copper-catalyzed oxoarylation of allenes using aromatic boronic acids as the pronucleophiles (Scheme IV-22).[185] They proposed the involvement of a Cu^{II}-Ar species which could add onto the allene with the same regioselectivity than that previously observed with other nucleophiles. The homolytic rupture of the [Cu-C] bond would generate an allyl radical, which could then be trapped by a molecule of TEMPO to furnish the product.

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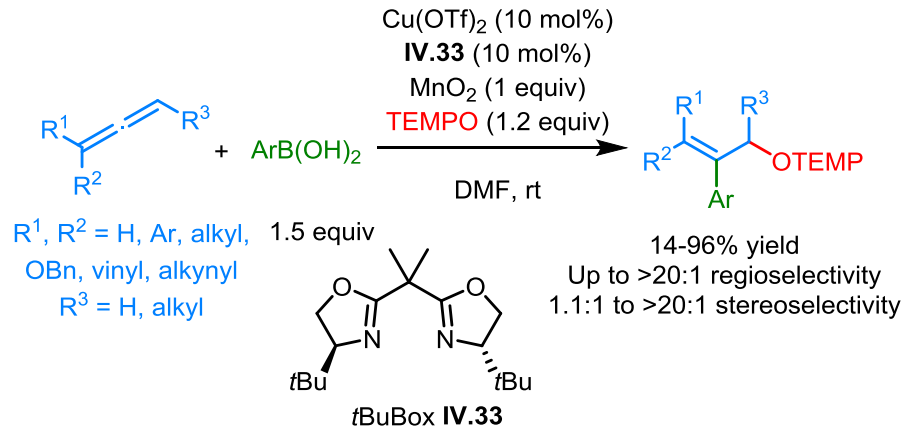
[184] K. Oisaki, D. Zhao, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2007**, *129*, 7439-7443.

[185] T. Itoh, Y. Shimizu, M. Kanai, *Org. Lett.* **2014**, *16*, 2736-2739.

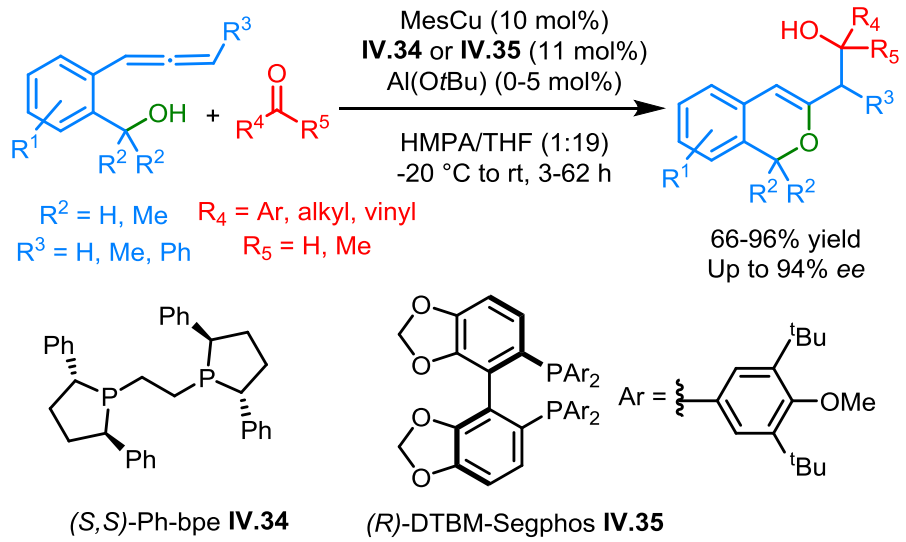


Scheme IV-22. Copper-catalyzed oxoarylation of allenes

Intramolecular versions of copper-catalyzed heteroatom additions on allenes were also reported. In this case, carbonyl derivatives were used to trap the allylcopper intermediate. The cyclization of benzylic alcohols on allenes placed on the *ortho* position was studied first in order to prepare the corresponding 1*H*-isochromenes (Scheme IV-23).[186] A similar synthesis of indoles from 2-allenyl-anilines was also reported.[187] In both cases, a six-membered transition state was proposed for the addition of the generated allylcopper species onto the carbonyl function.

[186] J. Kawai, P. K. Chikkade, Y. Shimizu, M. Kanai, *Angew. Chem. Int. Ed.* **2013**, *52*, 7177-7180.

[187] P. K. Chikkade, Y. Shimizu, M. Kanai, *Chem. Sci.* **2014**, *5*, 1585-1590.



Scheme IV-23. Catalytic oxycupration of allenes to synthesize 1*H*-isochromenes

III. Objectives of the Project

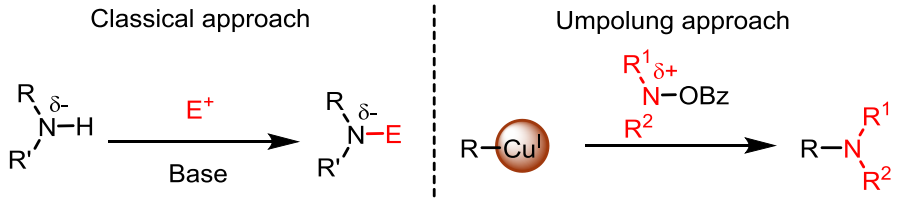
The literature reports on the copper-catalyzed functionalization of allenes attest on the increasing interest of several research groups for this topic. This strategy has led to the development of many three-component reactions between allenes, a pronucleophile and a chosen electrophile. This electrophile can be of different natures, such as a proton, an aldehyde, a ketone, an imine, a Michael acceptor, a cyano group, an allylic electrophile, an electrophilic nitrogen-based group or even CO_2. However, other interesting types of electrophiles haven't still been considered in such a type of transformation. The purpose of our work was to develop a new copper-catalyzed borofunctionalization method using an innovative electrophilic source. Among them, electrophilic amine species (**IV.36**) and acyl fluorides (**IV.37a** to **IV.39a**) presented in Scheme IV-24 have particularly drawn our attention.

IV.36

X = Cl: **IV.37a**
X = F: **IV.38a**
X = OBz: **IV.39a**

Scheme IV-24. Potential electrophiles for the borofunctionalization of allenes

Indeed, the use of electrophilic amine species has recently attracted some interest in the field of copper catalysis. Their use allows an umpolung-type synthesis of amines in the presence of various copper nucleophiles, as it has been extensively demonstrated by the groups of Buchwald[188] and Miura (Scheme IV-25).[39a,189]



Scheme IV-25. Classical approach vs umpolung approaches for the synthesis of amines

A similar transformation on allenic substrates with B_2Pin_2 hasn't been described yet. Their use would nevertheless lead to the synthesis of allylic amine bearing a versatile boron-based group on the C-C double bond (Scheme IV-26).

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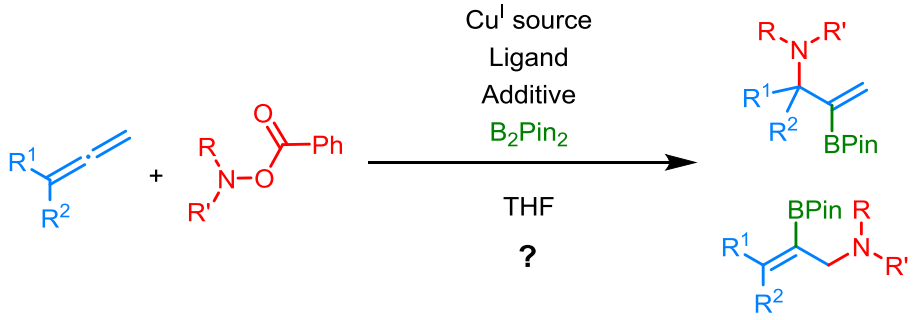
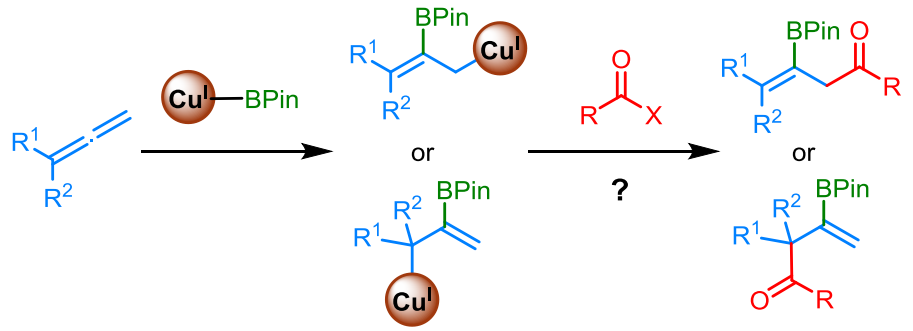
[188] Selected examples: (a) J. S. Bandar, M. T. Pirnot, S. L. Buchwald, *J. Am. Chem. Soc.* **2015**, *137*, 14812-14818; (b) S.-L. Shi, S. L. Buchwald, *Nat. Chem.* **2015**, *7*, 38-44; see also ref 182.

[189] Seleted example: R. Sakae, K. Hirano, M. Miura, *J. Am. Chem. Soc.* **2015**, *137*, 6460-6463.



Scheme IV-26. Copper-catalyzed allenes boroamination

Besides, when this project was initiated, acylating reagents (**IV.37a** to **IV.39a**) hadn't be considered in the field of allenes functionalization. However, their use would allow the preparation of β-boryl β,γ-unsaturated ketones with the creation of a new carbon-carbon bond and a new quaternary center in a single step (Scheme IV-27).

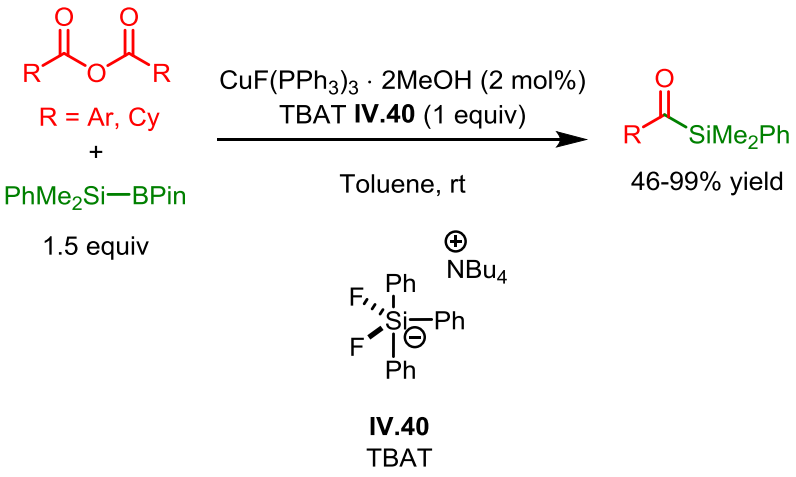


Scheme IV-27. Prospects for the copper-catalyzed boroacylation of allenes

Even by considering the literature on copper catalysis in general, the use of such reagents to perform the catalytic acylation of organocopper intermediates remains rare. To our knowledge, only two examples were reported before the beginning of this project.

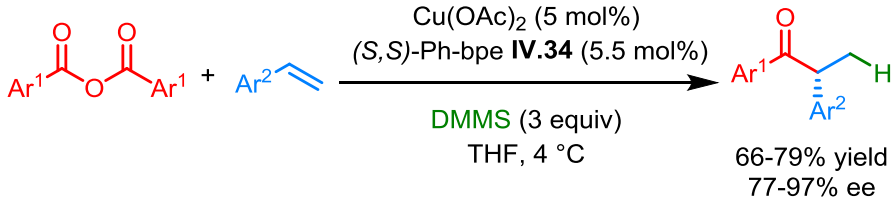
In 2013, Riant and co-workers developed a synthesis of acylsilanes starting from $PhMe_2SiBPin$ and an anhydride in the presence of a Cu^I catalyst

(Scheme IV-28).[190] In this reaction, the direct attack of the organocopper species onto the anhydride occured and led to the formal acylation of a Cu-Si complex.



Scheme IV-28. Synthesis of acylsilanes by copper-catalyzed silylation of anhydrides

More recently, Buchwald and co-workers reported the copper-catalyzed hydroacylation of styrenes using a silane as the hydride source and an anhydride as the acylating agent (Scheme IV-29).[191] In this case, the acylation of organocopper intermediates was part of a three-component coupling and was performed in an asymmetric fashion.

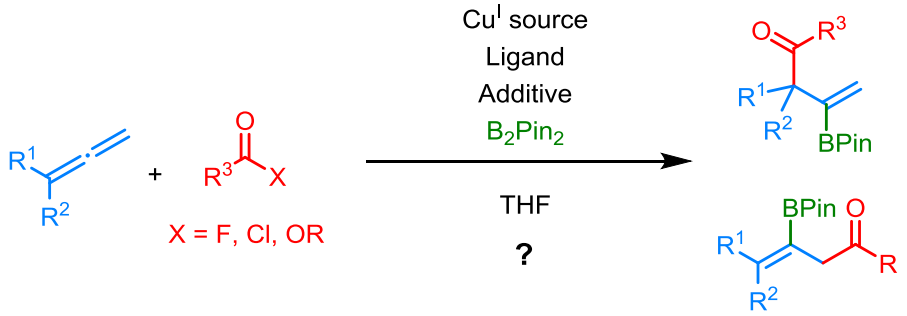


Scheme IV-29. Copper-catalyzed asymmetric hydroacylation of styrenes

[190] V. Cirriez, C. Rasson, O. Riant, *Adv. Synth. Catal.* **2013**, *355*, 3137-3140.

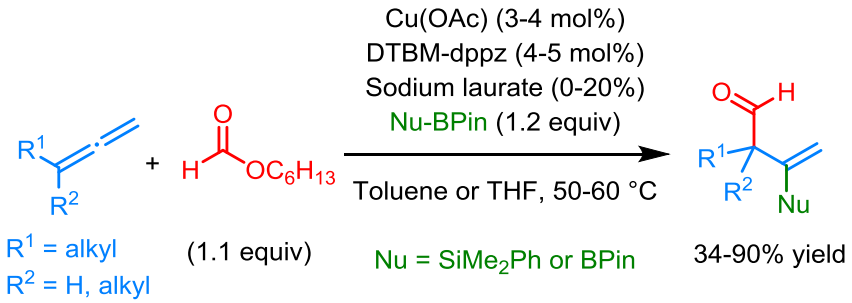
[191] J. S. Bandar, E. Ascic, S. L. Buchwald, *J. Am. Chem. Soc.* **2016**, *138*, 5821-5824.

In this context, the work made during this PhD will consist in investigating the potential borofunctionalization of allenes in the presence of new electrophilic acylating agents (Scheme IV-30).



Scheme IV-30. Objectives of the project for the boroacylation of allenes

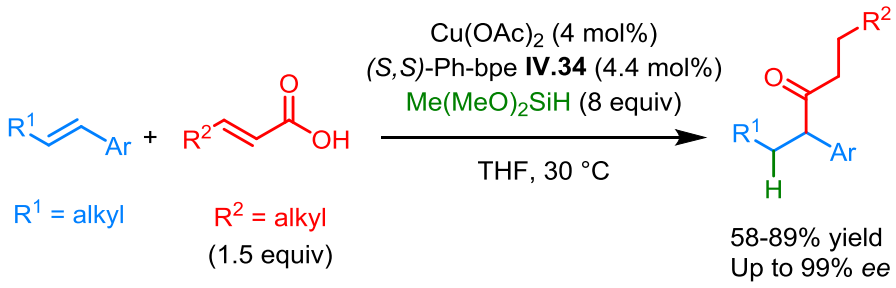
We have to mention here that during the development of this project, two additional similar transformations were reported in the literature. The groups of Tsuji and Fujihara reported the copper-catalyzed silyl- and boroformylation of allenes using formate ester as an electrophile (Scheme IV-31).[192] This method allows the synthesis of aldehydes with a structure close to our targeted products.



Scheme IV-31. Copper-catalyzed boroformylation of allenes

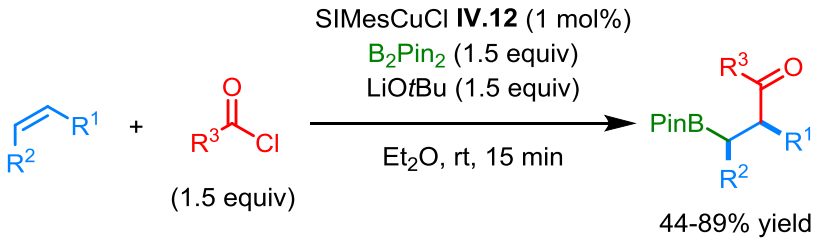
[192] T. Fujihara, A. Sawada, T. Yamaguchi, Y. Tani, J. Terao, Y. Tsuji, *Angew. Chem. Int. Ed.* **2017**, *56*, 1539-1543.

A few months after, Buchwald and co-workers developed a hydroacylation method of styrenes using α,β-unsaturated carboxylic acid as the acyl source (Scheme IV-32).[193]



Scheme IV-32. Asymmetric copper-catalyzed hydroacylation of styrenes

Finally, during the writing of this manuscript, Brown and co-workers reported the copper-catalyzed boroacylation of activated alkenes using acyl chlorides as the acylating reagents (Scheme IV-33).[194]



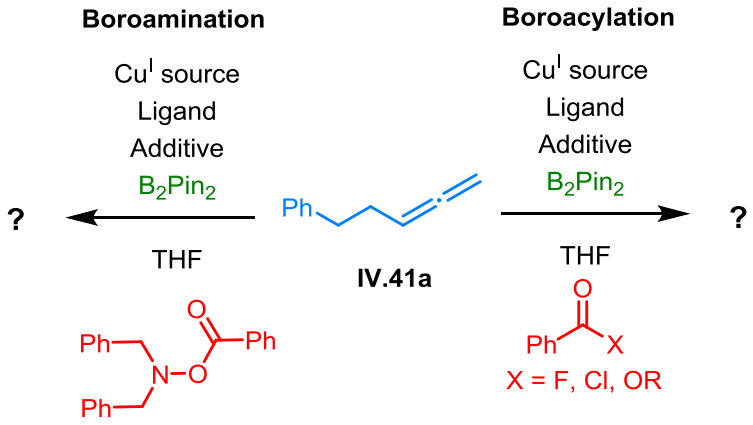
Scheme IV-33. Copper-catalyzed boroacylation of activated alkenes

[193] Y. Zhou, J. S. Bandar, S. L. Buchwald, *J. Am. Chem. Soc.* **2017**, *139*, 8126-8129.

[194] Y. Huang, K. B. Smith, M. K. Brown, *Angew. Chem. Int. Ed.* **2017**, *56*, doi: 10.1002/anie.201707323.

IV. Preliminary Results: Toward the Boroamination and Boroacylation of Allenes

To start our investigations, we decided to use a standard monosubstituted allene **IV.41a** and to submit it to standard copper catalysis conditions in the presence of an electrophilic amine or an acylating reagent (Scheme IV-34).

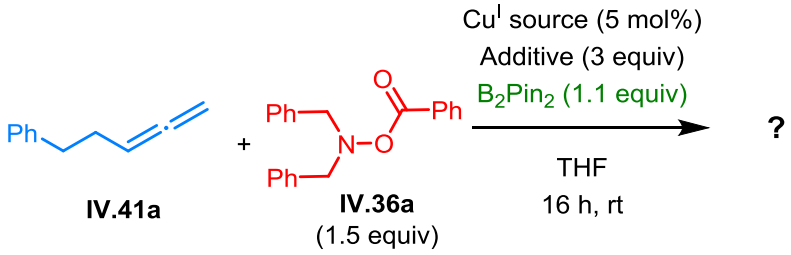


Scheme IV-34. Model substrate for the boroamination and -acylation of allenes

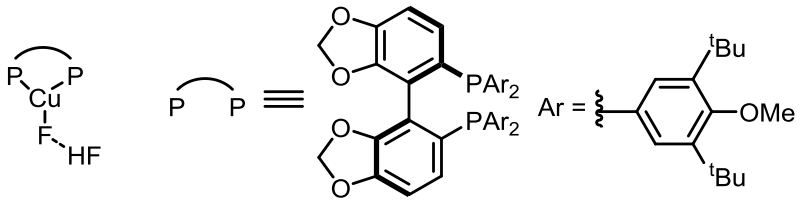
Tests for the boroamination of allenes

We carried out first tests by using procedures similar to those reported by the groups of Miura[189a] or Tortosa (Table IV-1).[39c] LiO*t*Bu was used as an additive in order to regenerate the copper catalyst, as this was assumed in these reports.

Table IV-1. First tests for the copper-catalyzed allene boroamination



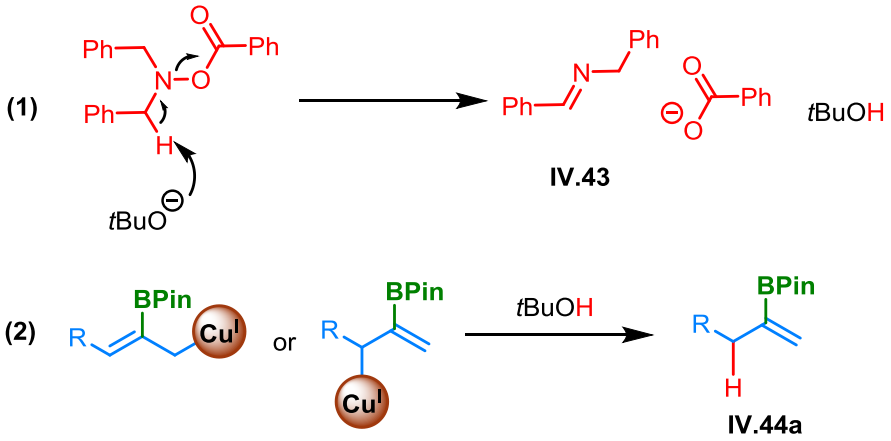
Entry	Cu catalyst	Additive	Result
1	$CuF(PPh_3)_3$	LiO*t*Bu	Complex mixture
2	IPrCuCl	LiO*t*Bu	Complex mixture
3	(**IV.42**)CuFHF	/	No conversion
4	(**IV.42**)CuFHF	LiO*t*Bu	Complex mixture



***(R)*-DTBM-Segphos**
IV.42

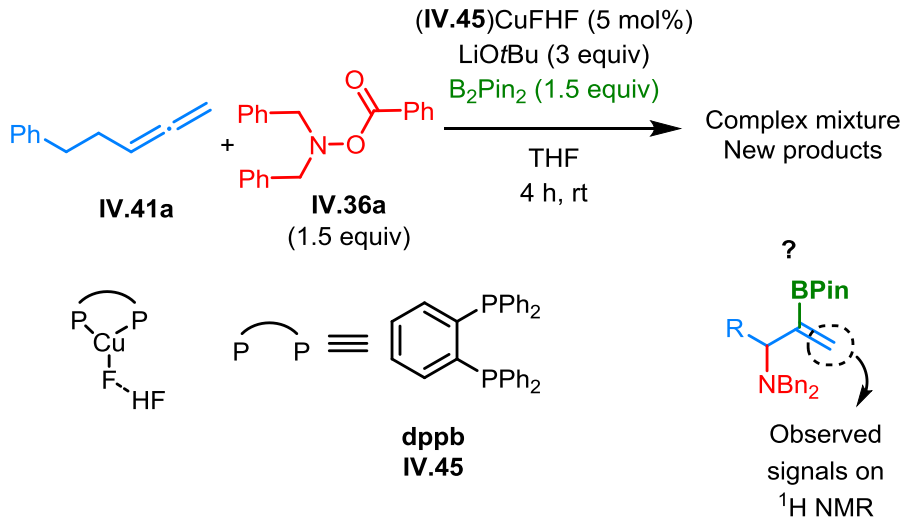
In these procedures, a solution of the allene and the amine was added on a mixture containing all the other reagents. In all cases, the starting material was still present in the crude reaction mixture and no interesting signal was observed by ^{1}H NMR spectroscopy. With exception of the signals of the starting materials and the solvents, the main products that were identified were the imine **IV.43** and the hydroboration product **IV.44a** (Scheme IV-35). The former may be formed by the deprotonation of the *O*-benzoyl amine by LiOtBu (Scheme IV-35, eq 1). This releases an alcohol which can

contribute to the protonation of the allylcopper intermediate (Scheme IV-35, eq 2).



Scheme IV-35. Possible formation of the observed by-products

The presence of these undesired compounds suggests a faster reaction between LiO*t*Bu and the amine than their involvement in copper catalysis. In the next tests, the reaction was set up by adding the solution of allene in mixture with the amine in a dropwise manner. This test was carried out in the presence of (dppb)CuFHF. Again, the starting materials and the previously observed side products were the major products observed by ^{1}H NMR spectroscopy.



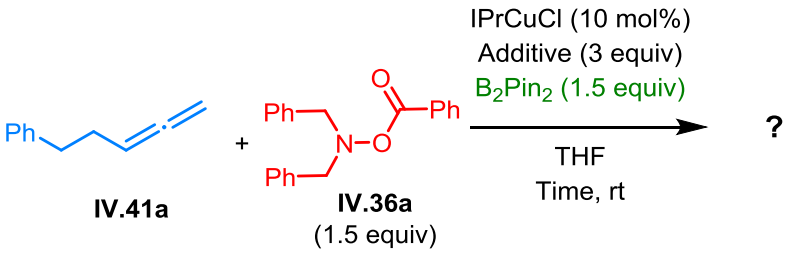
Scheme IV-36. Test for the copper-catalyzed boroamination of allenes

However, new NMR peaks corresponding to the presence of a terminal alkene moiety were observed, what was considered as a promising result. Unfortunately, purification by column chromatography furnished only side products and degradation products.

We then aimed to obtain a better conversion of the starting material, in order to facilitate the purification.

Three tests were carried during 3 hours using IPrCuCl as the copper source (Table IV-2). When LiOtBu was used as an additive, a mixture of several products was still obtained and interesting NMR signals were observed (entry 1). The use of a weaker base such as TMSONa completely switched off the catalytic activity as well as the side reactions (entry 2). Running the reaction for 24 h under the initial experimental conditions led to a complete conversion of the starting material and the formation of several products (entry 3).

Table IV-2. Tests for the copper-catalyzed allene boroamination



Entry	Additive	Time	Result
1	LiO*t*Bu	3 h	Complex mixture
2	TMSONa	3 h	Nothing occurs
3	LiO*t*Bu	24 h	Complete conversion / Complex mixture

A closer look to the crude ^{1}H NMR spectrum reveals the clear formation of at least three products (Figure IV-1):

- The doublets at 5.92 ppm and 5.67 ppm coupling together nicely fit with the presence of a terminal vinylic group. They might belong to the desired product (product 1).
- The doublets at 5.77 ppm and 5.35 ppm coupling together nicely fit with the presence of a terminal vinylic group. They might belong to the desired product (product 2).
- The small signals at 5.78 ppm and 5.63 ppm coupling together nicely fit with the presence of a terminal vinylic group. They belong to the hydroboration product **IV.44a**.
- The doublet at 4.86 ppm corresponds to the -CH_2- group of the imine **IV.43**.
- The singlet at 4.23 ppm corresponds to the electrophilic amine **IV.36a**.

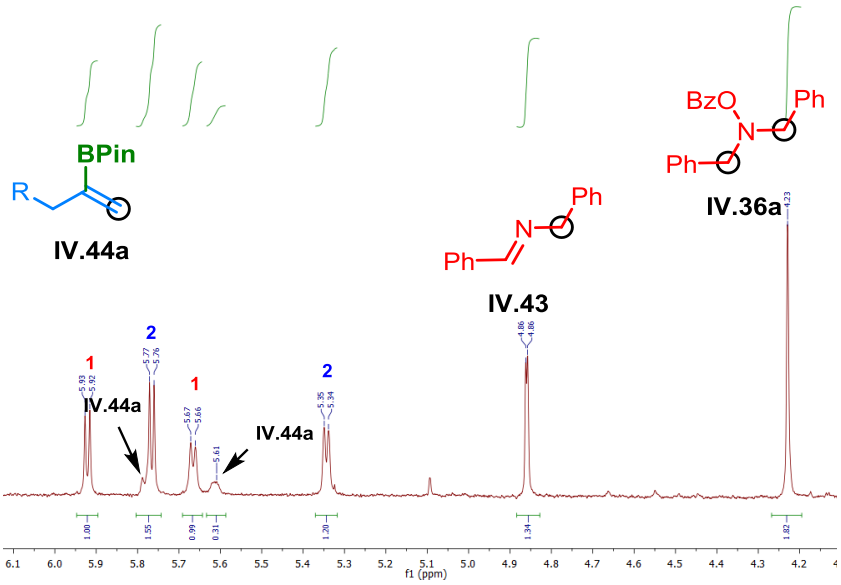


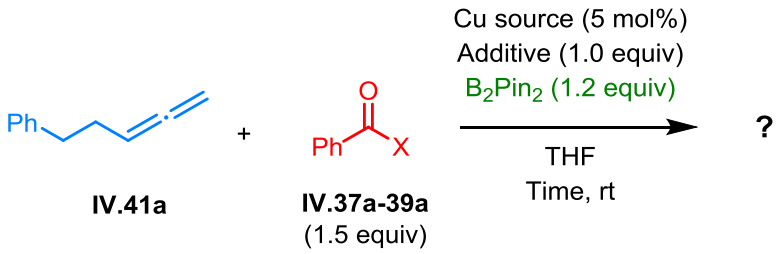
Figure IV-1. Vinylic zone of the ^{1}H crude NMR spectrum of the copper-catalyzed boroamination of allene ($CDCl_3$, 300 MHz)

Unfortunately, attempts to purify the crude mixture by flash chromatography led once again to degradation products.

Tests for the boroacylation of allenes

In parallel, tests were carried out with the aim to perform a boroacylation reaction of allenes (Table IV-3).

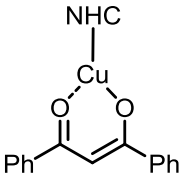
Table IV-3. First tests for the copper-catalyzed allene boroacylation



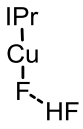
IV.41a

IV.37a-39a (1.5 equiv)

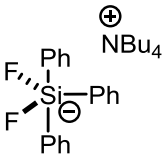
Entry	Cu catalyst	Additive	X	Time (h)	Result
1	**IV.46**	/	Cl	4	No product
2	**IV.46**	/	OBz	4	No product
3	**IV.46**	/	F	3	Traces of product
4	**IV.46**	LiO*t*Bu	OBz	16	No product
5	**IV.47**	/	OBz	2.5	No product
6	**IV.47**	**IV.40**	OBz	3	Traces of product
7	**IV.47**	/	Cl	3	No product
8	**IV.48**	/	F	3	Traces of product



IV.46: IMesCuDBM
NHC = IMes
IV.47: IPrCuDBM
NHC = IPr



IV.48



IV.40
TBAT

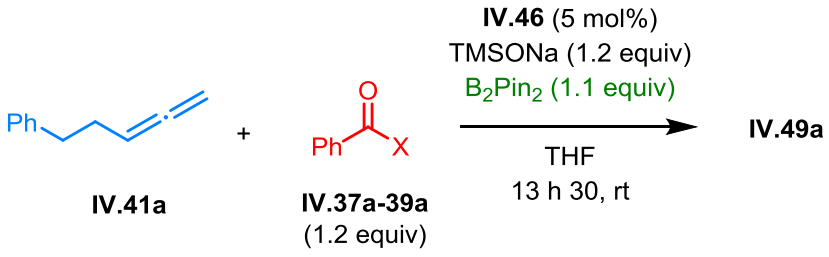
Three acylating agents were tested: benzoyl chloride **IV.37a**, benzoyl fluoride **IV.38a** and benzoic anhydride **IV.39a**. In the presence of IMesCuDBM (entries 1 to 4), IPrCuDBM (entries 5 to7) or IPrCuFHF (entry 8), no prod-

uct could be obtained in significative amount. The use of an additive such as LiO*t*Bu (entry 4) or TBAT (entry 6) was not efficient in promoting the boroacylation reaction. In the case of LiO*t*Bu, a direct attack of the alkoxide onto the anhydride was suspected. In several cases, the direct formation of hydroboration products were also observed.

Traces of a boroacylation product were actually observed in several cases, but these observations were made *a posteriori* when the structure and the characteristic peaks of the product were identified. These experiments did not allow the identification and the isolation of the desired compound.

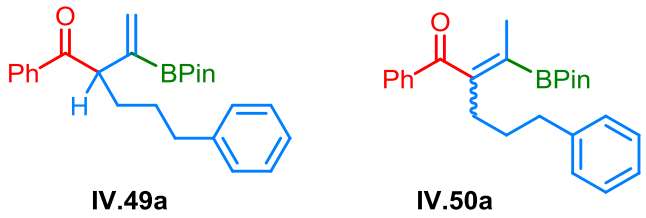
By using solid TMSONa as the additive, interesting signals could be observed during the analysis of the ^{1}H NMR spectrum of the crude mixture (Table IV-4). When the acyl fluoride was used as the acylating agent, a good and relatively selective conversion into a new product **IV.49a** was observed (entry 1). An attempt to separate this product by column chromatography led to its decomposition. A similar attempt with an anhydride used as the electrophile led to a poorer conversion (entry 2).

Table IV-4. Tests for the copper-catalyzed allene boroacylation



Entry	Cu catalyst	X	Result
1	**IV.46**	F	Product observed
2	**IV.46**	OBz	Product observed (poor conversion)

Another test performed under the conditions described in entry 1 of Table IV-4 allowed again a partial conversion of the allene into **IV.49a**. A new attempt of purification using silica gel neutralized with triethylamine was carried out. Two products were separated and obtained in small amounts: the expected product **IV.49a** and its isomerized product **IV.50a** (Scheme IV-37).



Scheme IV-37. Isolated products using neutralized silica column chromatography

Even if we were very enthusiastic with the isolation of compound **IV.49a**, the presence of its isomer **IV.50a** constituted an additional difficulty for the optimization of the process. It was assumed that the copper-catalyzed boro-acylation cleanly leads to the formation of **IV.49a**. As the hydrogen on the α-position of the ketone and the vinylboron group is relatively acidic, the isomerization of this compound should be easy to perform. Thus, the formation of this second product can occur at two stages:

- Either during the reaction: the basicity of the reaction medium might induce the isomerization of the compound. TMSONa or the organo-copper intermediates could deprotonate the product, which would then isomerize to its more stable form.
- Or during the purification process: the triethylamine present in the eluents during the purification might have the same effect and could induce the isomerization.

Unfortunately, the purification of product **IV.49a** using neutral alumina also led to the decomposition of the product.

A few other tests were carried out starting from the conditions used in Table IV-4. The use of TBAT or LiO*t*Bu as additives instead of TMSONa led to poorer conversion of the starting material into the desired compound.

A variation in the catalytic system was also envisioned. The use of $CuF(PPh_3)_3 \cdot 2MeOH$ as the copper source in combination with dppf **IV.23** led to a complete conversion of the starting material with a good ratio of the final product.

After these first investigations, we were optimistic in the possibility to optimize the reaction conditions and so in the development of an efficient copper-catalyzed boroacylation of allenes.

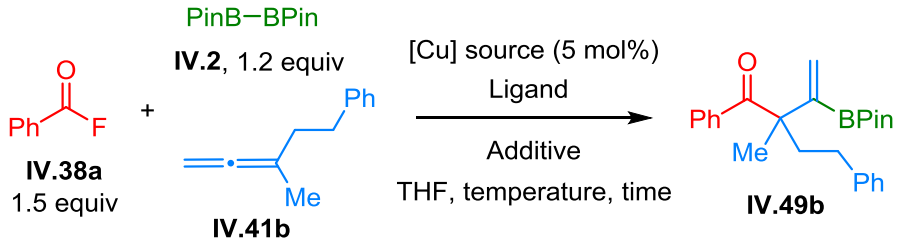
Strategic choices for the project

At this stage, we had carried out several tests to perform the borofunctionalization of allenes. Promising results were obtained for both the boroamination and the boroacylation. The strong competition in the field of borofunctionalization of allenes led us to focus on one of these two topics. Indeed, we suspected that other research groups were working on the same type of projects, and it would have been difficult for us to bring both projects into completion in a reasonable period of time.

Because electrophilic amination methods are already more developed in the field of copper catalysis than the corresponding acylations, we decided to focus on the latter. To our opinion, such transformation would be more innovative in the field and extremely useful for the construction of valuable building blocks.

V. Optimization of the Copper-Catalyzed Boroacylation of Allenes

During the preliminary tests, we realized that the model substrate was converted into a product which tended to decompose or isomerize during the purification step. This instability was attributed to the presence of an acidic hydrogen atom between the functional groups. We then decided to change our model substrate into the 1,1-disusbstituted allene **IV.41b** (Scheme IV-38). In this case, the obtained product would be the ketone **IV.49b**, which does not possess any acidic hydrogen atom at the problematic position. With this new substrate in hands, we started to optimize the reaction conditions. During this optimization, the reaction was carried out on 0.3 mmol of allene and ^{1}H NMR yields were assessed using 3,4,5-trimethoxybenzaldehyde as an internal standard. Additionally, instead of using solid TMSONa dissolved in THF, we decided to use TMSONa (1M in THF) directly used from the bottle purchased from the supplier.



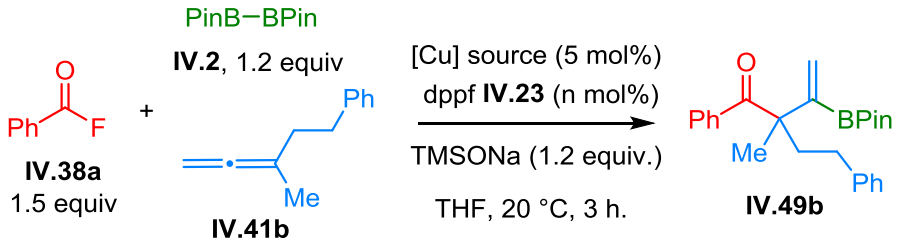
Scheme IV-38. New model reaction for the opimization of the reaction conditions

With this new substrate in hands, no purification problem was observed, and the expected product **IV.49b** was found to be stable on silica neutralized with triethylamine, thus allowing its purifrication by flash column chromatography. The optimization of the reaction conditions is presented in the next paragraphs.

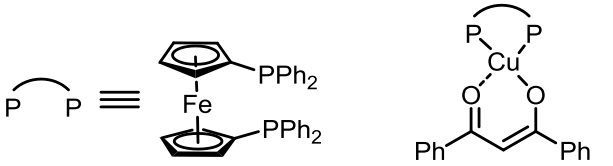
Optimization of the copper source

Preliminary tests showed us that dppf **IV.23** was a very suitable ligand and that TMSONa addition improved the conversion of the starting materials into the product. We screened first several copper sources in order to determine the most convenient one to use (Table IV-5).

Table IV-5. Screening of the copper sources



Entry	[Cu] source	n	Yield (%)
1	$[Cu(MeCN)_4]PF_6$	5	61
2	CuOAc	5	< 3
3	$Cu(OAc)_2$	7.5	73
4	CuI	5	< 3
5	$CuF(PPh_3)_3{\cdot}2MeOH$	5	73
6	(dppf)CuDBM **IV.51**	0	5
7	$[(dppf)CuCl]_2$	0	55



IV.23: dppf **IV.51**: dppfCuDBM

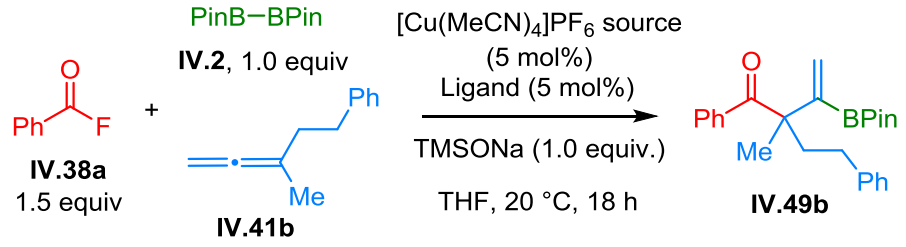
The cationic complex $[Cu(MeCN)_4]PF_6$ in combination with dppe furnished 61% yield of the desired product (entry 1). Copper(I) acetate was found to be completely inefficient to promote the reaction (entry 2), whereas copper(II) acetate gave 73% NMR yield (entry 3). In this case, an excess of dppf was added in order to reduce the copper(II) catalyst into a copper(I) complex. The use of copper(I) iodide didn't lead to any conversion of the starting material (entry 4). As showed previously, $CuF(PPh_3)_3{\cdot}2MeOH$ was also efficient in converting the reagents as 73% yield of the desired compound could be formed (entry 5). Finally, isolated complexes containing the dppf ligand were tested (entries 6-7). In these cases, no additional dppf was added. The (dppf)CuDBM **IV.51** only led to a poor conversion of the allenes, whereas the corresponding chloride led to a 55% yield of **IV.49b**. In all these tests, the yield of the undesired hydroboration product never exceeded 5%.

Optimization of the ligand

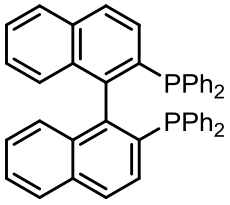
The last screening showed that copper(II) acetate and $CuF(PPh_3)_3{\cdot}2MeOH$ were the two best complexes to promote the transformation. Copper(II) acetate is a cheap commercial copper source, thus it seemed logical to us to keep it for the next step of the optimization. However, the double involvement of the phosphine in the process, as a reducing agent and as a ligand, pushed us to choose the cationic copper(I) complex $[Cu(MeCN)_4]PF_6$ to compare the ligands. Similarly, $CuF(PPh_3)_3{\cdot}2MeOH$ can be involved in ligand exchanges between triphenylphosphine and the studied diphosphine, which also makes the comparison difficult.

Thus, the next step was to screen several ligands in the presence of $[Cu(MeCN)_4]PF_6$ (Table IV-6).

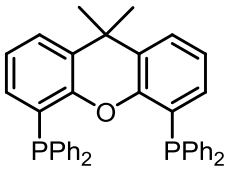
Table IV-6. Screening of ligands in the presence of $[Cu(MeCN)_4]PF_6$



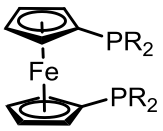
Entry	Ligand	Time (h)	Yield (%)	Yield by-product (%)
1	*rac*-binap **IV.52**	18	37	< 3
2	xantphos **IV.53**	18	< 3	10
3	dppf **IV.23**	18	58	< 3
4	**IV.54**	3	5	6
5	**IV.45**	3	10	11
6	**IV.55**	3	15	25
7	**IV.56**	3	30	5
8	PPh_3 (10 mol%)	3	< 3	20
9	PCy_3 (10 mol%)	3	5	25



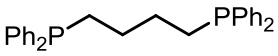
rac-binap **IV.52**



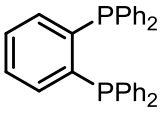
Xantphos **IV.53**



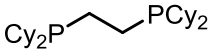
dppf **IV.23**, R = Ph
IV.54, R = Cy



IV.55



IV.45



IV.56

In comparison to dppf (entry 3), it appeared that changing the ligands had a detrimential effect on the yield of the desired compound. However, an intringuing result was obtained with several of the ligands tested. Another NMR signal in the region of vinylic hydrogens was observed in a recurrent manner. The yield of the corresponding product (if the peak corresponds to 1 H of the compound) is indicated on the second column in Table IV-6. This secondary product was mainly observed with monophosphines (entries 8-9, Figure IV-2) and with ligand **IV.54** (entry 4). It might be one of the other possible regioisomers of the product, possessing only one vinylic hydrogen atom.

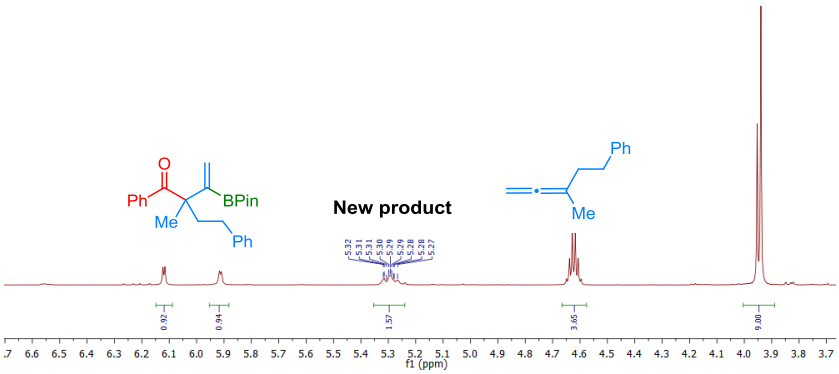


Figure IV-2. Vinylic zone of the ^{1}H crude NMR spectrum of the copper-catalyzed boroamination of allene with **IV.56** as the ligand ($CDCl_3$, 300 MHz)

The isolation of this secondary compound was attempted but no satisfactory result was obtained. Because of time limitation, this clue could not be investigated anymore. In the case of dppf ligand, this undetermined compound was never observed (entry 3).

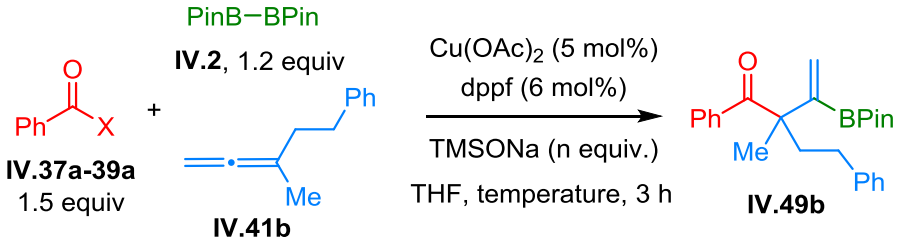
Again, no significative amounts of hydroboration products were observed during this part of the optimization.

Reaction conditions optimization

After finding suitable copper source and ligand, we decided to improve the reaction parameters to reach satisfying optimal reaction conditions (Table IV-7). Three aspects were considered: the reaction temperature, the amount of TMSONa and the nature of the acyl electrophile. Starting with copper(II) acetate and decreasing the amount of diphosphine to 6 mol% led to a decrease in efficiency: a 62% NMR yield was observed (entry 1). During the optimization, a similar procedure had been followed: copper(II) acetate and the dppf were mixed in THF, and the TMSONa in solution was added. Then B_2Pin_2 dissolved in THF was added, at which point the reaction mixture turned into a brown slurry. The allene and the acylating agent were finally

added as a solution in THF, which made the reaction mixture turn into a clear yellow solution. We were wondering if the addition of the B_2Pin_2 at the end of this procedure could still lead to the formation of the product. In this case, the desired compound **IV.49b** was not obtained anymore (entry 2). Explainations about this observation will be given in the next paragraphs.

Table IV-7. Final optimization step toward the optimal reaction conditions



Entry	T (°C)	n	X	Comment	Yield (%)
1	20 °C	1.2	F	/	62
2	20 °C	1.2	F	B_2Pin_2 was added at the end	< 3
3	0 °C	1.2	F	The reaction was cooled down to 0 °C after the addition of TMSONa	87
4	0 °C	0.2	F		11
5	0 °C	0	F		< 3
6	0 °C	0	Cl		10
7	0 °C	0	OBz		44

Then, assuming that a side reaction between TMSONa and the acyl fluoride could happen, we decided to cool down the reaction to 0 °C (entry 3). We were delighted to see that the yield of the transformation increased to 87% under these conditions. We then tried to decrease the amount of TMSONa, and it rapidly turned out that its presence in a stoichiometric amount was

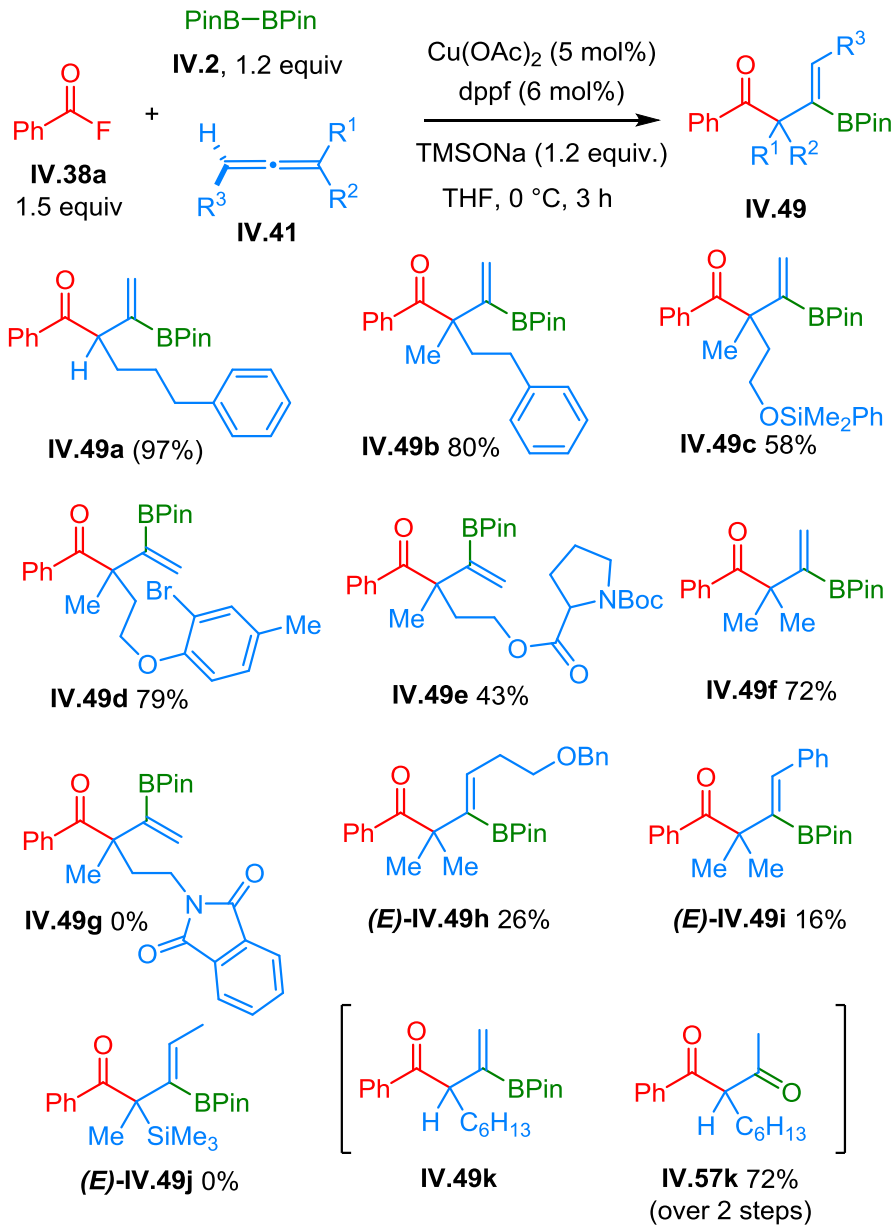
essential for the reaction to work properly (entries 4 and 5). Finally, we checked the reactivity of benzoyl chloride and benzoic anhydride under these new conditions. With the acyl chloride, the conversion was notably reduced and the yield of the transformation quite poor (entry 6). The reaction with the anhydride led to a 44% yield in the best case (entry 7). Unfortunately, this reaction was turning into a slurry once the addition of the B_2pin_2 was made and never came back to a homogeneous solution. The procedure with the anhydride led to quite irreproducible results and its use was not considered anymore as a potential alternative.

When we repeated the reaction on 0.5 mmol scale with the optimal conditions (entry 3), we could obtain the final product in 80% yield. At this stage, we considered that we had reached satisfying conditions to move to the scope study of this transformation.

VI. Scope of the Method

With the optimal reaction conditions in hand, we turned our attention to the application of this transformation to several allenes. In the presence of benzoyl fluoride, aliphatic allenes **IV.41a-i** were reacted in order to convert them into the corresponding boroacylated product **IV.49a-i** (Scheme IV-39). With the new optimal conditions, the reaction appeared to be very efficient with the monosubstituted allene **IV.41a**. Unfortunately, the product could still not be purified due to its instability over silica and alumina. The reaction proceeded well on allenes **IV.41b-f** in the presence of heteroatoms (N, O, Br, Si) which could have been sensitive to the reaction conditions. In particular, substrate **IV.41c** bearing a silicon-protected alcohol could be turned into the product in acceptable yield, despite the potential deprotection which could have happened in the presence of fluoride or TMSONa. A substituted phenol (**IV.41d**) or a protected amino acid derivative (**IV.41e**) were also

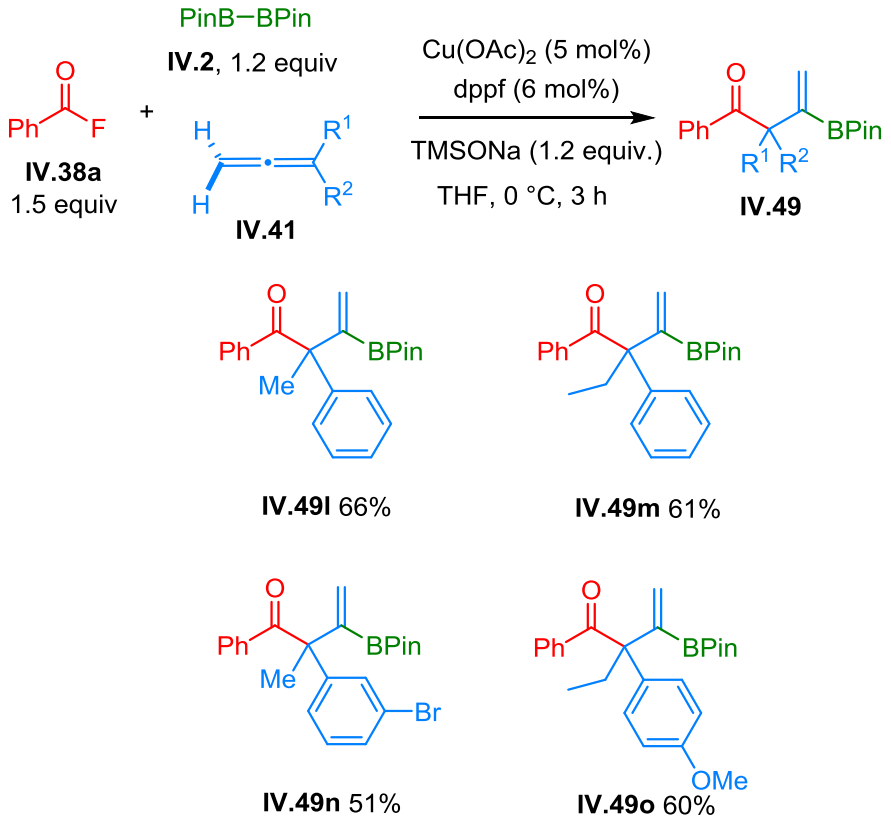
compatible with the reaction conditions. Substrate **IV.41g** did not lead to any conversion, probably due to a deactivation of the copper catalyst by the phthalimide moiety. The trisubstituted allenes **IV.41h** and **IV.41i** led to a poor lower yields, but only the *(E)*-isomer could be detected and isolated. These examples are very interesting as they furnish some pieces of information for the elucidation of the mechanism of the reaction that will be discuss in the next sections. The trisubstituted allenylsilane **IV.41j** only furnished a complex mixture of products from which none could be isolated and characterized. Finally, monosubstituted allene **IV.41k** was efficiently converted into the compound **IV.49k**. Such as **IV.49a**, this product turned out to be degraded during the purification by flash chromatography. The vinylboron moieity was therefore oxidized in situ into the corresponding ketone furnish the 1,3-dione **IV.57k**. A global yield of 72% over the two steps was obtained.



Scheme IV-39. Scope of the aliphatic allenes

We then moved to the scope of aromatic allenes **IV.41j-m** (Scheme IV-40). In this case, the main difficulty was the handling of the starting materials which were prompt to polymerize. Substrates **IV.41l-m** bearing a non-

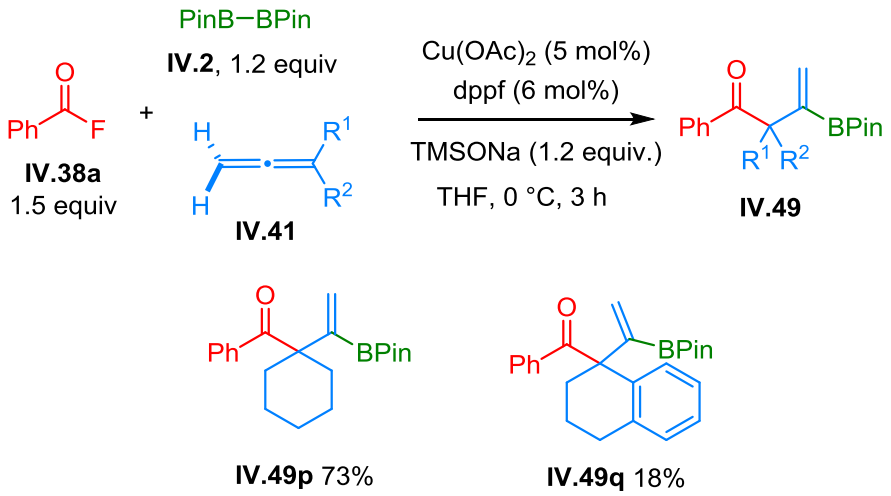
substituted phenyl group were converted into the corresponding products **IV.49l-m**. The presence of a bromide (**IV.41n**) or an electron-donating substituent (**IV.41o**) on the aromatic ring still allowed their conversion with acceptable yields. Although the yields of this serie of substrates remain lower than the previous ones, it should be noted that aromatic allenes were absent in the reaction scope of Tsuji's and Fujihara's report.[192]



Scheme IV-40. Scope of the aromatic allenes

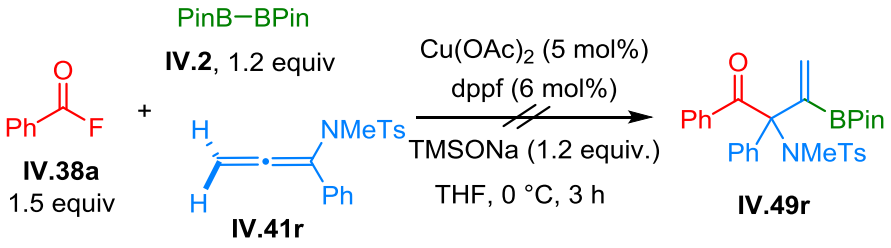
The use of exocyclic 1,1-disubstituted allenes such as **IV.41p-q** was attempted (Scheme IV-41). While the aliphatic substrate **IV.41p** was easily converted to the product in 73% yield, the aromatic derivative **IV.41q** only gave 18% yield of the final product. Again, this could be explained by the

intrinsic instability of aromatic allenes, which could be turned into several side products when submitted to the reaction conditions.



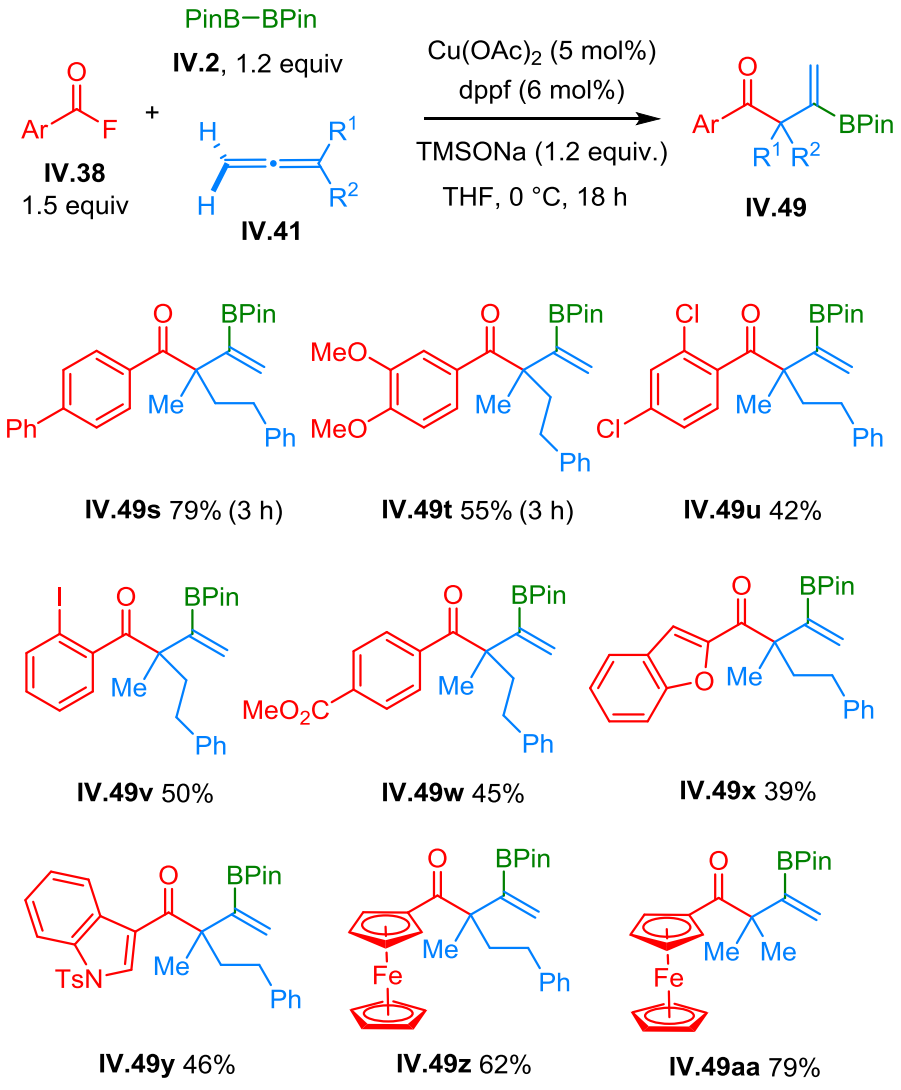
Scheme IV-41. Scope of the cyclic 1,1-disubstituted allenes

To complete the allenes scope, the allenamide **IV.41r** was subjected to the reaction conditions, but no reactivity was observed with this particular substrate (Scheme IV-42).



Scheme IV-42. Test with the allenamide **IV.38r**

After studying the allenes scope, we moved to the screening of several acyl fluorides (Scheme IV-43). Aromatic ones were usually found to react well in our reaction conditions. Most of the time, the reaction time had to be increased to 18 h in order to observe a complete conversion of the allene.

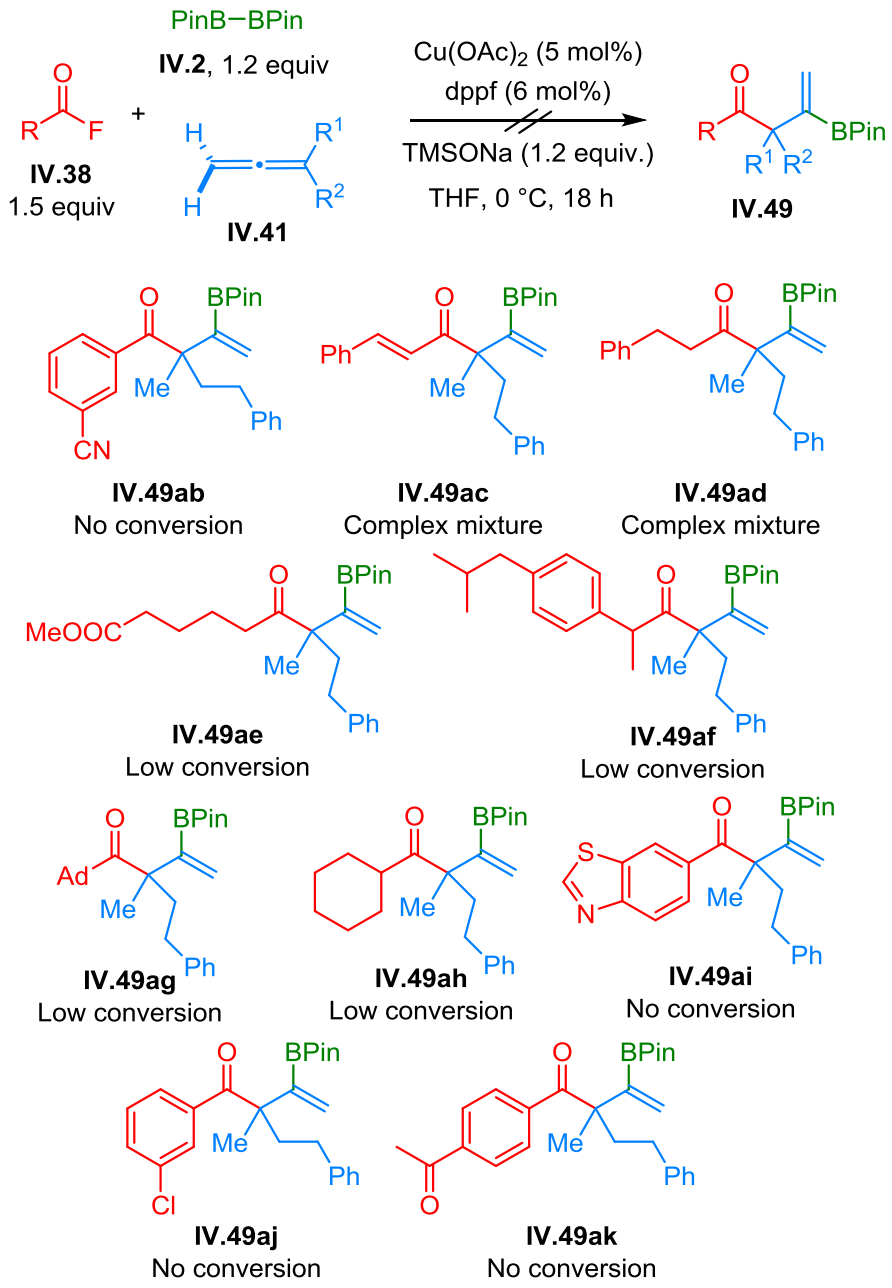


Scheme IV-43. Scope of the acyl fluorides: successful examples

Substituted benzoyl fluorides were put in the optimal reaction conditions and the corresponding products **IV.49s-w** were obtained in moderate to good yields. An acyl fluoride bearing an aromatic ring substituted by a phenyl group on the *para*-position led to 79% yield (**IV.49s**). Variously substituted

aromatic rings were tested and moderate but acceptable yields were obtained for electron-donating and withdrawing groups (**IV.49t-w**). The use of a less activated heterocycle such as a benzofuran or a protected indole led to lower but still encouraging yields of compounds **IV.49x-y**. Finally, a ferrocenyl acyl fluoride could be used to efficiently functionalize the allylcopper intermediate and furnish products **IV.49z-aa**.

Unfortunately, some limitations were observed in this process (Scheme IV-44). A cyano group on the acyl fluoride was not tolerated, as it led to a complete deactivation of the catalytic system (**IV.49ab**). Besides, the cinnamyl acyl fluoride led to a complex mixture from which no major compound could be isolated. The main limitation of our method lies however in the high decrease of reactivity when aliphatic acyl fluorides are used (**IV.49ad-ah**). Indeed, in these cases, a very low conversion into the presumed boroacylation product was obtained. Significant amounts of hydroboration products were systematically observed instead. Hypotheses related to their formation will be discussed in the next paragraph. A benzothiazole ring in the substrate also led to a regeneration of the starting materials (**IV.49ai**). Finally, the reaction was found to be not compatible with a chloro (**IV.49aj**) or a ketone (**IV.49ak**) substitutions on the aromatic ring. The former only gave a poor conversion while the latter led to decomposition products.



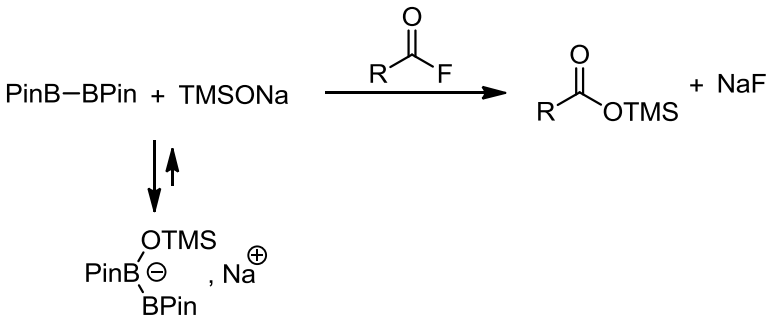
Scheme IV-44. Scope of acyl fluorides: unsuccessful examples

VII. Reaction Mechanism

Thanks to the experiments carried out during the optimization and the study of the reaction scope, the puzzle of the mechanistic cycle could be at least partially solved. This paragraph aims to highlight the key experiments that allow us to propose a mechanism for the transformation.

Role of the TMSONa

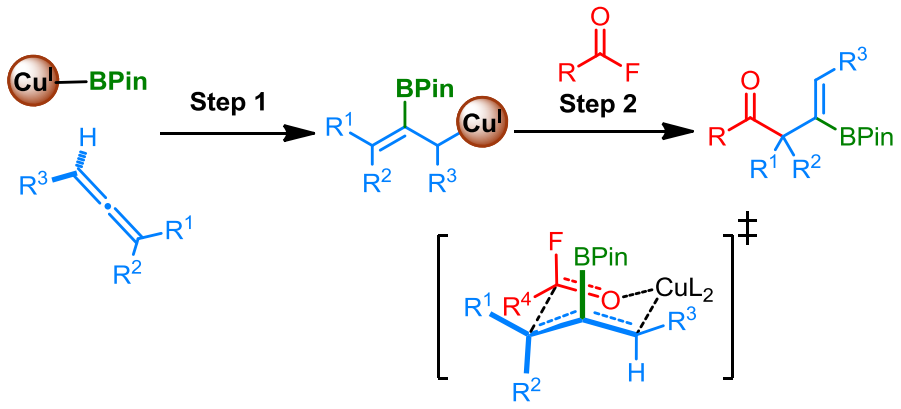
During the optimization of the reaction conditions, it turned out that the pre-mixing of the copper catalyst, B_2Pin_2 and TMSONa was necessary to observe some conversion of the starting materials. When B_2Pin_2 was added at the end of the procedure, no conversion was observed. Based on this result, we can envisage a complexation equilibrium between the trimethylsilanoate ion and the B_2Pin_2 (Scheme IV-45). The formation of this ate complex would reduce the possible reaction between the TMSONa and the acyl fluoride, which probably occurs if these reagents are put in presence in the absence of B_2Pin_2. Characteristic signals on the crude ^1H NMR spectra suggest the presence of benzoic acid derivatives, which would confort this hypothesis. Besides, this idea is also supported by the improved yield obtained at 0 °C compared to room temperature. Indeed, if the ate complex is pre-formed, a lower temperature would reduce the regeneration of free TMSONa which would then participate to the degradation of the acyl fluoride before its involvement in the copper-catalyzed reaction.



Scheme IV-45. Reaction involved in the absence of copper between TMSONa and an acyl fluoride

Regio- and stereoselectivity of the reaction

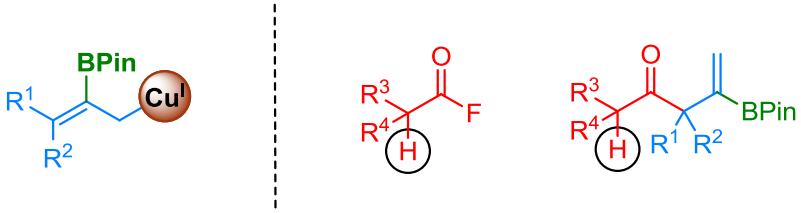
As it has been detailed in the introduction of this chapter, several mechanisms have been proposed to explain the regioselectivity of the copper-catalyzed borofunctionalizations of allenes. In our case, we consider that the observed regioselectivity is more likely due to a regioselective borocupration on the less hindered side of the allene (Scheme IV-46, step 1), followed by a regiospecific trapping of the electrophile via a Zimmerman-Traxeler mechanism (Scheme IV-46, step 2). This model also fits with the stereoselectivity observed in the case of the trisubstituted allenes **IV.41h-i**. In the proposed Zimmerman-Traxler transition state, the third substituent can adopt a pseudo-axial or pseudo-equatorial position. The more favourable equatorial position leads to the formation of the *(E)*-product, what is observed experimentally. A mechanism based on the borocupration on the more hindered site followed by an α-trapping of the electrophile would favour the formation of the *(Z)*-product, which has not been observed experimentally.



Scheme IV-46. Origin of the regio- and stereoselectivity of the process

Problems with the aliphatic acyl fluorides

The low conversion and selectivity observed in the case of aliphatic acyl fluorides could be explained by considering the presence of an acidic hydrogen atom at the α-position to the acyl group. If the basic allylcopper reacted with the acyl fluoride or with the resulting ketone, a net loss of the limitating reagent would be noted. Moreover, the reaction could also result into the loss of the acyl fluoride, which is also involved in the process.



Scheme IV-47. Possible acid-base reaction between the allylcopper intermediate and the acyl derivative

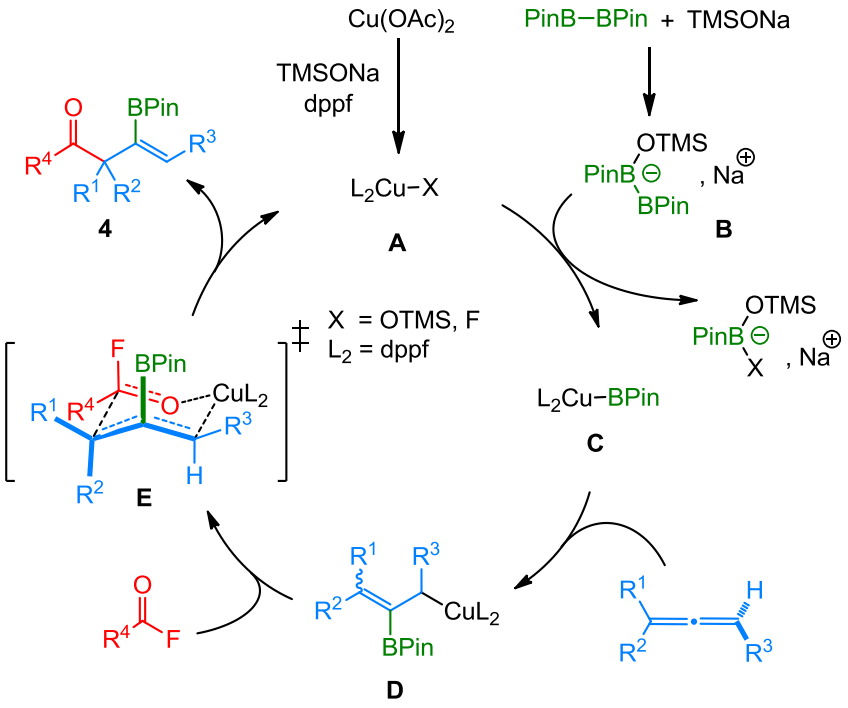
Several possibilities can be envisioned to deal with this problem:

- A new optimization of the ligand, which would favour the acylation reaction rather than the protonation of the allylcopper species.

- The temperature of the reaction could also be modified in order to observe how it does impact both reactions.

Catalytic cycle

On the basis of these observations, we could finally propose the following catalytic cycle (Scheme IV-48). Copper(II) acetate is turned into a copper(I) complex **A** in the presence of dppf and TMSONa.



Scheme IV-48. Proposed mechanism of the copper-catalyzed boroacylation of allenes

In parallel, B_2Pin_2 interacts with TMSONa in order to form the ate complex **B**. The reaction between **A** and **B** produces the active Cu-B species **C**. The regioselective borocupration occurs then to generate the allylcopper intermediate **D**. The γ-trapping of this intermediate by the acyl fluoride via a

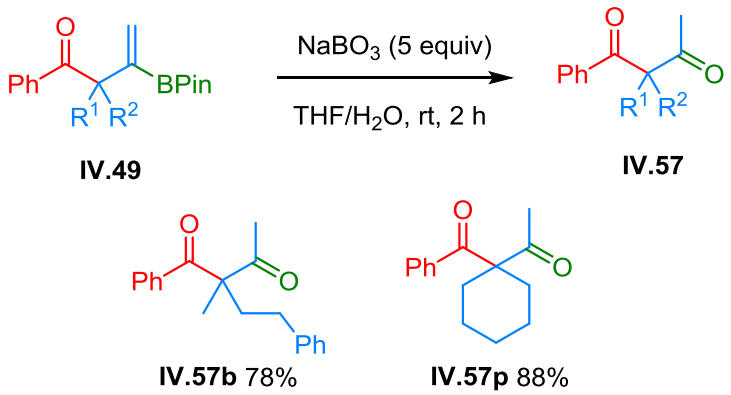
Zimmerman-Traxler transition state delivers the desired product and regenerates the active species **A**.

VIII. Valorization of the products

After the synthesis of a library of β-boryl β,γ-unsaturated ketones, we were interested in derivatizing these products into other functional groups.

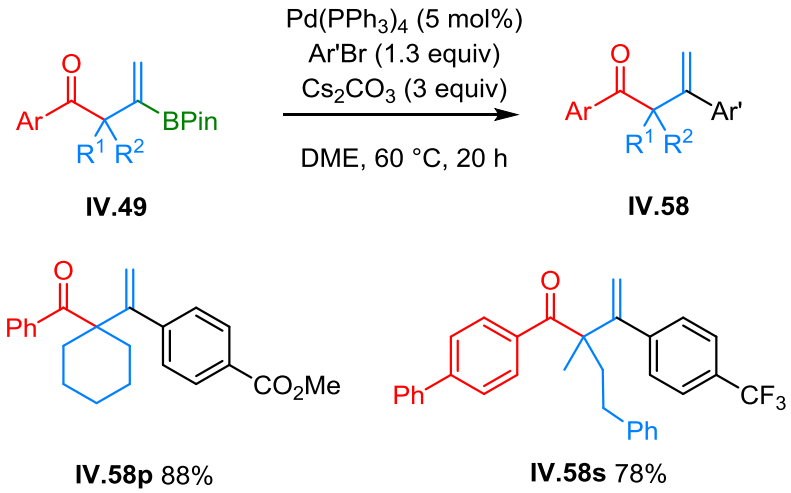
As carbon-boron bonds are easily oxidable into the corresponding carbon-oxygen bonds, vinylboron compounds are direct precursors to ketones. As mentioned previously, the in situ oxidation of the unstable compound **IV.49k** using sodium perborate allowed to isolate the 1,3-dione **IV.57k** in a good yield over two steps.

The same oxidation was also tested on isolated compounds **IV.49** and the corresponding diones were cleanly obtained (Scheme IV-49).



Scheme IV-49. Oxidation of compounds **IV.49** into the corresponding 1,3-diones **IV.57**

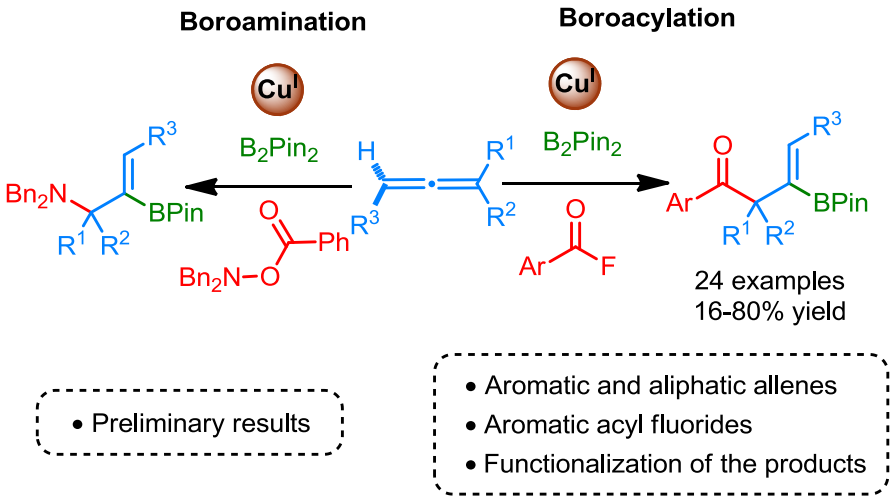
Besides, vinylboron compounds can easily be converted into styene derivatives by a palladium-catalyzed Suzuki coupling. The reaction of vinylboron compounds **IV.49** with aryl bromides in the presence of $Pd(PPh_3)_4$ allowed the straightforward preparation of coupling products **IV.58p** and **IV.58s** (Scheme IV-50).



Scheme IV-50. Derivatization of compounds **IV.49** by a Suzuki coupling

IX. Conclusions and Perspectives

The aim of this chapter was to study new copper-catalyzed borofunctionalization methods applied on allenes. While only preliminary results were obtained in the case of the boroamination of allenes, we were able to develop an efficient boroacylation method applicable to various allenyl moieties (Scheme IV-51).



Scheme IV-51. Summary of the results obtained in this chapter

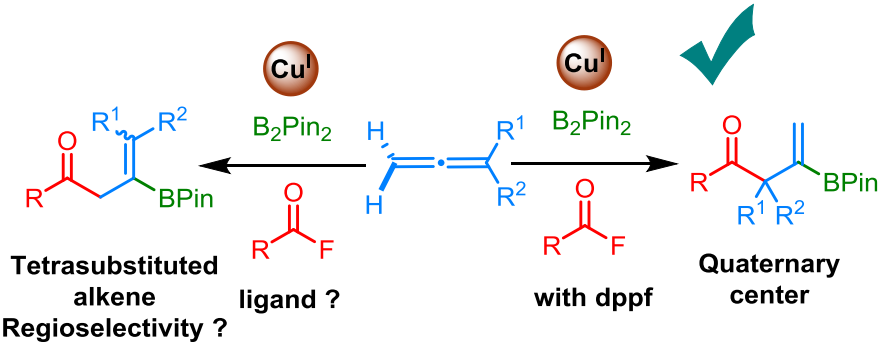
24 examples of boroacylation were successfully carried out on aliphatic as well as aromatic allenes. Aromatic and heteroaromatic acyl fluorides were also tolerated and could be incorporated in the final products. A few limitations and additional work still remain to be done and can be the object of further studies:

- Trisubstituted allenes could only be poorly converted into the desired products, although with an excellent *(E)*-selectivity. As these substrates have been rarely studied in borofunctionalization meth-

ods, it might be worthy to optimize the conditions in order to obtain the corresponding products in improved yields.

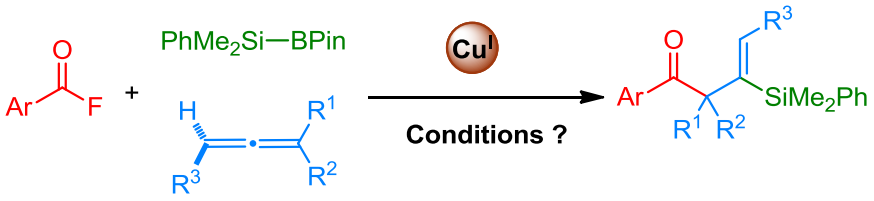
- Aliphatic acyl fluorides constitute the main limitation of our method at this stage. As discussed previously, several parameters might be envisonned in order to deal with this problem in order to significantly improve the value of the method.
- An enantioselective version of the method would be interesting, as the preparation of chiral quaternary centers remains a challenge nowadays. A screening of chiral ligands would hopefully lead to the obtention of an optimal method for the preparation of enantioenriched products.

One of the main perspectives on this project concerns the extension of the method to other selectivities and other types of functionalizations. For instance, the inversion of regioselectivity can be envisaged by changing the nature of the ligand (Scheme IV-52).[179] This would give access to tetrasubstituted vinylboron compounds bearing a ketone function.



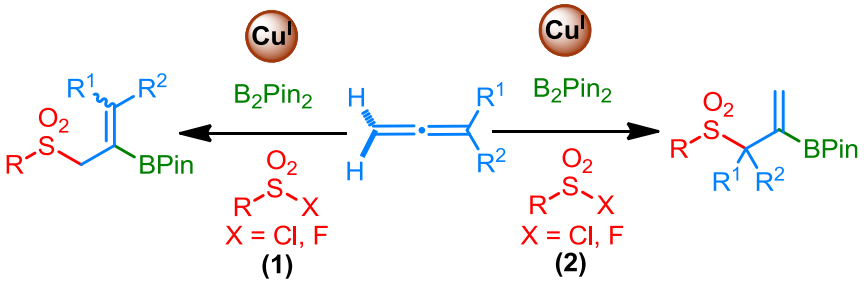
Scheme IV-52. Extention of the method to the reversed regioselectivity

Besides, the use of silylborane instead of B_2Pin_2 would lead to a synthesis of β-silyl β,γ-unsaturated ketones, which are also versatile building blocks in organic synthesis (Scheme IV-53).



Scheme IV-53. Synthesis of β-silyl β,γ-unsaturated ketones by copper-catalyzed silylacylation

Other unexplored electrophiles also have a significant interest in terms of post-functionalization. For instance, electrophilic equivalents of sulfones, such as sulfonyl chlorides or fluorides, would allow the preparation of allylic sulfones on a tetrasubstituted vinylboron moiety (Scheme IV-54, eq 1) or on a quaternary center (Scheme IV-54, eq 2). Such products would allow a panel of subsequent transformations, such as Julia olefination for the primary sulfones[195] (eq1) or radical-based allylic substitution for the tertiary sulfones (eq 2).[196]



Scheme IV-54. Extension of the method to the use of electrophilic sulfones

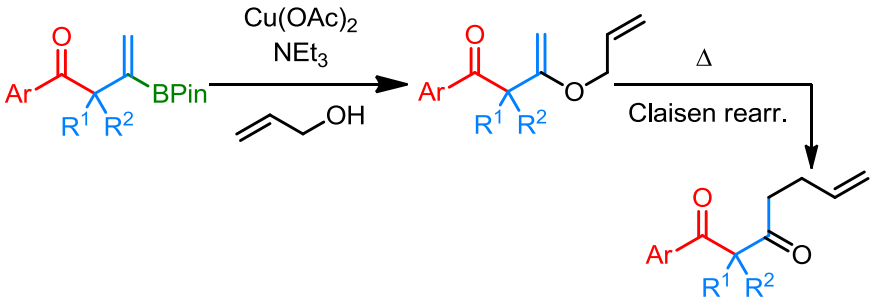
Finally, the last presented perspectives concern the post-functionalization of the obtained β-boryl β,γ-unsaturated ketones. As showed previously, the simple oxidation or a Suzuki coupling could be easily performed on the ob-

[195] M. Julia, J.-M. Paris, *Tetrahedron Lett.* **1973**, *14*, 4833-4836.

[196] N. Charrier, S. Z. Zard, *Angew. Chem. Int. Ed.* **2008**, *47*, 9443-9446.

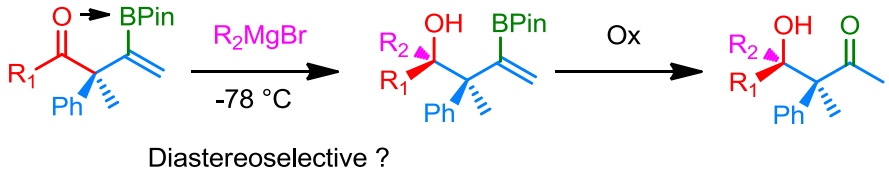
tained vinylboron moiety. However, more sophisticated transformations applied to our compounds might increase their synthetic value.

A Chan-Lam-Evans coupling between the vinylboron moiety and an allylic alcohol would furnish the corresponding enol ether (Scheme IV-55). The subsequent Claisen rearrangement would allow the transformation of the terminal part of the vinylboron into an allylic moiety. As one of the limitation of our method lies in the low yields obtained in the case of tertiary substrates, this application would encounter this drawback.



Scheme IV-55. Functionalization of the vinylboron moiety via a Chan-Lam-Evans coupling/Claisen rearrangement sequence

Last but not least, a diastereoselective functionalization of the final compounds could be attempted (Scheme IV-56). It has been shown that heteroatoms could coordinate the boron atom in an intramolecular fashion.[161a] The induced conformation could be at the origin of a Cram-chelate effect, and so allow a diastereoselective addition of Grignard reagents onto the ketone. The subsequent oxidation of the vinylboron moiety would deliver an aldol type product resulting from the formal addition of a quaternary enolate onto a ketone. If the first reaction could occur diastereoselectively, this would allow a modular synthesis of all possible stereoisomers of the aldol-type product.



Diastereoselective ?

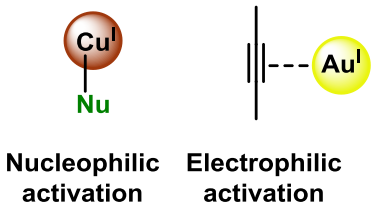
Scheme IV-56. Modular synthesis of aldol-type products

Chapter V: Towards the Development of Copper/Gold-Catalyzed 1,4-Reduction/Cyclization of Enones

This chapter presents a project which has been initiated at the beginning of this PhD. Because of my involvement in the projects presented in the previous chapters, this one has not been pursued by lack of time. Preliminary results are presented.

The previous chapters have shown the results obtained on projects involving gold(I) or copper(I) catalysis. Gold(I) complexes were used in transformations initiated by an electrophilic activation of an alkyne, which could be attacked by a nucleophile. Catalytic organocopper(I) chemistry was used for the transfer of nucleophilic species onto carbon-carbon unsaturations.

In this last chapter, we aimed to take advantage of both reactivities by elaborating a system where a nucleophile activated by copper would react with gold-coordinated carbon-carbon unsaturated bonds (Scheme V-1).

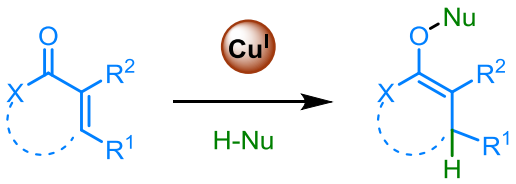


Scheme V-1. Reactivity of copper(I) and gold(I) complexes

I. Copper-Catalyzed Transfer of Nucleophiles on α,β-Unsaturated Carbonyls in One-Pot Processes: Context and Previous Work

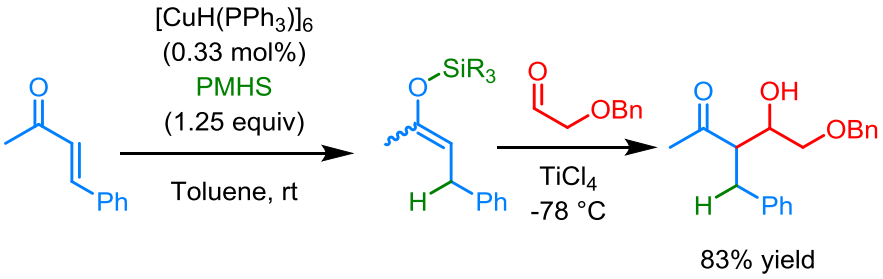
One of the first transformations studied in the field of copper(I)-mediated transfer of nucleophile was the reduction of Michael acceptors. While initially developed with stoichiometric amounts of copper hydride reagents,[42] this chemistry has rapidly evolved towards the elaboration of systems involving catalytic amounts of copper and silanes or boranes as the hydride donnors

(Scheme V-2). Detailled reviews on these developments are available and testify to their interest in the field of organic synthesis.[41,197]



Scheme V-2. Copper-catalyzed 1,4-reduction of Michael acceptors

The 1,4-addition of a copper(I) hydride species onto an enone generates a copper(I) enolate, which usually furnishes after trapping a silyl enol ether. While the first developments in this field usually hydrolysed this enol ether to deliver the ketone, the group of Lipshutz engaged this silyl enol ether in a Mukaiyama aldol reaction with an aldehyde (Scheme V-3).[198] This allowed the one-pot preparation of 1,4-reduction/aldolization products in good yields but in diasteromeric mixtures.



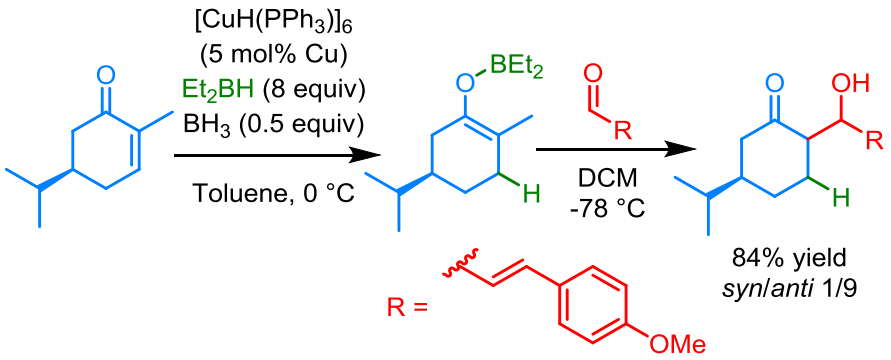
Scheme V-3. One-pot 1,4-reduction/aldolization of an enone by a copper reduction and Mukaiyama aldol reaction

---

[197] Selected reviews: (a) O. Riant, *Chemistry of Organocopper Compounds* (Wiley), **2009**, p. 731-773; (b) M. Shibasaki, M. Kanai, *Chem. Rev.* **2008**, *108*, 2853-2873; (c) S. Diez-Gonzalez, S. P. Nolan, *Acc. Chem. Res.* **2008**, *41*, 349-358.

[198] B. H. Lipshutz, W. Chrisman, K. Noson, P. Papa, J. A. Sclafani, R. W. Vivian, J. M. Keith, *Tetrahedron* **2000**, *56*, 2779-2788.

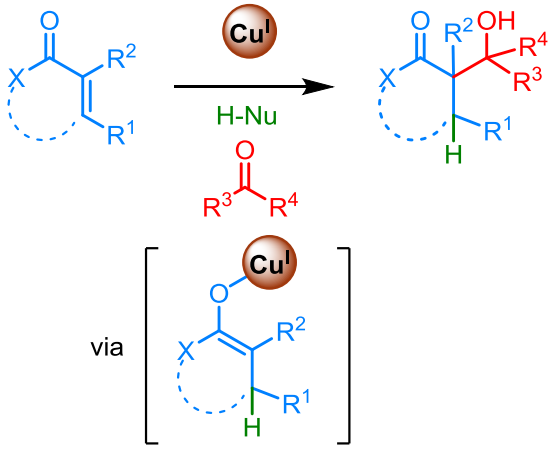
Using boranes as the hydride source allowed an improvement of this method, as good diastereomeric ratios were obtained and no additional Lewis acid had to be added for the Mukaiyama aldol reaction (Scheme V-4).[199]



Scheme V-4. One-pot 1,4-reduction/aldolization using a borane as the reducing agent

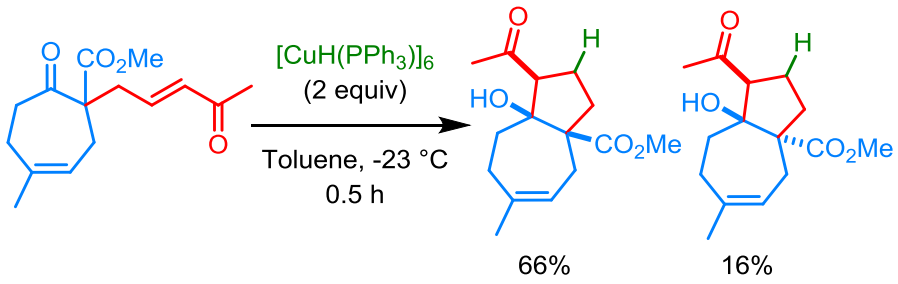
In these two examples, a stable enolate is produced in a stoichiometric amount. The production of this species is going through the generation of an intermediate copper enolate, which is then trapped with a silicon or boron species. Several research groups have focused their attention on the direct trapping of this enolate intermediate by an appropriate electrophile in order to obtain the desired compound via a domino process (Scheme V-5).

[199] B. H. Lipshutz, P. Papa, *Angew. Chem. Int. Ed.* **2002**, *41*, 4580-4582.



Scheme V-5. Copper-catalyzed 1,4-reduction/aldolization via a domino process

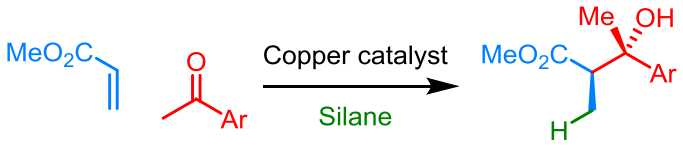
The group of Chiu was a pioneer in this area as they reported the first intramolecular 1,4-reduction/aldolization reaction using the Stryker's reagent as the hydride source (Scheme V-6).[200] The cyclized product was obtained with good yield and diastereoselectivity. Although this transformation uses a high amount of copper, it represents the first reported example of a copper-mediated reductive aldol process.



Scheme V-6. Diastereoselective intramolecular 1,4-reduction/aldolization of an enone

[200] (a) P. Chiu, B. Chen, K. F. Cheng, *Tetrahedron Lett.* **1998**, *39*, 9229-9232; (b) P. Chiu, C.-P. Szeto, Z. Geng, K.-F. Cheng, *Org. Lett.* **2001**, *3*, 1901-1903.

Application of this process in a catalytic fashion was reported by the groups of Shibasaki and Kanai[181] and by our group.[201] In the presence of a copper catalyst and a silane as the hydride source, the reductive coupling of methyl acrylate and aromatic ketones was made possible (Scheme V-7). The use of chiral ligands allowed the obtention of the desired product with good diastereo- and enantioselectivities.

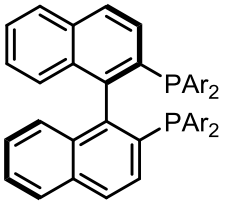


Shibasaki, Kanai and co-workers

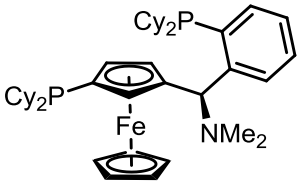
$CuF(PPh_3)_3{\cdot}2EtOH$ (5 mol%)
V.1 (5 mol%)
$(EtO)_3SiH$ (1.6 equiv)
THF, 0 °C, 12 h
100% yield
erythro/threo 55 : 45
29% *ee erythro*

Riant and co-workers

$CuF(PPh_3)_3{\cdot}2MeOH$ (1 mol%)
V.2 (1 mol%)
Ph_3SiH (1.6 equiv)
Toluene, -50 °C, 1 h
98% yield
erythro/threo 92 : 8
95% *ee erythro*



(R)-Binap **V.1**

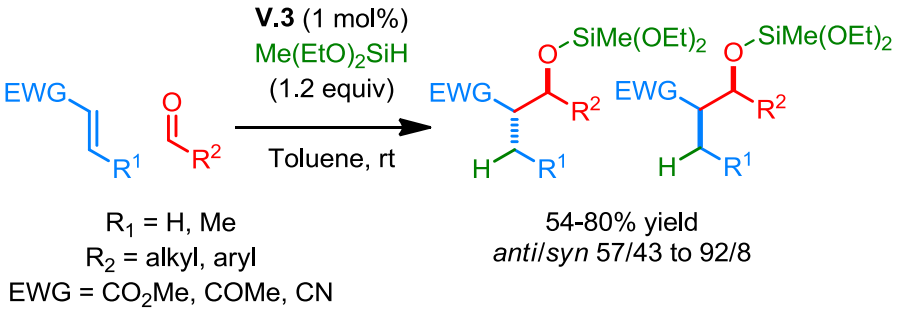


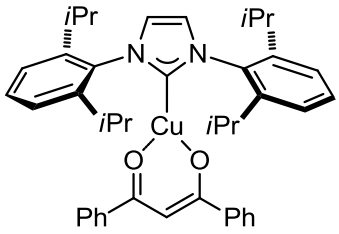
(R)-Taniaphos **V.2**

Scheme V-7. Reductive aldol coupling of methyl acrylate and aromatic ketones catalyzed by copper(I) complexes

[201] (a) J. Deschamp, O. Chuzel, J. Hannedouche, O. Riant, *Angew. Chem. Int. Ed.* **2006**, *45*, 1292-1297; (b) J. Deschamp, O. Riant, *Org. Lett.* **2009**, *11*, 1217-1220.

Our group also developed the analog transformation using aldehyde derivatives as electrophilic partners (Scheme V-8). [202] In this case, variable diastereoselectivities were obtained and the products were isolated as silicon-protected derivatives.





IPrCuDBM **V.3**

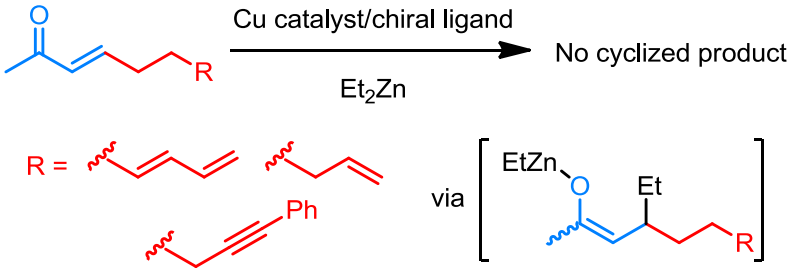
Scheme V-8. Reductive aldol coupling beteween Michael acceptors and aldehydes

The next step of such a strategy would be to develop a copper-catalyzed 1,4-addition/cyclization, on an unactivated carbon-carbon unsaturated bond. The group of Alexakis showed that the use of diethylzinc in the presence of a copper catalyst was uneffective to promote the cyclization onto a vinyl, dienyl or propargyl moiety (Scheme V-9).[203] On the other hand, the use of an

[202] (a) A. Welle, S. Díez-González, B. Tinant, S. P. Nolan, O. Riant, *Org. Lett.* **2006**, *8*, 6059-6062; (b) O. Chuzel, J. Deschamp, C. Chausteur, O. Riant, *Org. Lett.* **2006**, *8*, 5943-5946.

[203] K. Li, A. Alexakis, *Chem. - Eur. J.* **2007**, *13*, 3765-3771.

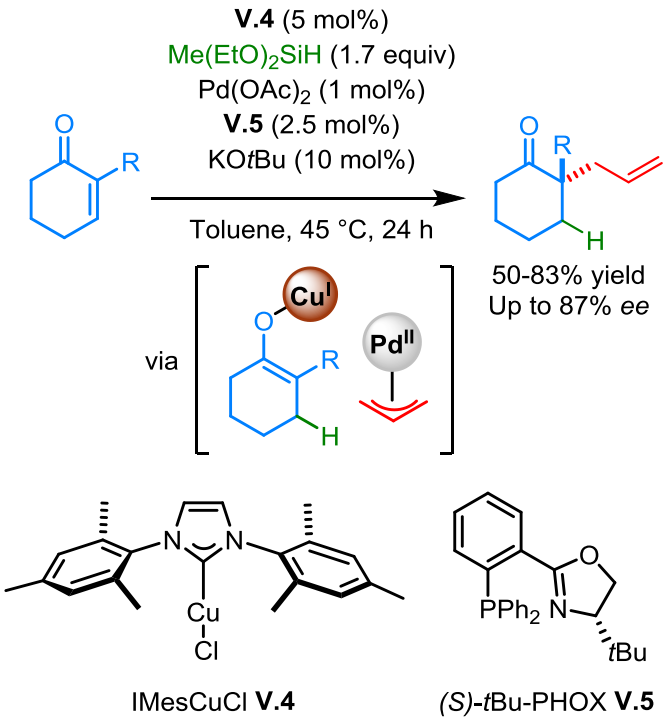
α,β-unsaturated ester as the second electrophile was found to be effective and cyclized products could be prepared in good yields.



Scheme V-9. Attempts of the copper-catalyzed conjugate addition/cyclization by the group of Alexakis

Finally, the possible trapping of the copper enolate intermediate by another organometallic species was envisioned. The dual catalysis process in which the 1,4-reduction of an enone is concomitant with the generation of a chiral π-allyl palladium species led to the formation of α-allylic enantioenriched ketones (Scheme V-10).[204]

[204] (a) F. Nahra, Y. Macé, D. Lambin, O. Riant, *Angew. Chem. Int. Ed.* **2013**, *52*, 3208-3212; (b) F. Nahra, Y. Macé, A. Boreux, F. Billard, O. Riant, *Chem. –Eur. J.* **2014**, *20*, 10970-10981.



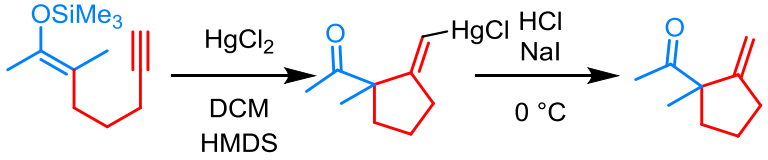
Scheme V-10. Cu/Pd dual catalysis for the enantioselective synthesis of allylated ketones

II. Gold-catalyzed Addition of Enolates on Unsaturated C-C Bonds

In the previous paragraph, we have shown that copper-catalyzed 1,4-reduction processes are well-known to deliver easily copper enolates that can be involved in further functionalization processes. However, the addition of enolates onto unactivated carbon-carbon unsaturations has not been reported using this strategy. Such reactions usually need the presence of an electrophilic activation of the double or triple bond.

Additions of silyl enol ethers onto unactivated C-C unsaturated bonds have been developed for decades with π-Lewis acidic metals as promoters. The

first example was reported in 1985 by the group of Drouin and Conia using mercury(II) chloride (Scheme V-11).[205] The analogous transformation on internal alkynes was reported in 1999 by Yamamoto and co-workers.[206]



Scheme V-11. Addition of a silyl enol ether on a mercury-activated alkyne (ref 205a)

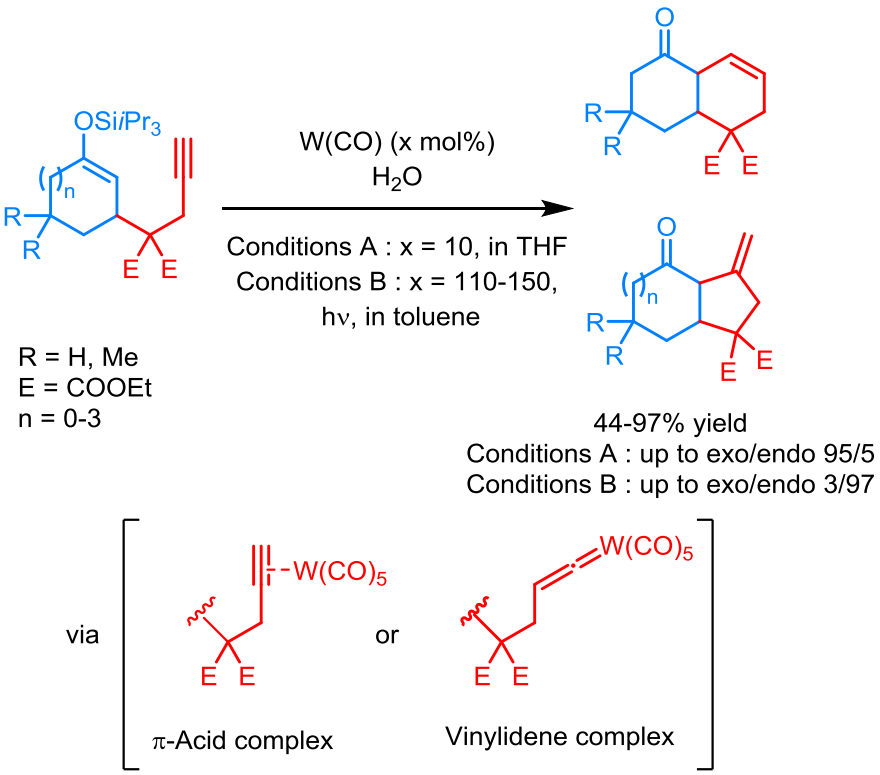
Tungsten pentacarbonyl $W(CO)_5$ was also used to catalyze the cyclization of silyl enol ethers onto unactivated alkynes. Several examples were reported by the group of Iwasawa (Scheme V-12)[207] In this case, an activation via a tungsten-alkyne π-acid complex was always confronted to the possible formation of a tungsten vinylidene.

---

[205] (a) J. Drouin, M. A. Boaventura, J. M. Conia, *J. Am. Chem. Soc.* **1985**, *107*, 1726-1729; (b) J. Drouin, M. A. Boaventura, *Tetrahedron Lett.* **1987**, *28*, 3923-3926.

[206] K.-i. Imamura, E. Yoshikawa, V. Gevorgyan, Y. Yamamoto, *Tetrahedron Lett.* **1999**, *40*, 4081-4084.

[207] (a) K. Maeyama, N. Iwasawa, *J. Am. Chem. Soc.* **1998**, *120*, 1928-1929 (b) N. Iwasawa, K. Maeyama, H. Kusama, *Org. Lett.* **2001**, *3*, 3871-3873; (c) N. Iwasawa, T. Miura, K. Kiyota, H. Kusama, K. Lee, P. H. Lee, *Org. Lett.* **2002**, *4*, 4463-4466.



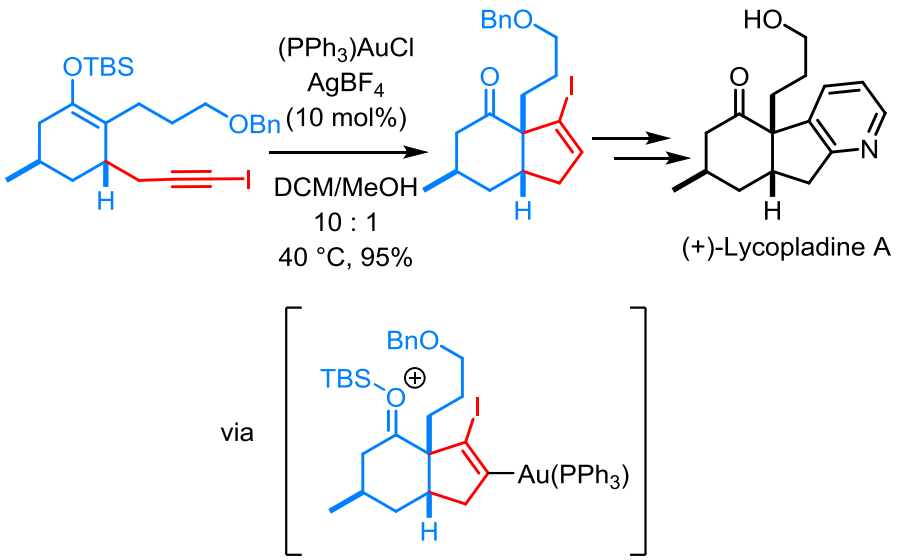
Scheme V-12. Tungsten-mediated addition of silyl enol ethers onto terminal alkynes (ref 207b)

Based on their previous work on gold-catalyzed Conia-ene cyclizations,[208] the group of Toste developed a general procedure for the cyclization of silyl enol ethers onto terminal, internal and functonalized alkynes.[209] This method was applied as a key step in the total synthesis of (+)-Lycopladine A in 2006

[208] J. J. Kennedy-Smith, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 4526-4527.

[209] (a) S. T. Staben, J. J. Kennedy-Smith, D. Huang, B. K. Corkey, R. L. LaLonde, F. D. Toste, *Angew. Chem. Int. Ed.* **2006**, *45*, 5991-5994; (b) E. C. Minnihan, S. L. Colletti, F. D. Toste, H. C. Shen, *J. Org. Chem.* **2007**, *72*, 6287-6289.

(Scheme V-13). A similar strategy was also applied by Nicolaou and co-workers in the total synthesis of Platencin.[210]

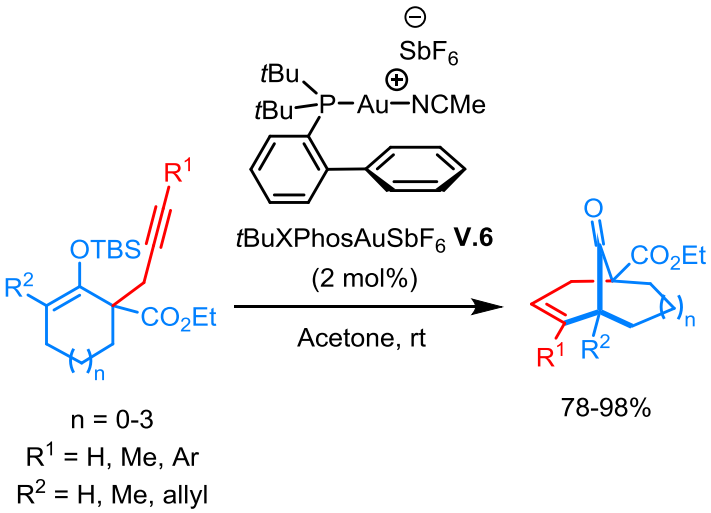


Scheme V-13. Gold-catalyzed cyclization as a key step in the synthesis of (+)-Lycopladine A (ref 209a)

Variants of this transformation were developed by several groups. The synthesis of fused bicycles was reported by Barriault and co-workers with a gold-catalyzed intramolecular addition of silyl enol ethers onto alkynes

[210] K. C. Nicolaou, G. S. Tria, D. J. Edmonds, *Angew. Chem. Int. Ed.* **2008**, *47*, 1780-1783.

(Scheme V-14).[211] The group of Mirguet and Michelet recently reported a similar cyclization using silyl dienol ethers as the substrates.[212]



Scheme V-14. Gold-catalyzed cyclization of silyl enol ethers onto alkynes (ref 211a)

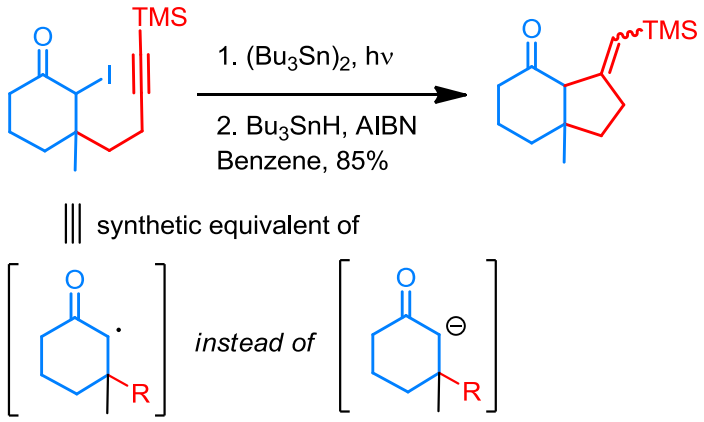
The same kind of cyclization based on radical chemistry was carried out by the group of Sha in the context of a total synthesis (Scheme V-15).[213] The strategy turned out to be effective for the synthesis of a 5-membered ring and is quite comparable to the methods cited previously.

---

[211] (a) F. Barabe, G. Betournay, G. Bellavance, L. Barriault, *Org. Lett.* **2009**, *11*, 4236-4238; (b) F. Barabe, P. Levesque, I. Korobkov, L. Barriault, *Org. Lett.* **2011**, *13*, 5580-5583.

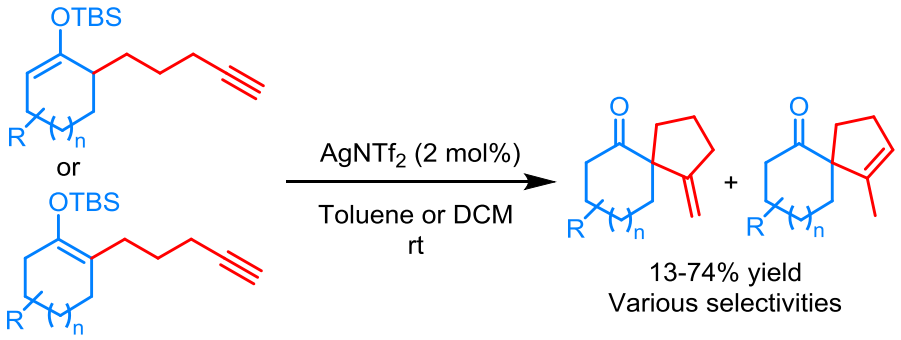
[212] A. Carrer, C. Pean, F. Perron-Sierra, O. Mirguet, V. Michelet, *Adv. Synth. Catal.* **2016**, *358*, 1540-1545.

[213] Y.-L. Kuo, M. Dhanasekaran, C.-K. Sha, *J. Org. Chem.* **2009**, *74*, 2033-2038.



Scheme V-15. Cyclization using a radical-based method

Finally, the use of a silver salt as the catalyst was showed to be efficient by the group of Miesch (Scheme V-16).[214] Various spirocycles could be prepared, with selectivities dependant on the used reaction conditions.

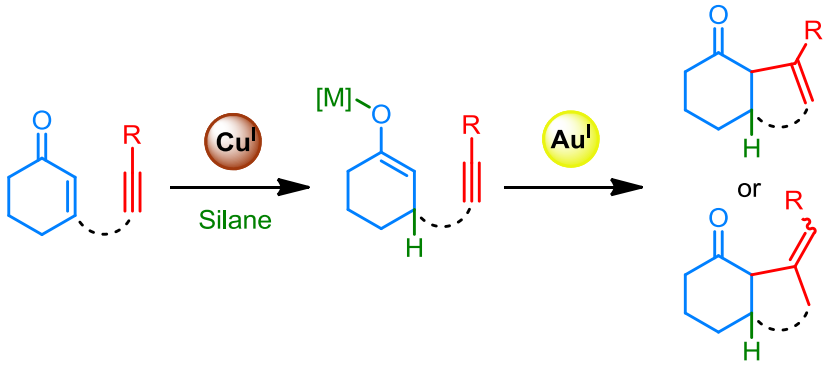


Scheme V-16. Silver-catalyzed cyclization of silyl enol ethers onto alkynes

[214] C. Schafer, M. Miesch, L. Miesch, *Chem. - Eur. J.* **2012**, *18*, 8028-8031.

III. Objectives of the Project

The previous paragraphs attest that copper(I) and gold(I) catalysis could be used as cooperative tools in a sequence of 1,4-reduction/addition of enones onto carbon-carbon unsaturations. Copper-catalyzed 1,4-reductions can be used to generate an enolate, which can then be subjected to gold catalysis to allow its intramolecular addition onto an alkyne (Scheme V-17). This would give an easy access to bicyclic structures which constitutes a synthetically interesting carbon skeleton.



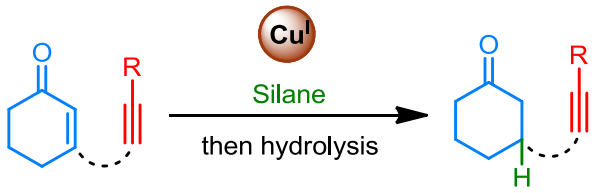
Scheme V-17. One-pot 1,4-reduction/addition of an enone onto an alkyne mediated by copper and gold complexes

The generation of a silicon-protected enol ether by copper catalysis will be studied first, in order to develop an appropriate substrate for gold catalysis. The extension of this method to a dual catalysis process where the copper enolate would directly react with the gold-activated alkyne is also envisioned.

IV. Results

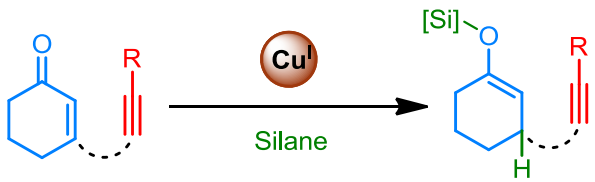
We will proceed step by step in order to elaborate our 1,4-reduction/addition reaction:

1) The 1,4-reduction of the enone followed by a hydrolysis will be tested first, and the resulting ketone will be isolated (Scheme V-18).



Scheme V-18. 1,4-reduction and hydrolysis of the enone

2) The 1,4-reduction of the enone will be applied alone in order to generate a silicon-protected enol ether, which in some cases might be isolated (Scheme V-19).



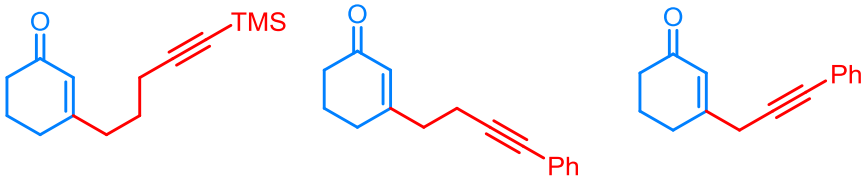
Scheme V-19. 1,4-reduction of the enone

3) The silyl enol ether isolated or generated in situ will be cyclized in the presence of a gold catalyst (Scheme V-17).

IV.1. First Substrates Synthesis and Tests

Substrates synthesis

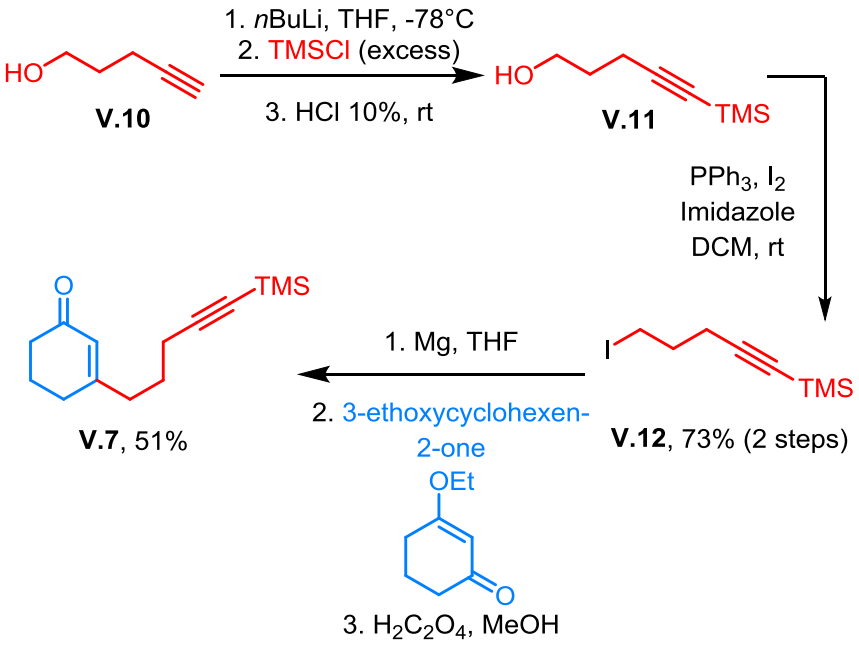
To start, we aimed to prepare enone substrates bearing an aliphatic chain on the β-position with an alkyne function. The three substrates we targeted are presented on Scheme V-20.



V.7 **V.8** **V.9**

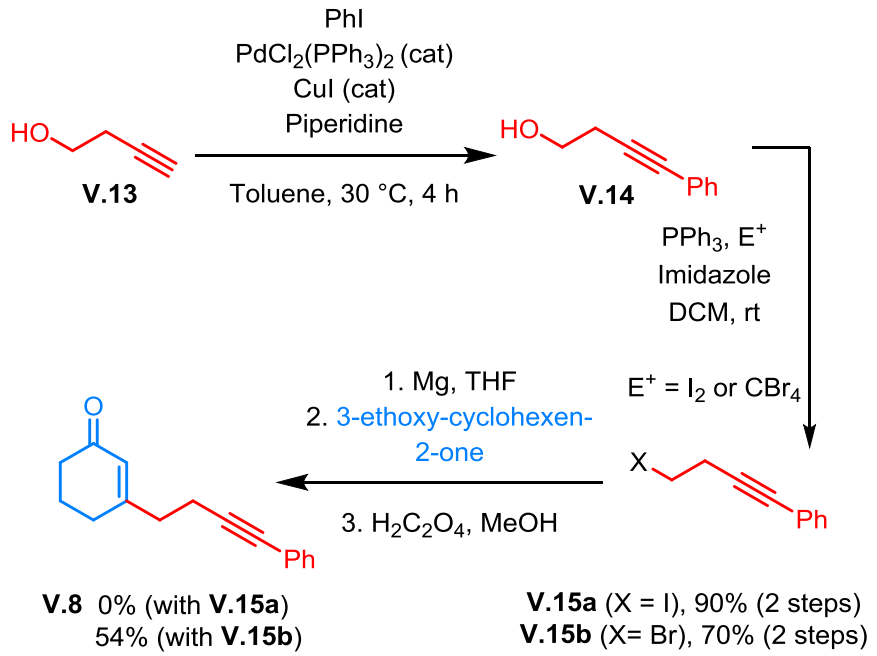
Scheme V-20. Targetted substrates for the study of the reaction

Substrate **V.7** was prepared as presented in Scheme V-21. A protection of alcohol **V.10** with a TMS group led to the formation of alcohol **V.11**. An Appel reaction allowed the synthesis of iodide **V.12** in good yield. Finally, this iodide was converted into a Grignard reagent, which was added onto 3-ethoxycyclohexen-2-one. After an acidic work-up with oxalic acid, the enone **V.7** was obtained in an acceptable yield.



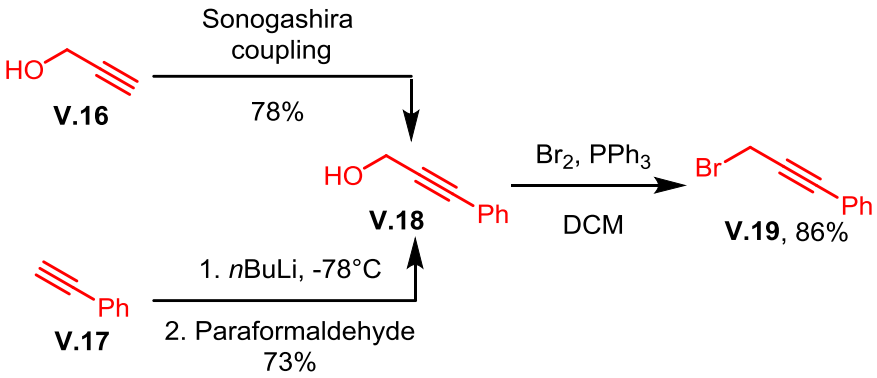
Scheme V-21. Synthesis of substrate **V.7**

A similar approach was used for the preparation of substrate **V.8** (Scheme V-22). A Sonogashira coupling between alkyne **V.13** and iodobenzene furnished alcohol **V.14**. The subsequent Appel reaction furnished iodide **V.15a** in 90% yield over 2 steps. Unfortunately, the previously used method did not allow us to obtain substrate **V.8** as expected. Using bromide **V.15b** as an alternative substrate allowed the preparation of the final compound.



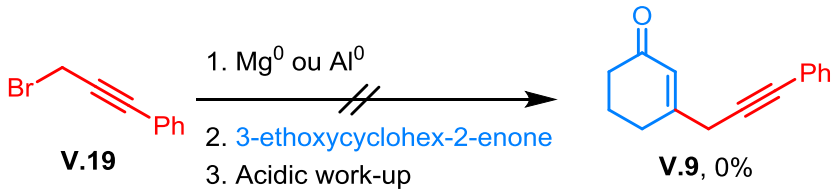
Scheme V-22. Synthesis of substrate **V.8**

Finally, the preparation of substrate **V.9** started by the synthesis of bromide **V.9** (Scheme V-23). This one could be obtained starting from propargyl alcohol **V.16** or phenylacetylene **V.17** which could both be converted easily into alcohol **V.18**. The Appel reaction yielded the desired bromide **V.19** in good yield.



Scheme V-23. Preparation of intermediate **V.19**

The conversion of this halide into an organometallic reagent was then attempted. Unfortunately, only complex mixtures were obtained using the standard procedure. Neither organomagnesium nor organoaluminium reagents led to the obtention of **V.9** (Scheme V-24). This is probably due to the instability of compound **V.9**, which possesses a very acidic proton on the propargylic and allylic position.



Scheme V-24. Attempts for the synthesis of enone **V.9**

Catalysis steps

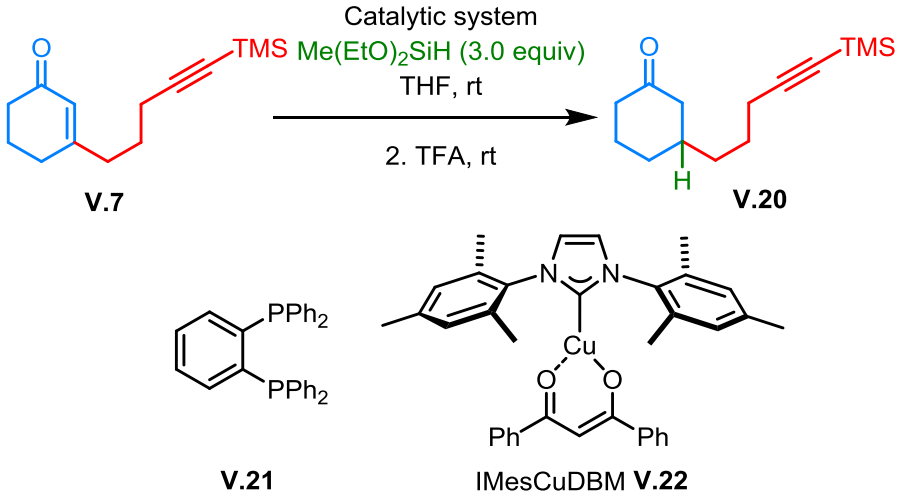
At this stage, we decided to test compounds **V.7** and **V.8** in copper-catalyzed 1,4-reduction processes. The results are presented in Table V-1.

The catalytic system reported by Lipshutz and co-workers[215] was initially tested. The mixture of BDP with $Cu(OAc)_2$ and in the presence of 3 equivalents of $Me(EtO)_2SiH$ allowed a partial conversion of enone **V.7** (entry 1). The addition of 3 equivalents *t*BuOH did not lead to a complete conversion (entry 2). To ensure the complete consumption of enone **V.7**, a higher amount of the ligand was used, and the concentration of the solution was increased (entry 3). In this case, a complete conversion was observed and the final ketone **V.20** was isolated in 68% yield. Another catalytic system based on the use of catalyst **V.22** in THF also led to a complete conversion (entry 4). Because of the stability of the copper catalyst **V.22** and its efficiency

[215] B. A. Baker, Ž. V. Bošković, B. H. Lipshutz, *Org. Lett.* **2008**, *10*, 289-292.

even in the absence of *t*BuOH, this last catalytic system was considered to be more convenient and was kept for further investigations.

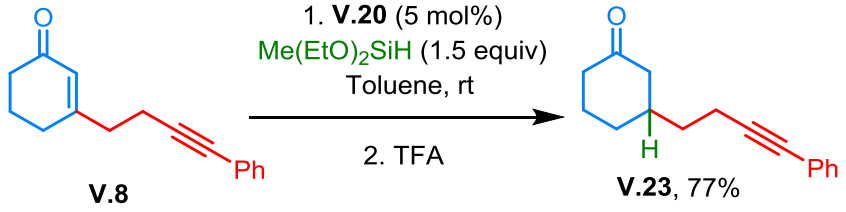
Table V-1. Tests for the 1,4-reduction of substrate **V.7**



Entry	Catalytic system	Additive	Solvent (Con-centration)	Conversion
1	$Cu(OAc)_2$ (5 mol%) **V.21** (0.5 mol%)	/	Toluene (0.16 $mol.L^{-1}$)	< 50%
2	$Cu(OAc)_2$ (5 mol%) **V.21** (0.5 mol%)	*t*BuOH (3 equiv)	Toluene (0.16 $mol.L^{-1}$)	< 50%
3	$Cu(OAc)_2$ (10 mol%) **V.21** (5 mol%)	*t*BuOH (3 equiv)	Toluene (0.70 $mol.L^{-1}$)	100% (68% yield)
4*	**V.22** (5 mol%)	/	THF (0.62 $mol.L^{-1}$)	100%

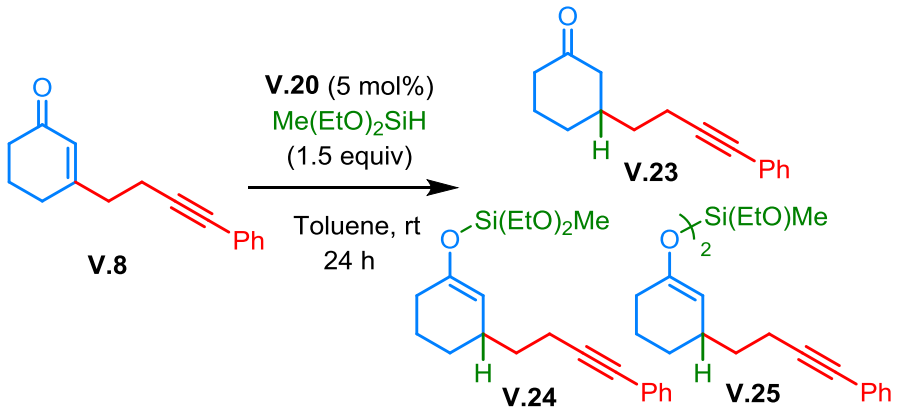
*1.7 equiv of silane were used

Using these last experimental conditions on substrate **V.8** led its 1,4-reduction to the ketone **V.23** in 77% yield.



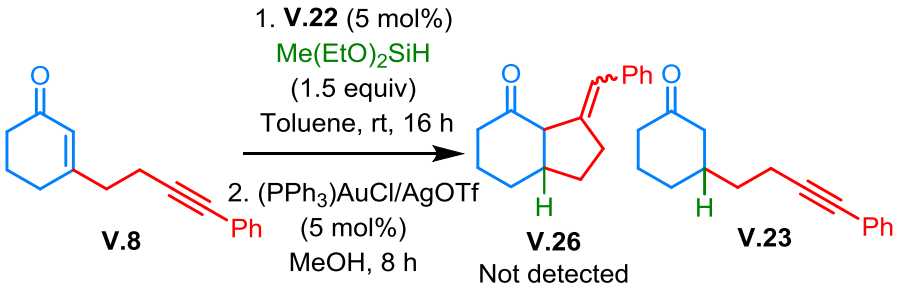
Scheme V-25. Copper-catalyzed reduction of the enone **V.8**

With this substrate, we decided to carry out the reduction without the subsequent hydrolysis (Scheme V-26). This experiment was carried out several times, and always led to similar results. The ratio between the different products are variable, which was attributed to the instability of the silyl enol ether on silica. The overall yield is around 60%. Three main products could be isolated: the 1,4-reduction/hydrolysis product **V.23**, and a mixture of two silyl enol ethers. The first one is product **V.24** which was expected. The second product was attributed to a silylated product where the silicon bears two enolate moieties (**V.25**). Even if these two structures are slightly different, their reactivity in gold catalysis conditions should remain similar, and thus they were used as a mixture for the next step.



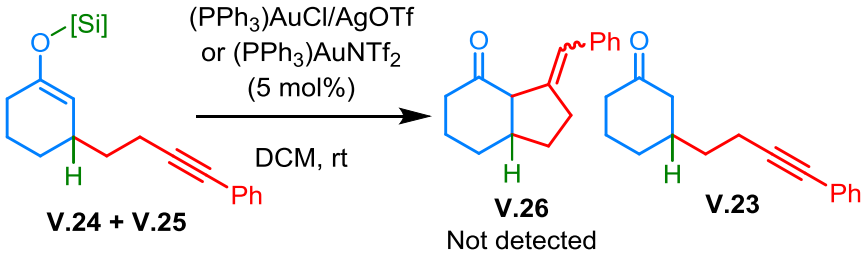
Scheme V-26. Copper-catalyzed 1,4-reduction of enone **V.8**

The next step was to attempt the copper-catalyzed 1,4-reduction and the gold-catalyzed cyclization in a one-pot fashion (Scheme V-27). After 16 h stirring in the reduction conditions, a gold catalyst was added with methanol and the mixture was stirred for an extra 8 h. Unfortunately, only some reduction product was identified in the crude mixture.



Scheme V-27. Attempt for the one-pot 1,4-reduction/cyclization of substrate **V.8**

The cyclization was also directly attempted on the mixture of silyl enol ethers previously isolated (Scheme V-28). Several catalytic systems were tried but again, only some reduction product was identified in the crude reaction mixture.

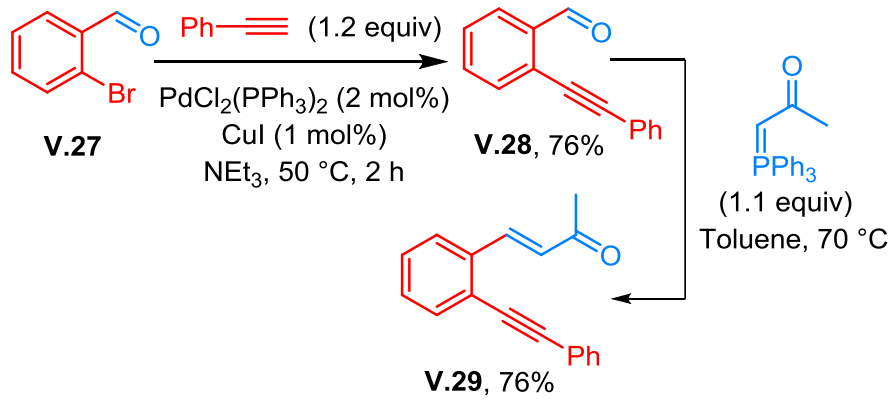


Scheme V-28. Attempt for a gold-catalyzed cyclization of silyl enol ether

We believe that the fast hydrolysis of the silyl enol ether prevents its cyclization into the desired compound **V.26**. In order to make the cyclization easier, we envisioned to try another substrate where both partner (silyl enol ether and alkyne) would adopt a conformation close to each other.

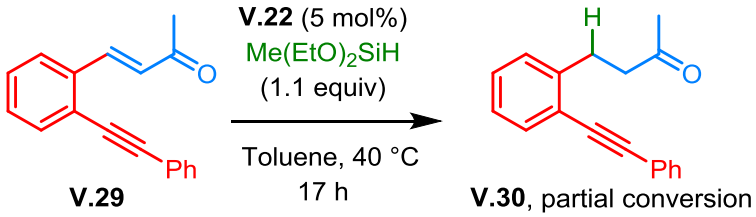
IV.2. Second Substrates Synthesis and Tests

The new substrate **V.29** was envisaged (Scheme V-29). Its synthesis started by a Sonogashira coupling between **V.27** and phenylacetylene, to yield the aldehyde **V.28**. The subsequent Wittig reaction led to the obtention of enone **V.29**.



Scheme V-29. Synthesis of substrate **V.29**

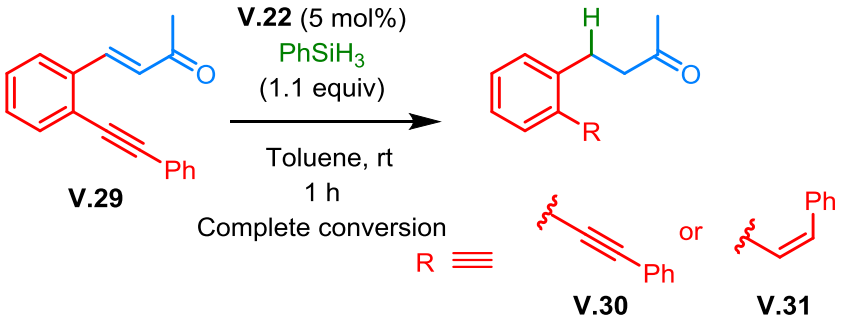
When the 1,4-reduction reaction was carried out, only a partial conversion was observed, which made the isolation of product **V.30** difficult (Scheme V-30).



Scheme V-30. Trial for the 1,4-reduction of substrate **V.28**

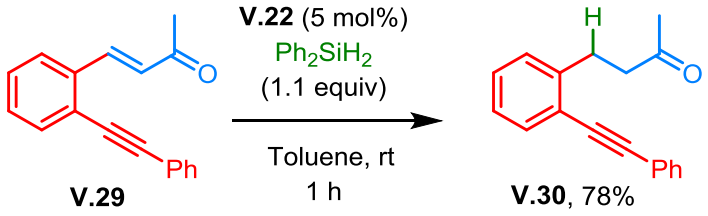
Other silanes were tested for this transformation. Phenyldimethylsilane did not lead to any conversion under the same reaction conditions. When phenylsilane was used, the reduction of the alkyne was observed as a side

reaction (Scheme V-31). Purification afforded mixtures of compound **V.30** with the overreduced form **V.31**.



Scheme V-31. 1,4-reduction of substrate **V.29** in the presence of phenylsilane

Using diphenylsilane Ph_2SiH_2 instead of phenylsilane still led to the formation of the overreduced product **V.31**, but isolation and characterization of the desired product was possible in this case (Scheme V-32).



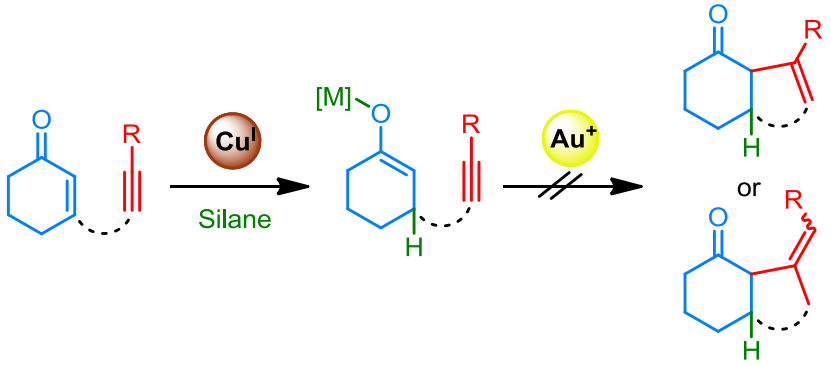
Scheme V-32. 1,4-reduction of substrate **V.29** in the presence of diphenylsilane

A preliminary test showed us that a one-pot 1,4-reduction/cyclization mediated by copper and gold complexes did not lead to the formation of an interesting product. As the reduction appeared to be less selective with this product than with the previous ones, we did not investigated further its reactivity.

V. Conclusions and Perspectives

In this chapter, a project combining copper(I) and gold(I) catalysis was initiated. Whereas the copper-catalyzed preparation of silyl enol ethers could be

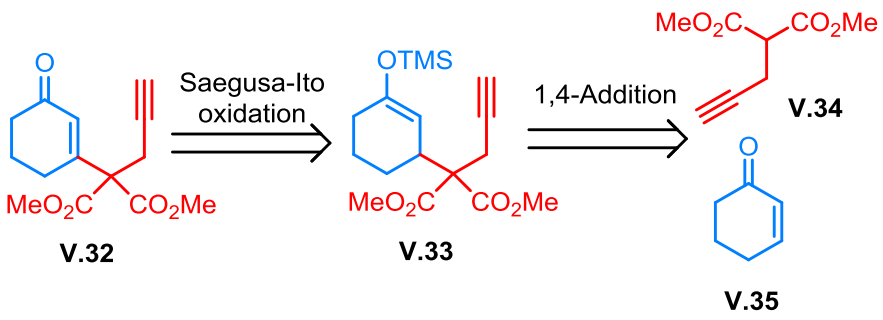
applied on our substrates, the products resulting from the gold catalysis haven't been observed so far (Scheme V-33).



Scheme V-33. 1,4-reduction/cyclization of enones mediated by copper and gold

As only a few tests have been carried out, we think that a lot of possibilities still remain for this project. The main problem encountered is the presumed low stability of the silyl enol ether in the reaction conditions. Silanes leading to more stable silyl enol ethers can be envisioned, such as phenyldimethylsilane or triethylsilane. Because these two silanes are less reactive, their transfer using copper might be more difficult to perform. Rhodium or palladium catalysis could be used instead, in order to efficiently generate the silyl enol ether and to validate our method.

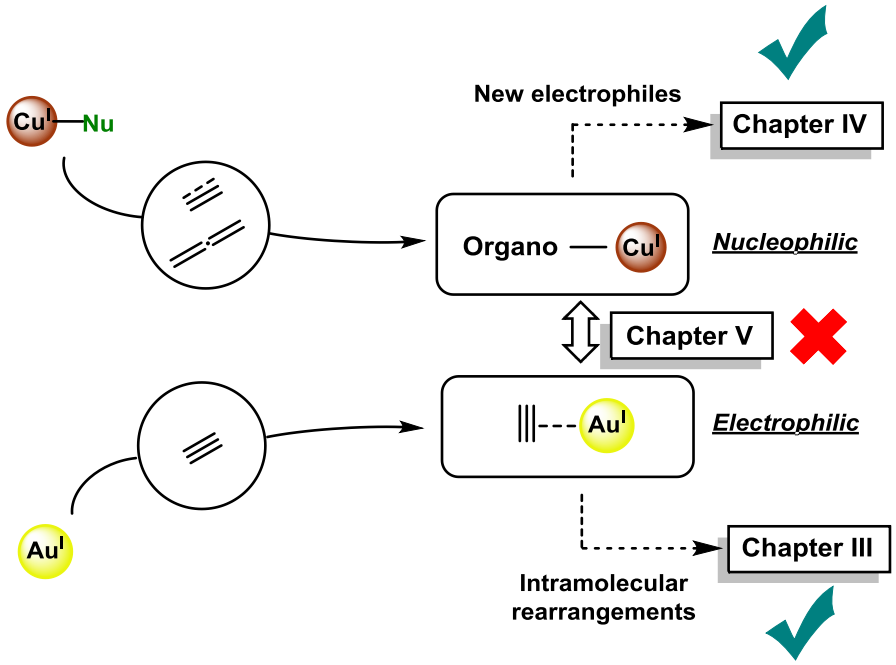
Besides, the use of substrates closer than those described in the literature can be envisioned as well. A lot of cyclization methods in gold catalysis rely on the use of a Thorpe-Ingold effect in order to bring the substrate into a favourable conformation.[209a] The preparation of a substrate of this type is described in Scheme V-34. Enone **V.32** could be prepared from silyl enol ether **V.33** by a Saegusa-Ito oxidation. This intermediate can be directly formed from propargyl malonate **V.34** and cyclohexanone **V.35**. As this substrate possesses several common structural features with the ones usually employed in literature,[209] it might be a better system to study the reaction.



Scheme V-34. Retrosynthesis of substrate **V.29**

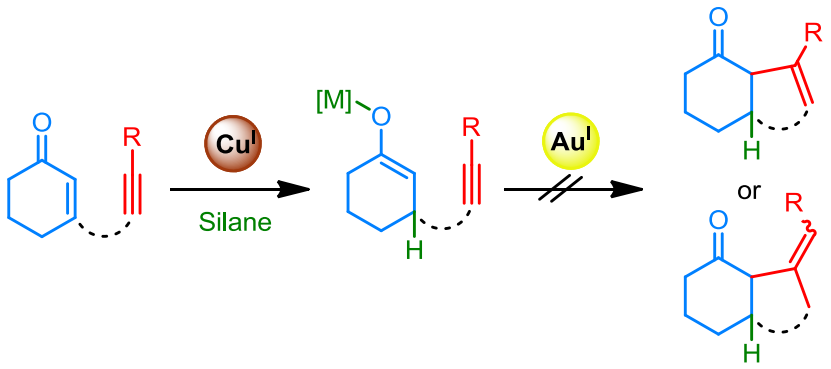
Chapter VI: General Conclusions

During this PhD, we had the opportunity to work on the developments of several methods involving gold(I) and copper(I) catalysis. The soft π-acidity of gold(I) complexes and the ability of copper(I) species to transfer nucleophiles were exploited throughout all this work (Scheme VI-1).



Scheme VI-1. Summary of the successful and unsuccessful projects during this PhD work

As shown in chapter V, the initial idea of combining the specific properties of gold(I) and copper(I) catalysis haven't led to any convincing result (Scheme VI-2). Our first investigations have allowed the elaboration of a work strategy to pursue this topic. Even if the desired transformation could not be observed, we are still convinced that several possibilities remain to be explored and have a real potential to allow this system to work.

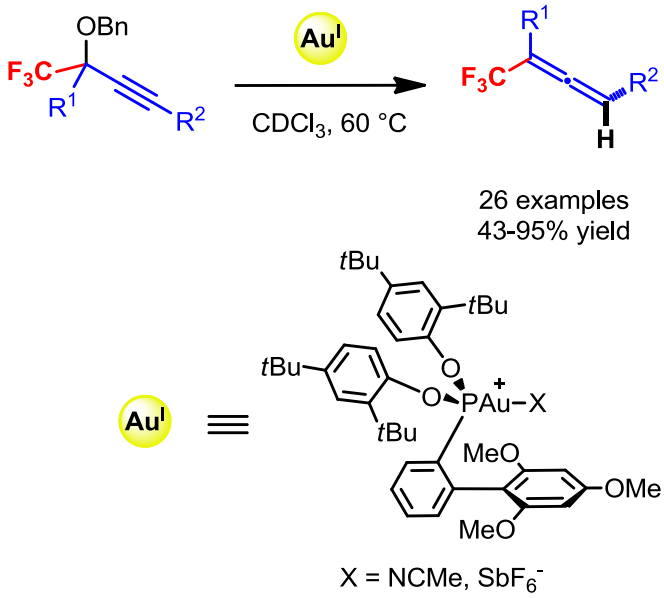


Scheme VI-2. 1,4-reduction/cyclization of enones mediated by copper and gold

Fortunately, this initial idea led us to explore the field of gold(I) and copper(I) catalysis separately in specific transformations, which allowed us to obtain more significant results.

In Chapter III, the gold-mediated activation of alkynes was applied to some intramolecular rearrangements, leading to the synthesis of interesting moieties. More particularly, we became interested in extending the scope of gold(I)-mediated transformations to the preparation of fluorinated synthetic intermediates. CF_3-allenes were prepared using a gold(I)-catalyzed hydride shift on trifluoromethyl- *O*-benzyl propargylic ethers. This transformation was optimized prior to be applied successfully on 26 examples (Scheme VI-3). The post-functionalization of these allenes was also studied in intra- and intermolecular fashions. The subsequent intramolecular reaction of an alcohol or an aromatic ring onto the gold-activated allene led to the preparation of CF_3-dihydrofurans and CF_3-indenes, respectively. Various intermolecular and transition metal-mediated transformations were also tested, with moderate success. Addition of boron- or silicon-based entities could be added onto a CF_3-allene using copper or palladium catalysis. Finally, the conversion of chirality during the 1,5-hydride shift process was demonstrated on the CF_3-substrates, but seemed to be very limited on standard *O*-benzyl propargylic ethers.

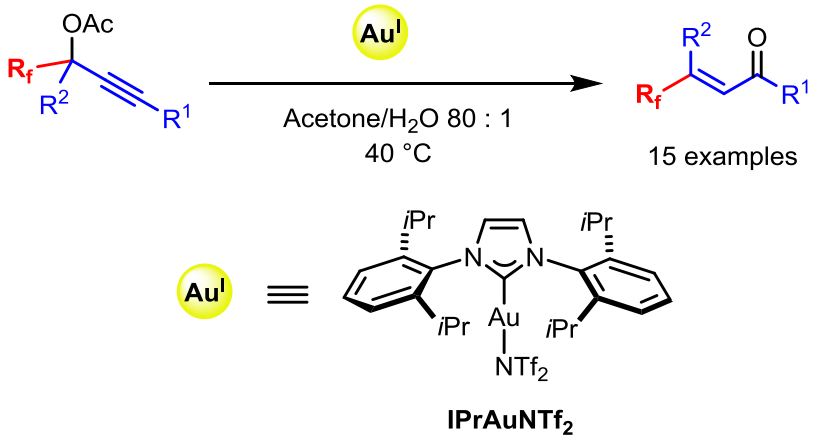
This very last point remains probably the point that can initiate several new projects, on standard allenes or on their trifluoromethylated analogs. As discussed at the end of Chapter III, the chirality transfer during the preparation or the application of allenes remains a subject of interest in the field, and the results we presented might initiate some promising pieces of research.



Scheme VI-3. Synthesis of CF_3-allenes by a gold-catalyzed hydride shift

On the other hand, the preparation of CF_3-enones was made possible using a gold-catalyzed [3,3]-acetate rearrangement. This optimized method was applied to the preparation of 14 disubstituted enones and 1 trisubstituted enone (Scheme VI-4). The involvement of this reaction in a one-pot process with other transformations such as a Diels-Alder reaction or a Michael addition was also successfully carried out. Even if the studied transformation was already well-known, we believe that its extension on CF_3-compounds displays advantages for some substrates and is therefore quite complementary to the other reported methods. This part of chapter is probably the one in this

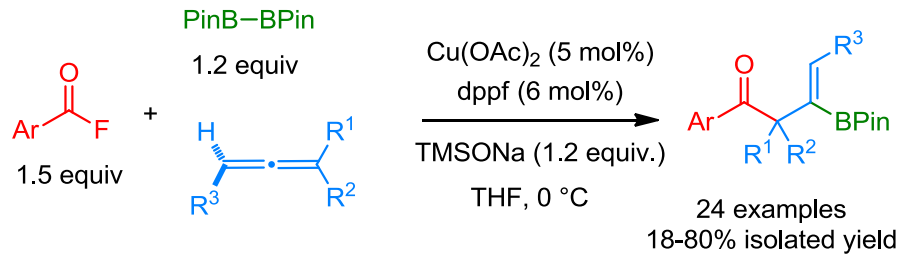
manuscript that won't lead to further developments, as it is itself an extension of an already known transformation.



Scheme VI-4. Synthesis of CF_3-enones by a gold-catalyzed acetate rearrangement

Finally, the chapter IV concerned the development of a new copper-catalyzed borofunctionalization method. The targeted boroamination reaction showed encouraging results, but most of the efforts were dedicated to the elaboration of a boroacylation method. After optimizing the reaction conditions, 24 β-boryl β,γ-unsaturated ketones were synthetized in modest to good yields (Scheme VI-5). Synthetic applications of these compounds still remain to be demonstrated.

As this chapter belongs to a topic of research which is currently in extension, the proposed perspectives of this work might be the object of future publications from other groups. However, we do believe that the valorization of the obtained products should be the object of further work in our group and could lead to particularly useful applications in the field of synthesis.



Scheme VI-5. Copper-catalyzed boroacylation of allenes

As it happens regularly in research, the most promising results were not obtained where they were expected. Whereas the initial objective of this work has not been reached and finally constitutes a minor chapter of this manuscript, it has opened the doors to unexpected projects and led to the obtention of exciting results in the related topics. Besides, these topics have allowed a revaluation *a posteriori* of the initial project with new and promising perspectives.

This last consideration closes this manuscript, associating the satisfaction of the developed methods to the hope of seeing someday the achievement of the perspectives they inspired.

Chapter VII: Experimental Part

I. General information

Characterized compounds

Most of the projects of this PhD work were carried out in collaboration with other researchers from one of the two laboratories. Although the whole projects were presented in the theoritcal part, only the products that were prepared by the author of this manuscript are presented in the experimental part. Due to the high number of compounds synthetized, only the final substrates, the compounds prepared by the studied catalytic steps and the inedited catalysts are described here. The isolation of the synthetic intermediates was confirmed by standard NMR spectroscopy methods, but their data is not reported here.

General methods and characterization parameters

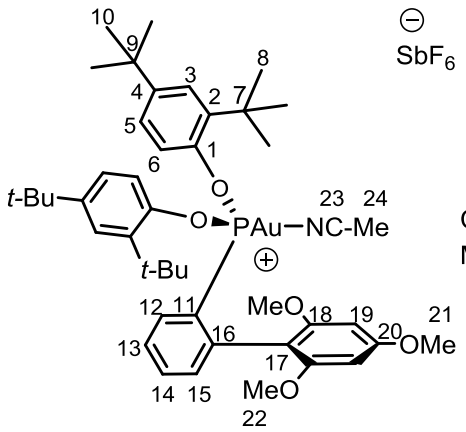
Unless otherwise noted, all reactions for the synthesis of substrates were performed under dry oxygen-free argon or nitrogen atmosphere. The scope of the gold-catalyzed reaction was carried out using deuterated chloroform dried on molecular sieves. Gold-catalyzed reactions were performed in an NMR tube using dichloroethane as an internal standard or in vials (under air). Thin Layer Chromatography were performed on aluminium plates bearing a 0.25 mm of Merck Silica Gel $60F_{254}$, visualized by fluorescence quenching at 254 nm and chemical revelation using acidic solution of para-anisaldehyde or basic solution of potassium permanganate. Flash chromatography was performed using silica gel 60 (40-63 µm). Commercial reagents were purchased from Acros, Fluorochem, TCI, Sigma-Aldrich, Alfa-Aesar and used as received. NMR analysis was performed at room temperature on Bruker DPX 300 MHz Fourier Transform Spectrometer operating at 300 /400/500 MHz for ^{1}H, 75/100/125 MHz for ^{13}C, 282 MHz for ^{19}F and 121

MHz for ^{31}P. Residual solvent peaks of $CDCl_3$ were used as internal references: 7.26 ppm for ^{1}H spectra and 77.16 ppm for ^{13}C spectra. The following abbreviations were used in order to describe de peaks multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, hex = hexuplet, hept = heptuplet, m = multiplet, br = broad. High resolution mass spectra were recorded by on a JMS-GCmateII mass spectrometer or on a Thermo Scientific QExactive. Infrared absorption was recorded as a liquid deposition on a ZnSe crystal on a Shimadzu FTIR 8400 Spectrophotometerspectra or in solutions in CCl_4 or $CDCl_3$ using NaCl cells on a Perkin-Elmer FT 2000 or Perkin-Elmer Spectrum Two.

II. Chapter III.II: Synthesis of Trifluoromethylated Allenes by Gold(I)-Catalyzed Hydride Shift

Preparation of the catalyst III.12

The phosphonite ligand as well as the corresponding LAuCl complex were prepared according to a literature procedure.[13b]



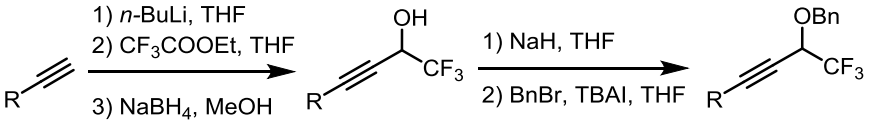
To a solution of $AgSbF_6$ (1 equiv) dissolved in a mixture of dry DCM and acetonitrile (DCM/MeCN 3:1, 0.1 mol.L^{-1}) was added a solution of [(Phosphonite)AuCl] (1 eq) in dry DCM (0.1 mol.L^{-1}) under nitrogen. The mixture was stirred 15 minutes at room temperature in the dark, then filtered on a pad of Celite®. The solvents were evaporated, then the **III.12** complex was washed with pentane to be obtained as a white solid.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	8.19 – 8.14 (m, 1H, H_{Ar}), 7.71 (t, *J* = 7.5 Hz, 1H, H_{Ar}), 7.60 (t, *J* = 7.5 Hz, 1H, H_{Ar}), 7.38 (s, 2H, H_3), 7.30 (t, *J* = 7.8 Hz, 1H, H_{Ar}), 7.20 – 7.18 (m, 4H, H_{5+6}), 6.35 (s, 2H, H_{19}), 3.95 (s, 3H, H_{21}), 3.63 (s, 6H, H_{22}), 2.41 (s, 3H, H_{24}), 1.30 (s, 2x18H, H_{8+10})
^{1}H NMR (δ, ppm) (400 MHz, CD_2Cl_2)	8.17 – 8.13 (m, 1H, H_{Ar}), 7.74 (t, *J* = 7.6 Hz, 1H, H_{Ar}), 7.62 (t, *J* = 7.7 Hz, 1H, H_{Ar}), 7.43 (s, 2H, H_3), 7.32 (t, *J* = 7.4 Hz, 1H, H_{Ar}), 7.20 – 7.18 (m, 2H, H_{5or6}), 7.14 – 7.12 (m, 2H, H_{5or6}), 6.31 (s, 2H, H_{19}), 3.91 (s, 3H, H_{21}), 3.62 (s, 6H, H_{22}), 2.41 (s, 3H, H_{24}), 1.31 (s, 18H, H_{8or10}), 1.29 (s, 18H, H_{8or10})
^{13}C NMR (δ, ppm) (75 MHz, CD_2Cl_2)	163.4 (C_{20}), 159.6 (C_{18}), 149.5 (d, *J* = 6.2 Hz, C_1), 146.6 (C_4), 139.7 (d, *J* = 6.2 Hz, C_2), 139.4 (d, *J* = 27.3 Hz, C_{16}), 134.4 (C_{Ar}), 134.3 (d, *J* = 11.7 Hz, C_{Ar}), 131.1 (d, *J* = 3.7 Hz, C_{Ar}), 128.6 (d, *J* = 9.1 Hz, C_{Ar}), 125.9 (C_{3orC5}), 124.7 (C_{3orC5}), 121.1 (C_{23}), 118.9 (d, *J* = 12.2 Hz, C_6), 109.1 (d, *J* = 10.7 Hz, C_{17}), 91.4 (C_{19}), 56.3 (C_{22}), 56.2 (C_{21}), 35.4 (C_{7or9}), 35.1 (C_{7or9}), 31.6 (C_{8or10}), 30.5 (C_{8or10}), 2.8 (C_{24}) The peak corresponding to C_{11} couldn't be observed because of its low intensity
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-79.6
^{31}P NMR (δ, ppm) (121 MHz, $CDCl_3$)	115.8
IR (cm^{-1}, $CDCl_3$)	2966 (s), 2908 (m), 2871 (m), 2333 (m), 2305 (w), 2258 (s), 1606 (s), 1584 (s), 1490 (s), 1463 (s), 1430 (m), 1415 (m), 1398 (m), 1365 (m), 1338 (m), 1274 (w), 1227 (s), 1206 (s), 1183 (s), 1158 (s), 1128 (s),

1079 (s), 1034 (w)

Preparation of the starting materials

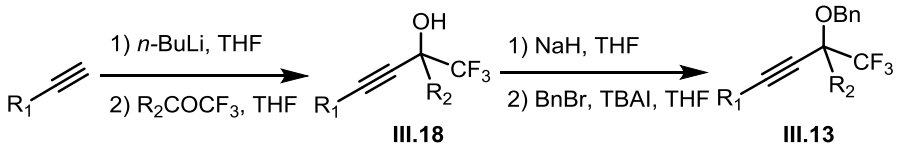
Procedure A for the preparation of α-trifluoromethyl secondary propargylic benzyl ethers:



To a solution of alkyne (1.0 eq) in THF (0.5 M) was added dropwise *n*-BuLi (1.1 equiv) at -78 °C. The mixture was stirred for 1 h at -78 °C and ethyl trifluoroacetate (1.5 equiv) was added. After the complete consumption of the alkyne (TLC), the mixture was diluted with MeOH (same volume than THF). The mixture was allowed to warm up to 0 °C and $NaBH_4$ (1.0 equiv) was added. The mixture was stirred overnight while warming up to room temperature. The reaction was then quenched with a saturated solution of NH_4Cl, extracted with Et_2O (x3), washed with water (x3) and brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the α-trifluoromethyl secondary propargylic alcohol. If necessary, the crude alcohol **III.18** was purified by flash column chromatography.

To a solution of the alcohol dissolved in THF (0.5 M) was added NaH (1.1 equiv) at 0 °C. Upon the end of the H_2 formation, benzyl bromide (1.2 equiv) and TBAI (0.05 equiv) were added. The mixture was stirred overnight while warming up to room temperature. The reaction was quenched with a saturated solution of NH_4Cl, extracted with Et_2O (x3), washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography gave the pure α-trifluoromethyl secondary propargylic benzyl ether **III.13**.

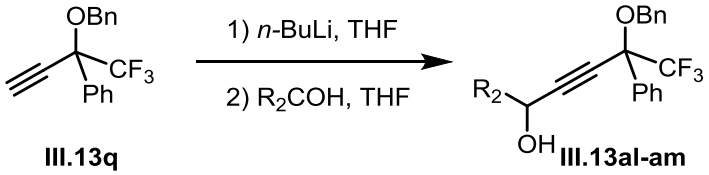
Procedure B for the preparation of α-trifluoromethyl tertiary propargylic benzyl ethers:



To a solution of alkyne (1.0 equiv) in THF (0.5 M) was added dropwise *n*-BuLi (1.1 equiv) at -78 °C. The mixture was stirred for 1 h at -78 °C and the trifluoromethyl ketone (1.0 equiv) was added. After the complete consumption of the alkyne (TLC), the mixture was quenched with a saturated solution of NH_4Cl, extracted with Et_2O (x3), washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography gave the pure α-trifluoromethyl tertiary propargylic alcohol **III.18**.

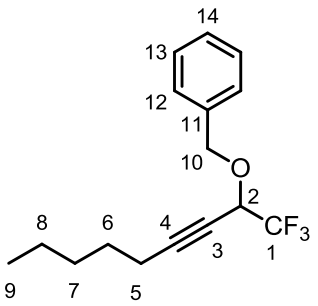
To a solution of the resulting alcohol (1.0 equiv) in THF (0.5 M) was added NaH (1.1 equiv) at 0 °C. Upon the end of the H_2 formation, benzyl bromide (1.2 equiv) and TBAI (0.05 equiv) were added. The mixture was stirred overnight while warming up to room temperature. The reaction was then quenched with a saturated solution of NH_4Cl, extracted with Et_2O (x3), washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography gave the pure α-trifluoromethyl tertiary propargylic benzyl ethers **III.13**.

Procedure C for the synthesis of propargylic alcohols-containing substrates:



To a solution of (2-(benzyloxy)-1,1,1-trifluorobut-3-yn-2-yl)benzene **III.13q** (1.0 equiv) in THF (0.5 M) was added dropwise *n*-BuLi (1.05 equiv) at -78 °C. The mixture was stirred 20 min at -78 °C and the carbonyl compound was added. After the complete conversion of the alkyne (TLC), the mixture was allowed to warm up at room temperature. The reaction was quenched with a saturated solution of NH_4Cl, extracted with Et_2O (x3), washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography afforded the pure α-trifluoromethyl tertiary propargylic benzyl ethers **III.13al-am**.

(((1,1,1-trifluorononon-3-yn-2-yl)oxy)methyl)benzene (III.13a)



$C_{16}H_{19}F_3O$
M = 284.32 g.mol^{-1}

Following procedure A starting with *n*-heptyne.

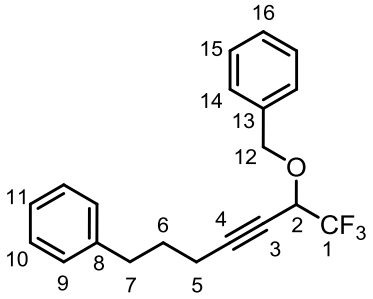
Flash chromatography: pure PE to PE/Et_2O 95 : 5.

Overall yield: 1.78 g (64 %) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.40 – 7.36 (m, 5H, H_{Ar}), 4.86 (d, *J* = 11.9 Hz, 1H, H_{10}), 4.69 (d, *J* = 11.9 Hz, 1H, $H_{10'}$), 4.48 (qt, *J* = 5.9, 2.1 Hz, 1H, H_2), 2.29 (td, *J* = 7.1, 2.1 Hz, 2H, H_5), 1.62 – 1.54 (m, 2H, H_6), 1.50 – 1.31 (m, 4H, H_{7+8}), 0.93 (t, *J* = 7.1 Hz, 3H, H_9)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	136.4 (C_{11}), 128.7 (C_{Ar}), 128.4 (C_{14}), 128.3 (C_{Ar}), 122.8 (q, *J* = 281.1 Hz, C_1), 90.6 (C_4), 71.0 (C_{10}), 70.5 (q, *J* = 2.3 Hz, C_3), 67.7 (q, *J* = 35.0 Hz, C_2)), 31.1 (C_7), 28.0 (C_6), 22.3 (C_8), 18.8 (C_5), 14.1 (C_9)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-78.0

IR (cm^{-1}, CCl_4)	2960 (w), 3033 (w), 3068 (m), 2959 (m), 2933 (m), 2874 (m), 2863 (m), 2238 (w), 1497 (w), 1456 (m), 1373 (w), 1275 (m), 1185 (s), 1158 (s), 1140 (s), 1090 (m)
MS (HRMS EI)	Calcd for $C_{16}H_{19}F_3O$: 284.1388 Found: 284.1388

(6-(benzyloxy)-7,7,7-trifluorohept-4-yn-1-yl)benzene (III.13g)



$C_{20}H_{19}F_3O$
Molecular Weight: 332.36 $g.mol^{-1}$

Following procedure A starting with 5-phenyl-1-pentyne (10.00 mmol).

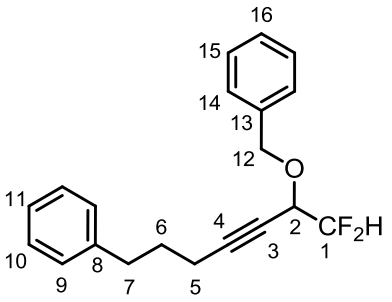
Flash chromatography: pure PE to PE/Et_2O 95 : 5.

Overall yield: 1.90 g (57 %) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.41 – 7.29 (m, 7H, H_{Ar}), 7.24 – 7.20 (m, 3H, H_{Ar}), 4.88 (d, J = 11.9 Hz, 1H, H_{12}), 4.71 (d, J = 11.9 Hz, 1H, $H_{12'}$), 4.51 (qt, J = 5.9, 2.1 Hz, 1H, H_2), 2.78 – 2.74 (m, 2H, H_7), 2.31 (td, J = 7.0, 2.0 Hz, 2H, H_5), 1.94 – 1.86 (m, 2H, H_6)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	141.3 (C_8), 136.3 (C_{13}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 126.2 (C_{Ar}), 122.8 (q, J = 281.2 Hz, C_1), 90.0 (C_4), 71.1 (q, J = 2.5 Hz, C_3), 71.1 (C_{12}), 67.7 (q, J = 35.0 Hz, C_2), 34.8 (C_7), 30.0 (C_6), 18.2 (C_5)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-78.0
IR (cm^{-1}, CCl_4)	3067 (w), 3030 (m), 2956 (m), 2865 (m), 2238 (w), 1497 (m), 1455 (m), 1274 (s), 1185 (s), 1157 (s), 1138 (s), 1090 (s)

MS (HRMS EI)	Calcd for $C_{20}H_{19}F_3O$: 332.1388	Found: 332.1390

(6-(benzyloxy)-7,7-difluorohept-4-yn-1-yl)benzene (III.13k)



$C_{20}H_{20}F_2O$
M = 314.37 g.mol^{-1}

Following procedure A starting with 5-phenylpent-1-yne and using ethyl difluoroacetate instead of ethyl trifluoroacetate.

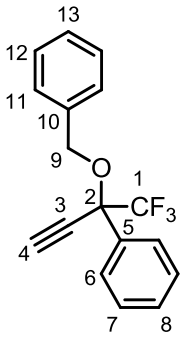
Flash chromatography: pure PE to PE/EtOAc 95 : 5.

Overall yield: 251 mg (66 %) of a pale yellow oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.38 – 7.29 (m, 7H, H_{Ar}), 7.22 – 7.18 (m, 3H, H_{Ar}), 5.74 (td, *J* = 55.7, 4.3 Hz, 1H, H_1), 4.85 (d, *J* = 11.8 Hz, 1H, H_{12}), 4.63 (d, *J* = 11.8 Hz, 1H, $H_{12'}$), 4.34 – 4.27 (m, 1H, H_2), 2.75 (t, *J* = 7.3 Hz, 2H, H_7), 2.30 (td, *J* = 7.2, 2.0 Hz, 2H, H_5), 1.88 (p, *J* = 7.2 Hz, 2H, H_6)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	141.4 (C_8), 136.8 (C_{13}), 128.7 (C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.3 (C_{Ar}), 128.3 (C_{Ar}), 126.1 (C_{Ar}), 113.8 (t, *J* = 246.2 Hz, C_1), 89.8 (C_4), 72.8 (dd, *J* = 6.7, 3.2 Hz, C_3), 71.0 (C_{12}), 69.0 (t, *J* = 27.5 Hz, C_2), 34.8 (C_7), 30.1 (C_6), 18.3 (C_5)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-126.0 (ddd, *J* = 284.2, 55.8, 9.6 Hz), -128.1 (ddd, *J* = 284.2, 55.8, 9.6 Hz)
IR (cm^{-1}, CCl_4)	3088 (w), 3067 (w), 3030 (m), 2928 (s, br), 2860 (m), 2238 (w), 1945 (w), 1870 (w), 1806 (w), 1746 (w), 1604 (w), 1497 (m), 1455 (m), 1382 (m), 1305 (m), 1264 (m), 1100 (s), 1029 (m)
MS	Calcd for $C_{20}H_{20}F_2O$: 314.1482	Found: 314.1490

(HRMS EI)

(2-(benzyloxy)-1,1,1-trifluorobut-3-yn-2-yl)benzene (III.13q)



$C_{17}H_{13}F_3O$
M = 290.28 g.mol^{-1}

Following procedure B starting using a commercial solution of ethynylmagnesium bromide (0.5 M in THF, 1.1 equiv, 11 mmol) and 2,2,2-trifluoroacetophenone (10.00 mmol).

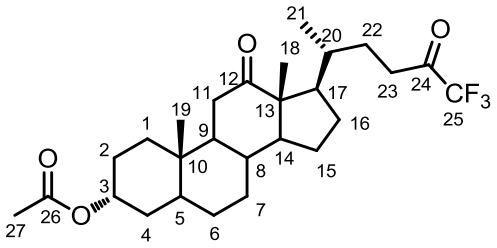
Flash chromatography: pure PE to PE/EtOAc 98 : 2.

Overall yield: 1.19 g (41 %) of a pale yellow oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.82 – 7.80 (m, 2H, H_{Ar}), 7.48 – 7.45 (m, 3H, H_{Ar}), 7.43 – 7.30 (m, 5H, H_{Ar}), 4.84 (d, *J* = 11.1 Hz, 1H, H_9), 4.44 (d, *J* = 11.1 Hz, 1H, $H_{9'}$), 2.95 (s, 1H, H_4)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	137.2 (C_{10}), 133.2 (C_5), 130.0 (C_{Ar}), 128.6 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 128.0 (C_{Ar}), 127.7 (C_{Ar}), 122.9 (q, *J* = 285.2 Hz, C_1), 79.6 (C_4), 79.5 (q, *J* = 31.4 Hz, C_2), 76.5 (C_3), 67.8 (C_9)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-79.5
IR (cm^{-1}, CCl_4)	3308 (m), 3093 (w), 3069 (w), 3034 (w), 2936 (w), 2875 (w), 2125 (w), 1499 (m), 1452 (m), 1384 (w), 1274 (s), 1191 (s), 1119 (s), 1102 (s), 1061 (s)
MS (HRMS EI)	Calcd for $C_{17}H_{13}F_3O$: 290.0918 Found: 290.0912

315

(3R,10S,13R,17R)-10,13-dimethyl-12-oxo-17-((R)-6,6,6-trifluoro-5-oxohexan-2-yl)hexadecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate



$C_{27}H_{39}F_3O_4$
M = 484.59 g.mol^{-1}

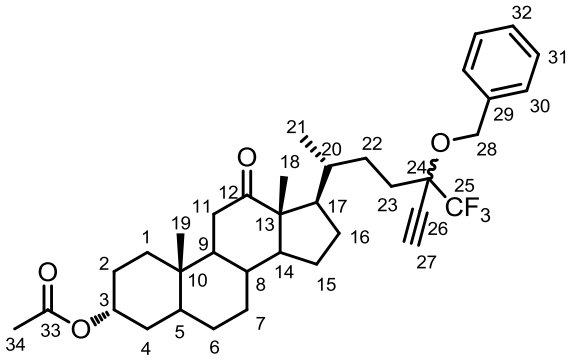
The trifluoromethyl ketone was prepared according to a literature procedure from the corresponding carboxylic acid.[216] To a solution of bile acid (1.00 equiv, 2.0 mmol, 865.1 mg) in DCM (14 mL) was added oxalyl chloride (1.00 equiv, 3.60 mmol, 457.0 mg, 0.31 mL) at room temperature. A drop of DMF was then added and the solution was stirred 1h at room temperature. The solvent and the excess of oxalyl chloride were evaporated under a flux of nitrogen. DCM (28 mL) was added and the solution was cooled to 0 °C. TFAA (5.80 equiv, 11.60 mmol, 2.436 g, 1.61 mL) was added, followed by a dropwise addition of pyridine (7.9 equiv, 26.07 mmol, 2.06 g, 2.10 mL). The mixture was stirred 3 hours (0 °C to rt) and was then carefully poured onto an ice/water mixture under stirring. The layers were separated, and the aqueous phase was extracted twice with DCM. The organic phases were washed with HCl (1M) and with brine, dried over $MgSO_4$ and concentrated under vacuum. Precipitation from a DCM/pentane mixture allowed the isolation of the trifluoromethyl ketone as a white solid (1.044 g, 2.16 mmol, 65% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	4.73 – 4.65 (m, 1H, H_3), 2.82 – 2.64 (m, 2H, H_{23}), 2.51 – 2.44 (m, 1H, H_{11}), 2.07 – 2.01 (m, 2H, $H_{11'+?}$), 2.01 (s, 3H, H_{27}), 1.93 – 1.28 (m, 19H), 1.13 – 1.03 (m, 2H, CH_2), 1.02 (s, 3H, H_{18}), 1.02 (s, 3H, H_{19}), 0.86 (d, J = 6.7 Hz, 1H, H_{21})

[216] Boivin, J.; El Kaim, L.; Zard, S. Z. *Tetrahedron*, **1995**, *51*, 2573–2584.

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	215.0 (C_{12}), 192.1 (q, *J* = 34.7 Hz, C_{24}), 170.9 (C_{26}), 115.7 (q, *J* = 292.3 Hz, C_{25}), 73.8 (C_3), 58.8 (CH), 57.6 (C_{13}), 46.3 (CH), 44.2 (CH), 41.4 (CH), 38.2 (C_{11}), 35.7 (CH), 35.5, (C_{10}), 35.3 (CH), 35.0 (CH_2), 33.7 (CH_2), 32.2 (CH_2), 28.0 (CH_2), 27.6 (CH_2), 27.0 (CH_2), 26.4 (CH_2), 26.1 (CH_2), 24.4 (CH_2), 22.9 (C_{18}), 21.6 (C_{27}), 18.7 (C_{21}), 11.8 (C_{19})
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	80.2
IR (cm^{-1}, neat)	2940 (br s), 2873 (m), 2257 (w), 1763 (m), 1720 (s), 1702 (s), 1465 (w), 1449 (w), 1383 (w), 1365 (w), 1251 (s), 1211 (s), 1157 (s), 1029 (m), 982 (w)
MS (HRMS APCI)	Calcd for $C_{27}H_{39}F_3O_4$: 484.2800 Found: 484.2791

(3R,10S,13R,17R)-17-((2R)-5-(benzyloxy)-5-(trifluoromethyl)hept-6-yn-2-yl)-10,13-dimethyl-12-oxohexadecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate (III.13s)



$C_{36}H_{47}F_3O_4$
M = 600.75 g.mol^{-1}

Following a modified version of procedure B starting with ethynylmagnesium bromide (1.2 equiv) and the synthetized trifluoromethylated ketone derived from bile acid (1.0 equiv) in Et_2O (0.1 M).

Flash chromatography: PE / EtOAc 9 : 1 to 8 : 2.

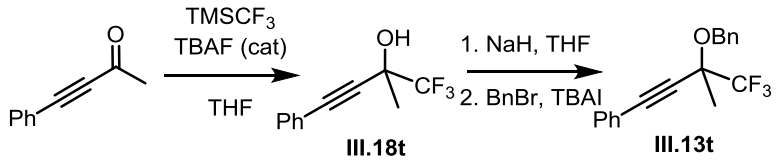
Overall yield: 24 % of a white solid.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.40 – 7.28 (m, 5H, $H_{30–32}$), 4.91 (d, *J* = 8.4 Hz, 1H, H_{28}, minor dia), 4.89 (d, *J* = 8.4 Hz, 1H, H_{28}, major dia), 4.76 – 4.74* (m, 1H, $H_{28'}$), 4.72 – 4.67 (m, 1H, H_3), 2.74 (s, 1H, H_{27}, minor dia), 2.73 (s, 1H, H_{27}, major dia), 2.50 – 2.44 (m, 1H, H_{11}), 2.07 – 2.03 (m, 2H, $H_{11'+?}$), 2.02 (s, 3H, H_{34}), 1.98 – 1.04 (m, 23H), 1.02 – 1.01 (m, 6H, H_{18+19}, major dia), 1.02 – 1.01 (m, 3H, H_{18or19}, minor dia), 0.99 (s, 3H, C*H*$_3$, H_{18or19}, minor dia), 0.87 (d, *J* = 6.6 Hz, 3H, H_{21}, major dia), 0.86 (d, *J* = 6.6 Hz, 3H, H_{21}, minor dia)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	214.9* (C_{12}), 170.8 (C_{12}), 137.9* (C_{29}), 128.5 (C_{30or31}), 127.8* (C_{30or31}), 127.7 (C_{32}), 124.4 (q, *J* = 288.9 Hz, C_{25})), 79.9* (C_{26}), 76.3* (C_{27}), 73.9 (C_3), 69.7* (C_{28}), 58.8* (CH), 57.6 (C_{13}), 46.4 (CH)*, 44.2 (CH), 41.5 (CH), 38.2 (C_{11}), 36.1* (CH), 35.8 (CH), 35.5 (C_{10}), 35.1 (CH_2), 32.5* (CH_2), 32.3 (CH_2), 28.7* (CH_2), 27.6* (CH_2), 27.1 (CH_2), 26.5 (CH_2), 26.2 (CH_2), 24.4* (CH_2), 22.9 (C_{18}), 21.6 (C_{27}), 19.0* (C_{21}), 11.8 (C_{19}) (quadruplet for C_{24} was not observed due to its assumed overlapping with the $CDCl_3$ peak)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-78.4 (major dia), -78.7 (minor dia)
IR (cm^{-1}, neat)	3305 (m), 3034 (w), 2941 (br s), 2873 (s), 2251 (s), 2122 (w), 1719 (s), 1702 (s), 1602 (w), 1498 (w), 1465 (m), 1454 (m), 1383 (m), 1365 (m), 1316 (w), 1250 (s), 1182 (s), 1122 (m), 1066 (m), 1029 (m), 981 (w)
MS (HRMS APCI)	Calcd for $C_{36}H_{47}F_3O_4$: 600.3426 Found: 600.3423

* Observed as doublets due to the slight chemical shift difference between the two diastereoisomers.

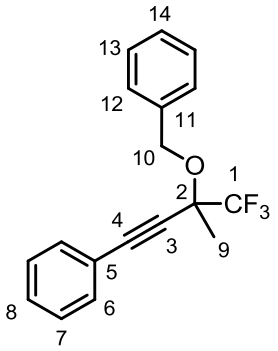
(3-(benzyloxy)-4,4,4-trifluoro-3-methylbut-1-yn-1-yl)benzene (III.13t)

Compound **III.13t** was prepared according to the synthetic pathways described below.



To a solution of 4-phenylbut-3-yn-2-one (1.0 equiv, 1 mmol, 144.2 mg) and trifluoromethyltrimethylsilane (1.2 equiv, 1.2 mmol, 170.6 mg, 0.18 mL) in THF (0.67 M) at 0 °C was added a catalytic amount of TBAF (1 M in THF, 0.1 equiv, 0.1 mmol, 0.1 mL) and the reaction was stirred 2 hours at 0 °C. Water and aqueous HCl were added and the solution was stirred overnight at room temperature. The mixture was extracted with Et_2O (3x), washed with water (1x), dried over $MgSO_4$ and concentrated over reduced pressure. Purification by flash chromatography (PE/EtOAc 9 : 1) afforded the desired alcohol **III.18t** as a yellow oil (166 mg, 66 % yield).

To a solution of alcohol **III.18t** (1.0 equiv, 0.5 mmol, 107.0 mg) in THF (1.0 mL) was added NaH (60% w/w, 1.2 equiv, 0.6 mmol, 24.0 mg) at 0 °C. Upon the end of the H_2 formation, benzyl bromide (1.4 equiv, 0.70 mmol, 119.5 mg, 83 µL) and TBAI (0.05 equiv, 0.025 mmol, 9.2 mg) were added. The mixture was then stirred overnight at room temperature. The reaction was then quenched with a saturated solution of NH_4Cl, extracted with Et_2O (x3), washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (PE / AcOEt 98 : 2) gave the pure product **III.13t** (106.9 mg, 0.35 mmol, 70%) as a yellow oil.

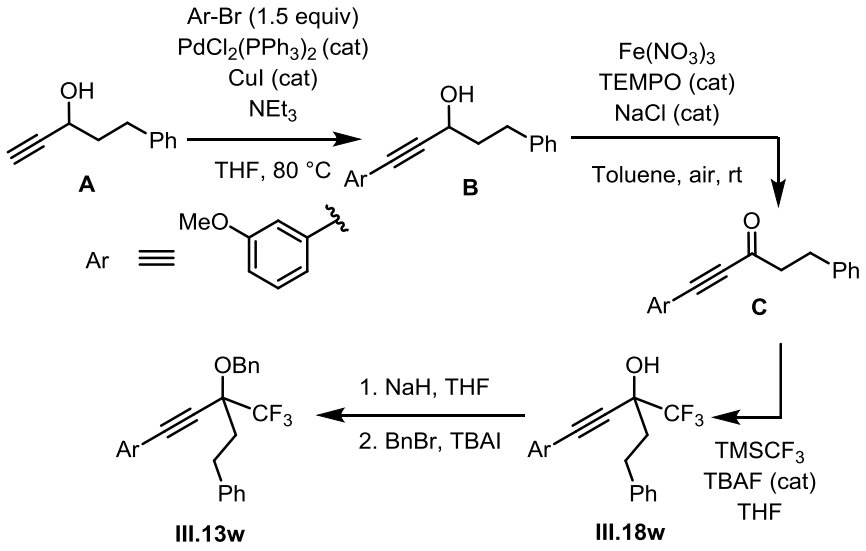


$C_{18}H_{15}F_3O$
M = 304.31 g.mol^{-1}

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.50 – 7.42 (m, 2H, H_6), 7.42 – 7.28 (m, 8H, H_{Ar}), 4.93 (d, *J* = 11.3 Hz, 1H, H_{10}), 4.85 (d, *J* = 11.3 Hz, 1H, $H_{10'}$), 1.77 (s, 3H, H_9)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	138.0 (C_{11}), 132.1 (C_{Ar}), 129.4 (C_{Ar}), 128.6 (C_{Ar}), 128.6 (C_{Ar}), 127.9 (C_{Ar}), 127.8 (C_{Ar}), 124.2 (q, *J* = 286.4 Hz, C_1), 121.4 (C_5), 89.1 (C_4), 82.5 (C_3), 74.5 (q, *J* = 31.0 Hz, C_2), 68.8 (C_{10}), 23.0 (C_9)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-80.2
IR (cm^{-1}, neat)	3069 (m), 3031 (m), 2930 (m), 2880 (m), 2359 (w), 2237 (m), 1952 (w), 1888 (w), 1809 (w), 1599 (w), 1491 (m), 1445 (m), 1377 (m), 1306 (m), 1267 (s), 1192 (s), 1176 (s) 1115 (s), 1113 (s), 1099 (s), 1026 (s), 939 (m), 916 (m), 885 (m)
MS (HRMS APCI)	Calcd for $C_{18}H_{16}OF_3$: 305.1148 Found: 305.1145 $[M+H]^+$

1-(3-(benzyloxy)-5-phenyl-3-(trifluoromethyl)pent-1-yn-1-yl)-3-methoxybenzene (III.13w)

Compound **III.13w** was prepared according to the synthetic pathways described below.



To a solution of 5-phenylpent-1-yn-3-ol **A** (1.0 equiv, 3.22 mmol, 516 mg), 3-bromoanisole (1.5 equiv, 4.84 mmol, 904 mg, 0.612 mL) and triethylamine (5.0 equiv, 24.2 mmol, 2.45 g, 3.27 mL) in THF (6 mL) were added $PdCl_2(PPh_3)_2$ (0.075 equiv, 0.242 mmol, 170 mg) and CuI (0.075 equiv, 0.242 mmol, 46 mg). The resulting mixture was stirred at 60 °C for 3 h. It was then filtered over a pad of silica eluting with diethylether, and the filtrate was washed with $NH_4Cl_{(sat)}$ and dried over magnesium sulfate. Flash chromatography purification (eluent: PE/EtOAc 9 : 1 to 85 : 15) afforded the alcohol **B** as an orange liquid (401.0 mg, 1.51 mmol, 31% yield).

Ketone **C** was prepared according to a literature procedure.[217] Alcohol **B** (1.0 equiv, 1.51 mmol, 401.0 mg) was mixed with $Fe(NO_3)_3$ (0.1 equiv, 0.151 mmol, 60.8 mg), TEMPO (0.1 equiv, 0.151 mmol, 23.6 mg) and NaCl (0.1 equiv, 0.151 mmol, 8.8 mg) in toluene (1.5 mL) and the solution was stirred overnight at room temperature under air. Direct purification by flash column

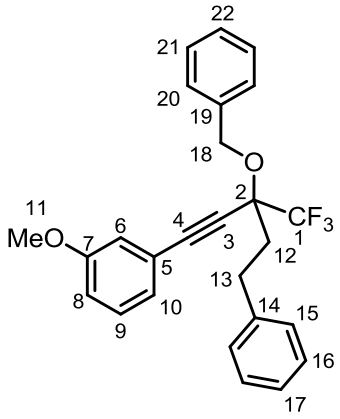
[217] S. Ma, J. Liu, S. Li, B. Chen, J. Cheng, J. Kuang, Y. Liu, B. Wan, Y. Wang, J. Ye, Q. Yu, W. Yuan, S. Yu, *Adv. Synth. Catal.* **2011**, *353*, 1005-1017.

chromatography (eluent: PE/EtOAc 95 : 5) afforded the desired ketone **C** as a yellow oil (272.2 mg, 1.03 mmol, 68% yield).

To a solution of ketone **C** (1.0 equiv, 1.03 mmol, 272.2 mg) and trifluoromethyltrimethylsilane (1.2 equiv, 1.24 mmol, 175.9 mg, 0.183 mL) in THF (1.5 mL) at room temperature was added a catalytic amount of TBAF (1 M in THF, 0.1 equiv, 0.1 mmol, 0.1 mL) and the reaction was stirred 1 h at room temperature. Water and aqueous HCl were added and the solution was extracted with Et_2O (3x), dried over $MgSO_4$ and concentrated over reduced pressure. As some protected alcohol remained present in the crude mixture, it was dissolved in THF (1.5 mL) and TBAF (1 M in THF, 1.0 equiv, 1.03 mmol, 1.03 mL) was added. After 1 h stirring at room temperature, water and Et_2O were added. The solution was extracted with Et_2O (3x), dried over $MgSO_4$ and concentrated over reduced pressure. Purification by flash chromatography (PE/EtOAc 9 : 1 to 85 : 15) afforded the desired alcohol **III.18w** as a yellow oil (200.6 mg, 0.60 mmol, 58 % yield).

To a solution of alcohol **III.18w** (1.0 equiv, 0.6 mmol, 200.6 mg) in THF (0.9 mL) was added NaH (60% w/w, 1.2 equiv, 0.72 mmol, 28.8 mg) at 0 °C. Upon the end of the H_2 formation, benzyl bromide (1.2 equiv, 0.72 mmol, 123.1 mg, 86 µL) and TBAI (0.05 equiv, 0.030 mmol, 11.1 mg) were added. The mixture was then stirred overnight at room temperature. The reaction was then quenched with a saturated solution of NH_4Cl, extracted with Et_2O (x3), washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (pure PE to PE / AcOEt 95 : 5) gave the pure product **III.13w** as a colourless oil.

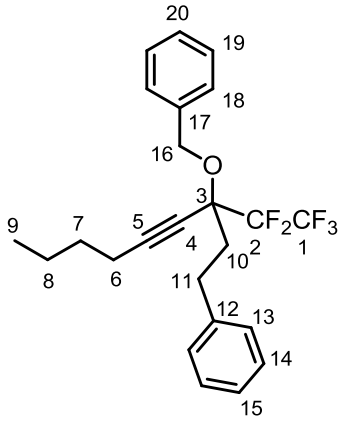
This compound could also be prepared using a Sonogashira coupling between compound **III.13r** and 3-bromoanisole.[52,86]



$C_{26}H_{23}F_3O_2$
M = 424.45 g.mol^{-1}

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.42 – 7.27 (m, 8H, H_{Ar}), 7.25 – 7.16 (m, 3H, H_{Ar}), 7.12 (dt, *J* = 7.6, 1.2 Hz, 1H, H_{Ar}), 7.03 – 7.00 (m, 1H, H_{Ar}), 6.96 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H, H_{Ar}), 5.03 (d, *J* = 11.2 Hz, 1H, H_{18}), 4.87 (d, *J* = 11.2 Hz, 1H, $H_{18'}$), 3.83 (s, 3H, H_{11}), 3.03 – 2.98 (m, 2H, H_{13}), 2.35 – 2.20 (m, 2H, H_{12})
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	159.7 (C_7), 141.3 (C_{14}), 138.1 (C_{19}), 129.7 (C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.6 (C_{Ar}), 128.0 (C_{Ar}), 127.9 (C_{Ar}), 126.3 (C_{Ar}), 124.8 (C_9), 124.6 (q, *J* = 288.3 Hz, C_1), 122.3 (C_5), 117.1 (C_6), 116.1 (C_8), 90.9 (C_4), 81.00 (C_3), 77.7 (q, *J* = 29.7 Hz, C_2), 70.0 (C_{18}), 55.5 (C_{11}), 37.7 (C_{12}), 30.2 (C_{13})
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-78.2
IR (cm^{-1}, CCl_4)	3067 (w), 3032 (m), 3009 (w), 2964 (m), 2942 (m), 2876 (w), 2838 (w), 2251 (s), 2232 (w), 1711 (w), 1604 (m), 1577 (m), 1482 (m), 1466 (m), 1456 (m), 1322 (m), 1287 (m), 1259 (s), 1225 (m), 1183 (s), 1121 (s), 1095 (m), 1065 (m), 1051 (m)
MS (HRMS EI)	Calcd for $C_{26}H_{23}F_3O_2$: 424.1650 Found: 424.1658

(3-(benzyloxy)-3-(perfluoroethyl)non-4-ynyl)benzene (III.13z)



$C_{24}H_{25}F_5O$
M = 424.45 g.mol^{-1}

Following a modified version of procedure B starting with 1-hexyne (1.3 equiv), *n*-BuLi (1.2 equiv) and 1,1,1,2,2-pentafluoro-5-phenylpentan-3-one (1 equiv) (prepared according to a literature procedure[218] using ethyl pentafluoropropionate instead of ethyl trifluoroacetate) in THF (0.3 M).

Flash chromatography: pure PE to PE / EtOAc 95 : 5.

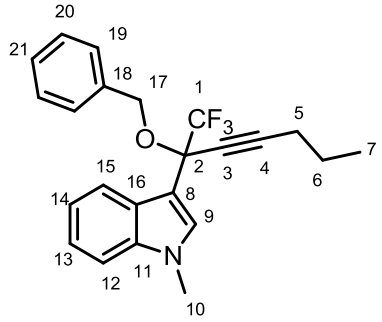
Overall yield: 54%.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.39 – 7.29 (m, 7H, H_{Ar})), 7.24 – 7.20 (m, 3H, H_{Ar}), 4.92 (d, *J* = 11.1 Hz, 1H, H_{16}), 4.78 (d, *J* = 11.1 Hz, $H_{16'}$), 3.00 – 2.86 (m, 2H, H_{11}), 2.39 (t, *J* = 6.9 Hz, 2H, H_6), 2.31 – 2.23 (m, 1H, H_{10}), 2.19 – 2.11 (m, 1H, $H_{10'}$), 1.64 – 1.57 (m, 2H, H_7), 1.54 – 1.45 (m, 2H, H_8), 0.97 (t, *J* = 7.3 Hz, 3H, H_9)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	141.4 (C_{12}), 138.1 (C_{17}), 128.6 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.0 (C_{Ar}), 127.9 (C_{Ar}), 126.2 (C_{Ar}), 119.3 (qt, *J* = 288.5, 35.9 Hz, C_1), 113.9 (tq, *J* = 264.1, 35.1 Hz, C_2), 93.5 (C_5), 78.1 (t, *J* = 23.3 Hz, C_3), 72.2 (C_4), 69.6 (C_{16}), 37.9 (C_{11}), 30.5 (x2) (C_{7+10}), 22.0 (C_8), 18.6 (C_6), 13.7 (C_9)
^{19}F NMR (δ, ppm)	-79.4 (s), -118.7 (d, *J* = 276.5 Hz), -120.2 (d, *J* =

[218] K. Fuchibe, H. Jyono, M. Fujiwara, T. Kudo, M. Yokota, J. Ichikawa, *Chem. - Eur. J.* **2011**, *17*, 12175-12185.

(282 MHz, $CDCl_3$)	275.7 Hz)
IR (cm^{-1}, CCl_4)	3089 (w), 3067 (w), 3031 (w), 2961 (m), 2937 (m), 2875 (m), 2259 (m), 1604 (w), 1497 (m), 1455 (m), 1431 (w), 1381 (w), 1342 (m), 1276 (w), 1217 (s), 1183 (s), 1143 (s), 1098 (s), 1074 (s), 1028 (m)
MS (HRMS EI)	Calcd for $C_{24}H_{25}F_5O$: 424.1826 Found: 424.1840

3-(2-(benzyloxy)-1,1,1-trifluorohept-3-yn-2-yl)-1-methyl-1H-indole (III.13af)



$C_{23}H_{22}F_3NO$
$M = 385.42\ g.mol^{-1}$

2,2,2-trifluoro-1-(1-methyl-1H-indol-3-yl)ethan-1-one (CAS : 318-54-7) was synthetized using literature procedures.[219]

Substrate **III.13af** was prepared following a modified version of procedure B starting with *n*-pentyne (1.5 equiv), *n*-BuLi (1.2 equiv) and 2,2,2-trifluoro-1-(1-methyl-1H-indol-3-yl)ethan-1-one (1.0 equiv) in THF (0.75 $mol.L^{-1}$).

Flash chromatography: PE/EtOAc 95 : 5 to 90 : 10.

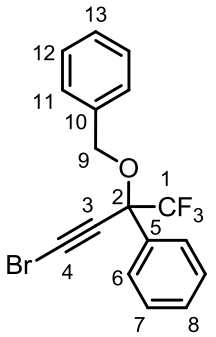
Overall yield: 962 mg (48 %) of a yellow sticky oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.93 (d, *J* = 8.0 Hz, 1H, H_{15}), 7.37 – 7.26 (m, 8H, H_{Ar}), 7.17 – 7.14 (m, 1H, H_{13or14}), 4.77 (d, *J* = 11.1 Hz, 1H, H_{17}), 4.39 (d, *J* = 11.1 Hz, 1H, $H_{17'}$), 3.78 (s, 3H, H_{10}), 2.37 (t, *J* = 7.0 Hz, 2H, H_5), 1.66 (hex, *J* = 7.2 Hz, 2H, H_6), 1.06 (t, *J* = 7.4 Hz, 3H, H_7)

[219] (a) B. Raimer, T. Wartmann, P. G. Jones, T. Lindel, *Eur. J. Org. Chem.* **2014**, *25*, 5509–5520; (b) Monsanto Company, **1999**, US5994270 A1

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	138.1 (C_{11or18}), 137.7 (C_{11or18}), 131.8 (C_9), 128.4 (C_{19or20}), 128.0 (C_{19or20}), 127.6 (C_{21}), 125.8 (C_{indole}), 124.0 (q, *J* = 284.9 Hz, C_1), 122.3 (C_{indole}), 121.8 (C_{indole}), 120.3 (C_{indole}), 109.6 (C_{indole}), 108.8 (C_{indole}), 89.9 (C_4), 76.9 (q, *J* = 32.9 Hz, C_2), 74.4 (C_3), 67.1 (C_{17}), 33.2 (C_{10}), 22.0 (C_6), 20.8 (C_5), 13.6 (C_7)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-79.3
IR (cm^{-1}, CCl_4)	3941 (w), 3692 (w), 3053 (m), 2986 (m), 2937 (m), 2875 (w), 2830 (w), 2685 (w), 2520 (w), 2409 (w), 2305 (m), 2258 (m), 1615 (w), 1546 (m), 1498 (w), 1454 (m), 1423 (m), 1370 (w), 1337 (m), 1265 (s), 1184 (s), 1172 (s), 1155 (m), 1133 (m), 1066 (m), 1040 (m), 980 (w)
MS (HRMS EI)	Calcd for $C_{23}H_{22}F_3NO$: 385.1653 Found: 385.1646

(2-(benzyloxy)-4-bromo-1,1,1-trifluorobut-3-yn-2-yl)benzene (III.13ah)



$C_{17}H_{12}BrF_3O$
M = 369.18 g.mol^{-1}

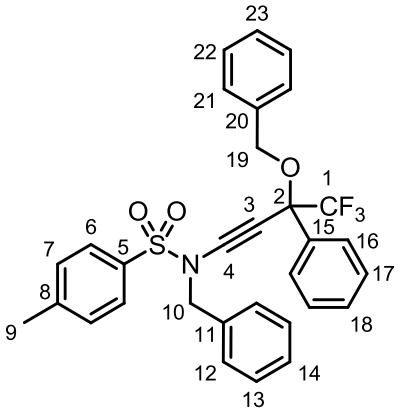
The compound was prepared according to a standard literature procedure.[220] To a solution of **III.13q** (1.0 equiv, 3 mmol, 872 mg) in acetone (0.25 mol.L^{-1}, 12 mL) were added *N*-bromosuccinimide (1.2 equiv, 3.6 mmol, 641 mg)

[220] R. E. Maleczka, L. R. Terrell, D. H. Clark, S. L. Whitehead, W. P. Gallagher, I. Terstiege, *J. Org. Chem.* **1999**, *64*, 5958-5965.

and silver nitrate (0.05 equiv, 0.15 mmol, 25 mg). The solution was stirred at room temperature until complete conversion of the alkyne. Acetone was removed under reduced pressure, and petroleum ether was added to the grey slurry. The suspension was filtered over Celite® and the obtained crude mixture was purified by flash chromatography to yield 1.07 g (96% yield) of the desired compound as a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.75 – 7.73 (m, 2H, H_{Ar}), 7.47 – 7.38 (m, 3H, H_{Ar}), 7.38 – 7.30 (m, 5H, H_{Ar}), 4.79 (d, *J* = 11.1 Hz, 1H, H_9), 4.44 (d, *J* = 11.1 Hz, 1H, $H_{9'}$)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	137.1 (C_{10}), 133.3 (C_5), 130.1 (C_{Ar}), 128.6 (C_{Ar}), 128.6 (C_{Ar}), 128.3 (C_{Ar}), 128.0 (C_{Ar}), 127.7 (C_{Ar}), 122.8 (q, *J* = 285.4 Hz, C_1), 80.4 (*J* = 31.7 Hz, C_2), 75.6 (C_{3or4}), 68.0 (C_5), 52.4 (C_{3or4})
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-79.3
IR (cm^{-1}, CCl_4)	3069 (w), 3035 (w), 2927 (s, br), 2855 (m), 2214 (w), 1701 (w), 1498 (w), 1452 (w), 1382 (w), 1274 (m), 1191 (s), 1129 (m), 1072 (m), 1030 (w)
MS (HRMS EI)	Calcd for $C_{17}H_{12}BrF_3O$: 368.0024 Found: 368.0023

N-benzyl-N-(3-(benzyloxy)-4,4,4-trifluoro-3-phenylbut-1-yn-1-yl)-4-methylbenzenesulfonamide (III.13ai)



$C_{31}H_{26}F_3NO_3S$
M = 549.60 g.mol^{-1}

Phenanthroline (0.2 equiv, 0.1 mmol, 18 mg), K_3PO_4 (2.0 equiv, 1 mmol, 212 mg), $CuSO_4$ (0.1 equiv, 0.05 mmol, 13 mg), N-benzyl-4-methylbenzenesulfonamide (2 equiv, 1 mmol, 261 mg) were introduced as solids in a flame-dried Schlenk under argon. After three vacuum/argon cycles, toluene (1 mL) was added, immediately followed by bromide **III.13ah** (1 equiv, 0.5 mmol, 185 mg) and rinced with toluene (0.5 mL). The resulting solution was stirred at 60 °C for 24 h. The reaction mixture was filtered on Celite® with ethyl acetate, and the solvents were evaporated under reduced pressure. Purification by flash chromatography (PE/EtOAc 8 : 2) yielded 273 mg (49 % yield) of the desired product as a white solid.

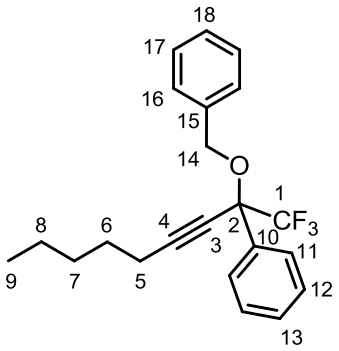
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 7.77 (d, *J* = 8.3 Hz 2H, H_7), 7.52 – 7.50 (m, 2H, H_{Ar}), 7.40 – 7.26 (m, 13H, H_{Ar}), 7.23 – 7.20 (m, 2H, H_{Ar}), 4.56 (d, *J* = 2.8 Hz, 2H, H_{10}), 4.36 (d, *J* = 11.3 Hz, 1H, H_{19}), 4.14 (d, *J* = 11.3 Hz, 1H, $H_{19'}$), 2.42 (s, 3H, H_9)

^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$): 145.1 (C_8), 137.3 (C_{20}), 134.2 ($C_{Ar\text{-}q}$), 133.7 ($C_{Ar\text{-}q}$), 133.6 ($C_{Ar\text{-}q}$), 130.0 (C_{Ar}), 129.5 (C_{Ar}), 129.1 (C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.2 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 127.7 (C_{Ar}), 127.6 (C_{Ar}), 127.4 (C_{Ar}), 122.9 (q, *J* = 285.1 Hz, C_1), 83.9 (C_4), 79.8 (q, *J* = 31.3 Hz, C_2), 67.1 (C_{19}), 65.2 (C_3), 55.2 (C_{10}), 21.6

(C_9)

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-79.3
IR (cm^{-1}, CCl_4)	2361 (w), 2253 (m), 1597 (m), 1497 (m), 1452 (m), 1371 (m), 1271 (m), 1171 (s), 1090 (m), 1051 (br m), 922 (m), 893 (m), 814 (m)
MS (HRMS EI)	Calcd for $C_{31}H_{27}O_3NF_3S$: 550.1651 [M+H^+] Found: 550.1658

(2-(benzyloxy)-1,1,1-trifluoronon-3-yn-2-yl)benzene (III.13aj)



$C_{22}H_{23}F_3O$
M = 360.41 g.mol^{-1}

Following procedure B starting with *n*-heptyne and 2,2,2-trifluoroacetophenone.

Flash chromatography: pure PE to PE/EtOAc 98 : 2.

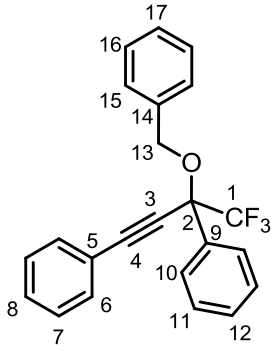
Overall yield: 558 mg (77 %) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.83 – 7.80 (m, 2H, H_{Ar}), 7.47 – 7.31 (m, 8H, H_{Ar}), 4.84 (d, J = 11.3 Hz, 1H, H_{14}), 4.44 (d, J = 11.1 Hz, 1H, $H_{14'}$), 2.42 (t, J = 7.1 Hz, 2H, H_5), 1.69 – 1.62 (m, 2H, H_6), 1.51 – 1.45 (m, 2H, H_7), 1.44 – 1.34 (m, 2H, H_8), 0.95 (t, J = 7.2 Hz, 3H, H_9)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	137.8 (C_{15}), 134.5 (C_{10}), 129.6 (C_{Ar}), 128.5 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 127.8 (C_{Ar}), 127.6 (C_{Ar}), 123.3 (q, J = 285.0 Hz, C_1), 92.6 (C_4), 79.6 (q, J = 31.4 Hz, C_2), 73.2 (C_3), 67.5 (C_{14}), 31.2 (C_7), 28.0 (C_6), 22.2 (C_8), 18.9 (C_5), 14.1 (C_9)
^{19}F NMR (δ, ppm)	-79.6

(282 MHz, $CDCl_3$)

IR (cm^{-1}, CCl_4)	3069 (w), 3034 (w), 2960 (m), 2934 (m), 2863 (m), 2245 (w), 1498 (w), 1451 (m), 1381 (w), 1276 (w), 1189 (s), 1161 (s), 1070 (m), 1030 (m)
MS (HRMS EI)	Calcd for $C_{22}H_{23}F_3O$: 360.1701 Found: 360.1690

(3-(benzyloxy)-4,4,4-trifluorobut-1-yne-1,3-diyl)dibenzene (III.13ak)



$C_{23}H_{17}F_3O$
M = 366.38 $g.mol^{-1}$

Following procedure B starting starting with commercial phenylacetylene and 2,2,2-trifluoroacetophenone (2.00 mmol);

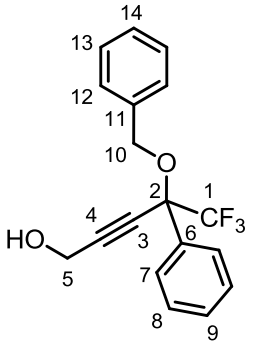
Flash chromatography: pure PE to PE/EtOAc 95 : 5.

Overall yield: 580 mg (79 %) of a white solid.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.92 – 7.82 (m, 2H, H_{Ar}), 7.62 – 7.59 (m, 2H, H_{Ar}), 7.52 – 7.33 (m, 11H, H_{Ar}), 4.95 (d, *J* = 11.3 Hz, 1H, H_{13}), 4.57 (d, *J* = 11.3 Hz, 1H, $H_{13'}$)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	137.6 (C_{14}), 134.0 (C_9), 132.3 (C_{Ar}), 129.9 (C_{Ar}), 129.7 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.5 (C_{Ar}), 128.5 (C_{Ar}), 127.9 (C_{Ar}), 127.7 (C_{Ar}), 123.2 (q, *J* = 285.2 Hz, C_1), 121.3 (C_5), 91.1 (C_4), 81.8 (C_3), 80.1 (q, *J* = 31.4 Hz, C_2), 67.8 (C_{13})
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-79.2
IR	3068 (m), 3034 (m), 2930 (w), 2873 (w), 2234 (m),

(cm^{-1}, CCl_4)	1949 (w), 1882 (w), 1805 (w), 1600 (w), 1491 (m), 1451 (m), 1383 (s), 1280 (s), 1204 (s), 1189 (s), 1177 (s), 1098 (s), 1061 (m), 1000 (m)
MS (HRMS EI)	Calcd for $C_{23}H_{17}F_3O$: 366.1231 Found: 366.1238
MP	46.5 – 47.0 °C

4-(benzyloxy)-5,5,5-trifluoro-4-phenylpent-2-yn-1-ol (III.13al)



$C_{18}H_{15}F_3O_2$
M = 320.31 g.mol^{-1}

Following procedure C starting with **III.13q** (2 mmol) and paraformaldehyde (5 equiv).

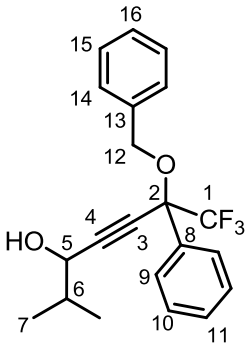
Flash chromatography: PE/EtOAc 75 : 25.

Overall yield: 490 mg (75 %) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.78 – 7.75 (m, 2H, H_{Ar})), 7.46 – 7.30 (m, 8H, H_{Ar}), 4.79 (d, *J* = 11.4 Hz, 1H, H_{10}), 4.46 (d, *J* = 11.4 Hz, 1H, $H_{10'}$) 4.46 (s, 2H, H_5), 1.67 (br, 1H, OH)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	137.5 (C_{11}), 133.5 (C_6), 130.0 (C_{Ar}), 128.5 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 127.9 (C_{Ar}), 127.6 (C_{Ar}), 123.0 (q, *J* = 285.2 Hz, C_1), 89.5 (C_4), 79.6 (q, *J* = 31.6 Hz, C_2), 78.6 (C_3), 67.8 (C_{10}), 51.1 (C_5)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-79.4
IR (cm^{-1}, CCl_4)	3618 (m), 3093 (w), 3069 (w), 3034 (w), 2919 (w), 2872 (w), 1958 (w), 1814 (w), 1498 (m), 1451 (m), 1381 (m), 1276 (m), 1190 (s), 1150 (s), 1089 (m),

	1071 (m), 1030 (m)
MS (HRMS EI)	Calcd for $C_{18}H_{15}F_3O_2$: 320.1024 Found: 320.1018

6-(benzyloxy)-7,7,7-trifluoro-2-methyl-6-phenylhept-4-yn-3-ol (III.13am)



$C_{21}H_{21}F_3O_2$
M = 362.39 g.mol^{-1}

Following procedure D starting with **III.13q** (1 mmol) and isobutyraldehyde (1.5 equiv).

Flash chromatography: PE/EtOAc 85 : 15.

Overall yield: 224 mg (62 %) of a colorless oil. The product was obtained as a mixture of two diastereomers.

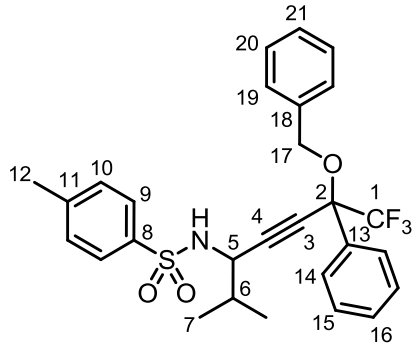
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.78 – 7.76 (m, 2H, H_{Ar}), 7.46 – 7.44 (m, 3H, H_{Ar}), 7.40 – 7.32 (m, 5H, H_{Ar}), 4.79 (d, *J* = 11.0 Hz, 1H, H_{12}), 4.47* (d, *J* = 11.4 Hz 1H, $H_{12'}$), 4.38 – 4.36 (m, 1H, H_5), 2.05 – 1.96 (m, 1H, H_6), 1.83 (br, 1H, OH), 1.05 (m, 6H, H_7)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	137.4* (C_{13}), 133.5* (C_8), 129.8 (C_{Ar}), 128.4 (C_{Ar}), 128.4 (C_{Ar}), 128.2 (C_{Ar}), 127.8 (C_{Ar}), 127.4 (C_{Ar}), 123.0 (q, *J* = 285.0 Hz, C_1), 91.1* (C_4), 79.5 (q, *J* = 31.4 Hz, C_2), 78.3 (C_3), 67.8 (C_{5or12}), 67.6 (C_{5or12}), 34.5 (C_6), 18.1 (C_7), 17.3 ($C_{7'}$)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-79.5
IR (cm^{-1}, CCl_4)	3619 (m), 3093 (w), 3069 (w), 3034 (w), 2963 (m), 2928 (m), 2874 (m), 2856 (m), 2242 (w), 1498 (w), 1467 (m), 1451 (m), 1382 (m), 1275 (m), 1190 (s),

1151 (m), 1091 (m), 1071 (m), 1031 (m), 995 (m)

MS (HRMS EI) Calcd for $C_{21}H_{21}F_3O_2$: 362.1494 Found: 362.1481

* Observed as doublets due to the slight chemical shift difference between the two diastereoisomers.

N-(6-(benzyloxy)-7,7,7-trifluoro-2-methyl-6-phenylhept-4-yn-3-yl)-4-methylbenzenesulfonamide (III.13an)



$C_{28}H_{28}F_3NO_3S$
M = 515.59 g.mol^{-1}

The substrate (white solid) was obtained as a mixture of two diastereomers using a literature procedure involving **III.13q**, *n*-BuLi and 4-methyl-N-(2-methyl-1-tosylpropyl)benzenesulfonamide.[221]

Flash chromatography: PE/EtOAc 80 : 20.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) 7.77 (d, *J* = 8.2 Hz, 2H, H_9), 7.53 – 7.51 (m, 2H, H_{Ar}), 7.44 – 7.26 (m, 8H, H_{Ar}), 7.11 (d, *J* = 7.9 Hz, 2H, H_{10}, dia 1), 7.10 (d, *J* = 7.9 Hz, 2H, H_{10}, dia 2), 5.22 (d, *J* = 9.6 Hz, 1H, NH, dia 1), 4.99 (d, *J* = 9.6 Hz, 1H, NH, dia 2), 4.37 (d, *J* = 11.4 Hz, 1H, H_{17}, dia 1), 4.32 (d, *J* = 11.5 Hz, 1H, H_{17}, dia 2), 4.23 – 4.08 (m, 2H, $H_{5+17'}$), 2.20 (s, 3H, H_{12}, dia 1), 2.18 (s, 3H, H_{12}, dia 2), 2.05 – 1.99 (m, 1H, H_6), 1.05 (d, *J* = 6.8 Hz, 6H, H_7)

^{13}C NMR (δ, ppm) 143.8* (C_{11}), 137.4* (C_{8or18}), 137.3 (C_{8or18}), 133.2

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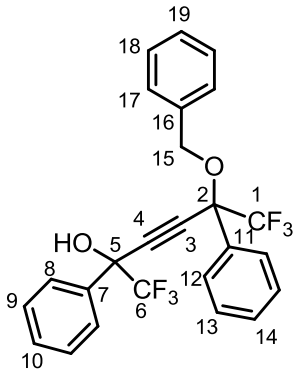
[221] Stanton, G. R.; Göllü, M.; Platoff, R. M.; Rich, C. E.; Caroll, P. J.; Walsh, P. J. *Adv. Synth. Catal.* **2013**, *355*, 757–764.

(75 MHz, $CDCl_3$)	(C_{13}), 129.9 (C_{10}), 129.9 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.2 (C_{Ar}), 128.0* (C_{Ar}), 127.4* (C_{Ar}), 127.2* (C_9), 122.8 (q, J = 285.1 Hz, C_1), 88.4* (C_4), 79.3 (q, J = 31.6 Hz, C_2), 77.8 (C_3), 67.6 (C_{17}), 51.5* (C_5), 34.3 (C_6), 21.5* (C_{12}), 18.8 (C_7), 17.8 ($C_{7'}$)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-79.7, -79.7
IR (cm^{-1}, neat)	3252 (br m), 3051 (w), 2962 (m), 2928 (m), 2878 (w), 2362 (w), 1734 (w), 1599 (w), 1497 (w), 1450 (m), 1389 (w), 1331 (m), 1277 (m), 1176 (br s), 1151 (br s), 1092 (s), 1068 (s), 1030 (m), 1003 (w), 916 (m)
MS (HRMS ESI)	Calcd for $C_{28}H_{28}F_3NO_3S$: 538.1634 [M+Na^+] Found: 538.16311

* Observed as doublets due to the slight chemical shift difference between the two diastereomers.

5-(benzyloxy)-1,1,1,6,6,6-hexafluoro-2,5-diphenylhex-3-yn-2-ol (III.13ao)



$C_{25}H_{18}F_6O_2$
M = 464.40 g.mol^{-1}

Following procedure $ starting with **III.13q** (0.5 mmol) and trifluoro-methylacetophenone (1.5 equiv).

Flash chromatography: PE/EtOAc 90 : 10.

Overall yield: 119 mg (51 %) of a colorless oil. The product was obtained as a mixture of two diastereoisomers.

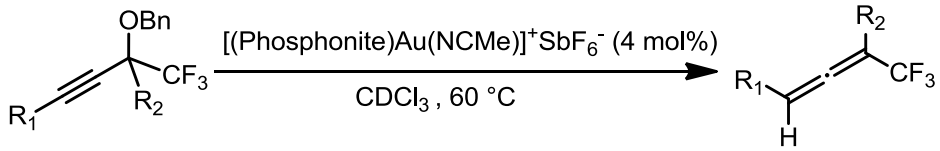
^{1}H NMR (δ, ppm)	7.78 – 7.73 (m, 4H, H_{Ar}), 7.51 – 7.42 (m, 6H, H_{Ar}),

(300 MHz, $CDCl_3$)	7.38 – 7.31 (m, 5H, H_{Ar}), 4.77 (d, *J* = 11.3 Hz, 1H, H_{15}, dia 1), 4.76 (d, *J* = 11.6 Hz, 1H, H_{15}, dia 2), 4.57 (d, *J* = 11.6 Hz, 1H, $H_{15'}$, dia 1), 4.55 (d, *J* = 11.3 Hz, 1H, $H_{15'}$, dia 2), 3.07 (br s, 1H, OH, dia 1), 2.96 (br s, 1H, OH, dia 2)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	137.0* (C_{16}), 134.1* (C_{11}), 132.6 (C_7), 130.2 (C_{Ar}), 130.0 (C_{Ar}), 128.7 (C_{Ar}), 128.5 (C_{Ar}), 128.5 (C_{Ar}), 128.1* (C_{Ar}), 128.0* (C_{Ar}), 127.5* (C_{Ar}), 127.0 (C_{Ar}), 123.1 (q, *J* = 285.2 Hz, C_{1or6}), 122.7 (q, *J* = 285.7 Hz, C_{1or6}), 86.6 (C_4), 81.5 (C_3), 79.6 (q, *J* = 31.7 Hz, C_2), 73.2 (q, *J* = 32.7 Hz, C_5), 68.2* (C_{15})
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-79.3* (F_1), -81.3* (F_2)
IR (cm^{-1}, neat)	3063 (w), 2359 (w), 1607 (w), 1480 (w), 1452 (m), 1383 (w), 1350.1 (w), 1274 (br m), 1176 (br s), 1067 (br m), 1032 (w), 1015 (w), 949 (w), 908 (w)
MS (HRMS ESI)	Calcd for $C_{25}H_{18}F_6O_2Na$: 487.1103 [*M*+Na^+] Found: 487.1126

* Observed as doublets due to the slight chemical shift difference between the two diastereoisomers.

Catalysis step

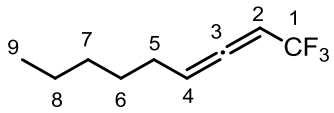
General procedure D:



To a solution of propargylic benzylic ether (1 equiv) in dry $CDCl_3$ (0.2 $mol.L^{-1}$) was added PhosphoniteAuSbF_6 **III.12** (4 mol%) and the reaction was heated up to 60 °C. Upon completion on the reaction (NMR), the solvent was evaporated and purification by flash chromatography gave the pure trifluoromethylated allene.

Crude NMR yield was provided by adding 1,2-dichloroethane as an internal standard.

1,1,1-trifluorononona-2,3-diene (III.14a)



$C_9H_{13}F_3$
M = 178.19 g.mol^{-1}

Following general procedure D starting with **III.13a** (0.20 mmol, reaction time: 1 h).

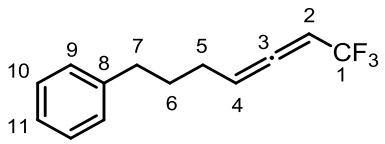
Flash chromatography: pentane

Yield: Colorless oil (crude NMR yield: 85 %).

The product could not be isolated because of its low boiling point. Some pentane remains present on the spectra.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	5.71 – 5.63 (m, 1H, H_4), 5.44 – 5.37 (m, 1H, H_2), 2.14 – 2.08 (m, 2H, H_5), 1.47 – 1.43 (m, 2H, H_6), 1.34 – 1.29 (m, 4H, H_{7+8}), 0.91 – 0.88 (m, 3H, H_9)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	205.3 (q, *J* = 5.8 Hz, C_3), 123.0 (q, *J* = 270.2 Hz, C_1), 98.6 (C_4), 85.9 (q, *J* = 38.9 Hz, C_2), 31.2 (C_7), 28.3 (C_6), 27.7 (C_5), 22.5 (C_8), 14.1 (C_9)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-61.6
MS (HRMS EI)	Calcd for C_8H_{13}: 109.1017 [*M*-CF_3] Found: 109.1020

(1,1,1-trifluorononona-2,3-dien-2-yl)benzene (III.14g)



$C_{13}H_{13}F_3$
M = 226.24 g.mol^{-1}

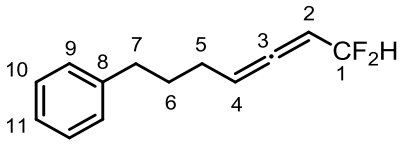
Following general procedure D starting with **III.13g** (0.40 mmol, reaction time: 1 h 40) and 3 mol% catalyst.

Flash chromatography: PE/EtO_2 96 : 4.

Yield: 83.3 mg (90%) of a yellow oil (crude NMR yield: 89%).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.32 – 7.28 (m, 2H, H_{10}), 7.23 – 7.18 (m, 3H, H_{9+11}), 5.74 – 5.66 (m, 1H, H_4), 5.48 – 5.41 (m, 1H, H_2), 2.70 – 2.66 (m, 2H, H_7), 2.19 – 2.13 (m, 2H, H_5), 1.83 – 1.76 (m, 2H, H_6)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	205.4 (q, *J* = 5.9 Hz, C_3), 141.8 (C_8), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 127.0 (C_{11}), 123.0 (q, *J* = 270.0 Hz, C_1), 98.3 (C_4), 86.2 (q, *J* = 38.9 Hz, C_2), 35.2 (C_7), 30.2 (C_6), 27.1 (C_5)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-61.5
IR (cm^{-1}, CCl_4)	3087 (w), 3066 (w), 3029 (m), 2938 (m), 2861 (m), 1979 (m), 1604 (w), 1497 (m), 1454 (m), 1430 (m), 1297 (m), 1260 (s), 1134 (s), 869 (m)
MS (HRMS EI)	Calcd for $C_{13}H_{13}F_3$: 226.0969 Found: 226.0973

(7,7-difluorohepta-4,5-dien-1-yl)benzene (III.14k)



$C_{13}H_{14}F_2$
M = 208.25 g.mol^{-1}

Following general procedure D starting with **III.13k** (0.20 mmol, reaction time: 1 h).

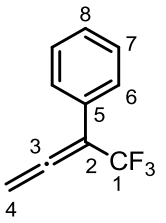
Flash chromatography: pentane.

Yield: 29.5 mg (75 %) of a pale yellow oil (crude NMR yield 79%).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.32 – 7.28 (m, 2H, H_{10}), 7.23 – 7.17 (m, 3H, H_{9+11}), 6.10 (td, *J* = 56.6, 6.2 Hz, 1H, H_1), 5.55 (hex, *J* = 7.0 Hz, 1H, H_4), 5.40 (m, 1H, H2), 2.67 (m, 2H, H_7), 2.13 (qd, *J* = 7.2, 2.0 Hz, 2H, H_5), 1.78 (p, *J* = 7.5 Hz, 2H, H_6)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	206.2 (t, *J* = 12.2 Hz, C_3), 141.9 (C_8), 128.6 (C_{9or10}), 128.5 (C_{9or10}), 126.0 (C_{11}), 114.6 (t, *J* = 237.1 Hz, C_1), 96.0 Hz (t, *J* = 1.8 Hz, C_4), 88.7 (t, *J* = 28.8 Hz,

	C_2), 35.3 (C_7), 30.5 (C_6), 27.4 (t, J = 2.8 Hz, C_5)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-108.0 (d, J = 56.6Hz)
IR (cm^{-1}, CCl_4)	3066 (w), 3029 (m), 2930 (m), 2859 (m), 1973 (m), 1604 (w), 1497 (m), 1454 (m), 1439 (m), 1354 (m), 1133 (m), 1102 (s), 1060 (s), 1031 (s), 871 (m)
MS (HRMS EI)	Calcd for $C_{13}H_{14}F_2$: 208.1064 Found: 208.1053

(1,1,1-trifluorobuta-2,3-dien-2-yl)benzene (III.14q)



$C_{10}H_7F_3$
M = 184.16 g.mol^{-1}

Following general procedure D starting with **III.13q** (0.20 mmol, reaction time: 1 h).

Flash chromatography: pentane.

Yield: Colorless oil (crude NMR yield: 90%).

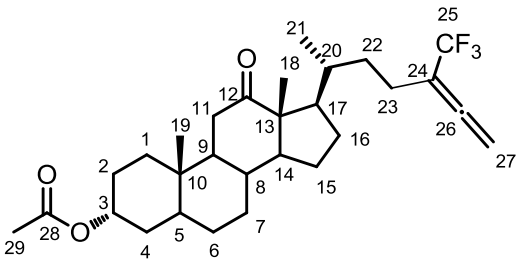
The product could not be isolated because of its low boiling point. Some pentane remains present on the spectra.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.46 – 7.44 (m, 2H, (H_{Ar}), 7.40 – 7.30 (m, 3H, H_{Ar}), 5.54 (q, J = 3.5 Hz, 2H, H_4)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	208.7 (q, J = 4.1 Hz, C_3), 129.3 (C_5), 128.8 (C_{Ar}), 128.4 (C_{Ar}), 127.2 (C_{Ar}), 123.5 (q, J = 273.7 Hz, C_1), 102.0 (J = 34.5 Hz, C_2), 83.6 (C_4)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-61.4
IR (cm^{-1}, CCl_4)	3091 (w), 3068 (w), 3035 (w), 2929 (w), 2874 (w), 2259 (s), 1958 (s), 1710 (m), 1594 (m), 1572 (m), 1479 (m), 1456 (m), 1406 (m), 1386 (m), 1321 (s),

1271 (m), 1190 (s, br), 1146 (s), 1076 (s), 1029 (s)

MS (HRMS EI) Calcd for $C_{10}H_7F_3$: 184.0500 Found: 184.0499

(3R,10S,13R,17R)-10,13-dimethyl-12-oxo-17-((R)-5-(trifluoromethyl)hepta-5,6-dien-2-yl)hexadecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate (III.14s)



$C_{29}H_{41}F_3O_3$
M = 494.63 g.mol^{-1}

Following general procedure D starting with **III.13s** (0.046 mmol, reaction time: 26 h).

Flash chromatography: PE/EtOAc 90 : 10.

Yield: 20.7 mg (91 %) of a white solid.

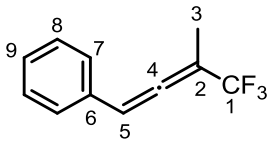
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 5.20 – 5.15 (m, 2H, H_{27}), 4.73 – 4.65 (m, 1H, H_3), 2.48 (t, *J* = 12.2 Hz, 1H, H_{11}), 2.27 – 2.17 (m, 1H), 2.06 – 2.01 (m, 3H, $H_{11+?}$), 2.01 (s, 3H, H_{29}), 1.92 – 1.02 (m, 21H), 1.02 (s, 2x3H, H_{28+19}), 0.87 (d, *J* = 5.9 Hz, 3H, H_{21})

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$) 214.9 (C_{12}), 206.6 (q, *J* = 5.1 Hz, C_{26}), 170.8 (C_{28}), 124.0 (q, *J* = 271.7 Hz, C_{25}), 99.1 (q, *J* = 34.5 Hz, C_{24}), 82.2 (C_{27}), 73.9 (C_3), 58.8 (CH), 57.7 (C_{13}), 46.6 (CH), 44.2 (CH), 41.5 (CH), 38.3 (C_{11}), 35.8 (CH), 35.7 (CH), 35.5 (C_{10}), 35.1 (CH_2), 33.1 (CH_2), 32.3 (CH_2), 27.7 (CH_2), 27.1 (CH_2), 26.5 (CH_2), 26.2 (CH_2), 24.5 (CH_2), 23.0 (CH_2), 22.9 (C_{18}), 21.6 (C_{29}), 18.9 (C_{21}), 11.8 (C_{19})

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$) 65.2

IR (cm^{-1}, neat)	2937 (br s), 2872 (s), 2251 (s), 1985 (w), 1955 (w), 1722 (s), 1702 (s), 1602 (w), 1464 (m), 1450 (m), 1383 (m), 1365 (m), 1337 (m), 1307 (m), 1258 (s), 1158 (s), 1123 (s), 1029 (m)
MS (HRMS APCI)	Calcd for $C_{29}H_{41}F_3O_3$: 494.3008 Found: 494.3000

(3-(benzyloxy)-4,4,4-trifluoro-3-methylbut-1-yn-1-yl)benzene (III.14t)



$C_{11}H_9F_3$
M = 198.18 g.mol^{-1}

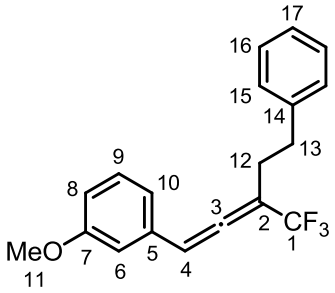
Following general procedure D starting with **III.13t** (0.20 mmol, reaction time: 1 h).

Flash chromatography: pentane.

Yield: 36.0 mg (91 %) of a colorless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.38 – 7.25 (m, 5H, H_{Ar}), 6.56 – 6.50 (m, 1H, H_5), 1.97 (d, J = 3.0 Hz, 3H, H_3)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	204.1 (q, J = 3.9 Hz, C_4), 132.1 (C_6), 129.0 (C_8), 128.3 (C_9), 127.5 (C_7), 123.6 (q, J = 273.8 Hz, C_1), 100.2 (C_5), 98.0 (q, J = 35.2 Hz, C_2), 13.2 (C_3)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-66.5
IR (cm^{-1}, neat)	2922 (s), 2853 (s), 2366 (w), 2355 (m), 2350 (m), 1661 (m), 1634 (m), 1456 (w), 1375 (w), 1275 (w), 1261 (w), 1117 (w)
MS (HRMS APCI)	Calcd for $C_{11}H_{10}F_3$: 199.0729 Found: 199.0729 [M+H^+]

1-methoxy-3-(5-phenyl-3-(trifluoromethyl)penta-1,2-dienyl)benzene (III.14w)



$C_{19}H_{17}F_3O$
M = 318.33 g.mol^{-1}

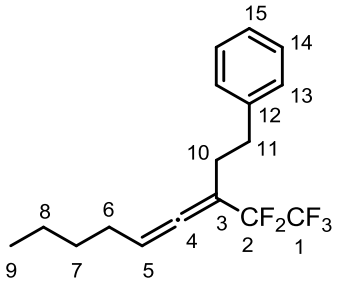
Following general procedure D starting with **III.13w** (0.20 mmol, reaction time: 12 h).

Flash chromatography: PE / Et_2O 50 : 1.

Yield: 57.8 mg (91%) of a colorless oil (crude NMR yield: 96%).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.27 – 7.21 (m, 3H, H_{Ar}), 7.20 – 7.16 (m, 3H, H_{Ar}), 6.83 – 6.79 (m, 2H, H_{Ar}), 6.76 – 6.75 (m, 1H, H_{Ar}), 6.53 (hept, J = 3.3 Hz, 1H, H_4), 3.79 (s, 3H, H_{11}), 2.90 – 2.77 (m, 2H, H_{13}), 2.63 – 2.57 (m, 2H, H_{12})
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	204.2 (q, J = 4.1 Hz, C_3), 160.0 (C_7), 140.6 (C_{14}), 133.3 (C_5), 130.0 (C_{Ar}), 128.6 (C_{15or16}), 128.5 (C_{15or16}), 126.3 (C_{Ar}), 123.6 (q, J = 274.5 Hz, C_1), 120.1 (C_{Ar}), 113.9 (C_{Ar}), 112.9 (C_{Ar}), 102.5 (q, J = 34.0 Hz, C_2), 101.9 (C_4), 55.4 (C_{11}), 33.6 (C_{13}), 28.4 (C_{12})
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-65.0
IR (cm^{-1}, CCl_4)	3066 (w), 3030 (w), 3007 (w), 2940 (w), 2838 (w), 2253 (s), 1965 (w), 1599 (m), 1584 (m), 1493 (m), 1469 (m), 1455 (m), 1440 (m), 1408 (w), 1304 (m), 1288 (m), 1261 (s), 1158 (s), 1125 (s), 1051 (m)
MS (HRMS EI)	Calcd for $C_{19}H_{17}F_3O$: 318.1231 Found: 318.1226

(3-(perfluoroethyl)nona-3,4-dienyl)benzene (III.14z)



$C_{17}H_{19}F_5$
M = 318.32 g.mol^{-1}

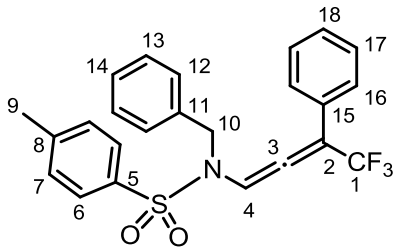
Following general procedure D starting with **III.13z** (0.20 mmol, reaction time: 23 h).

Flash chromatography: pentane.

Yield: 50.7 mg (80%) of a colorless oil (crude NMR yield: 94%).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.33 – 7.28 (m, 2H, H_{Ar}), 7.25 – 7.18 (m, 3H, H_{Ar}), 5.65 – 5.67 (m, 1H, H_5), 2.76 (td, J = 8.4, 3.6 Hz, 2H, H_{11}), 2.53 – 2.39 (m, 2H, H_{10}), 2.08 – 1.99 (m, 2H, H_6), 1.39 – 1.32 (m, 4H, H_{7+8}), 0.92 (t, *J* = 6.9 Hz, 3H, H_9)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	204.1 (t, *J* = 7.4 Hz, C_4), 141.0 (C_{12}), 128.5 (C_{13or14}), 128.5 (C_{13or14}), 126.3 (C_{15}), 119.4 (qt, *J* = 286.6, 38.9 Hz, C_1), 113.4 (tq, *J* = 253.2, 37.3 Hz, C_2), 99.2 (C_5), 96.5 (t, *J* = 26.3 Hz, C_3), 34.0 (C_{11}), 30.9 (C_7), 27.9 (C_{6or10}), 27.9 (C_{6or10}), 22.3 (C_8), 13.9 (C_9)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-84.4 (s), -113.2 (s)
IR (cm^{-1}, CCl_4)	3088 (w), 3066 (w), 3030 (w), 2960 (m), 2930 (m), 2874 (w), 2861 (w), 2252 (m), 1971 (w), 1604 (w), 1497 (w), 1455 (m), 1364 (w), 1334 (m), 1202 (br s), 1129 (m), 1087 (m), 1030 (w)
MS (HRMS EI)	Calcd for $C_{17}H_{19}F_5$: 318.1407 Found: 318.1406

N-benzyl-4-methyl-N-(4,4,4-trifluoro-3-phenylbuta-1,2-dien-1-yl)benzenesulfonamide (III.14ai)



$C_{24}H_{20}F_3NO_2S$
M = 443.48 g.mol^{-1}

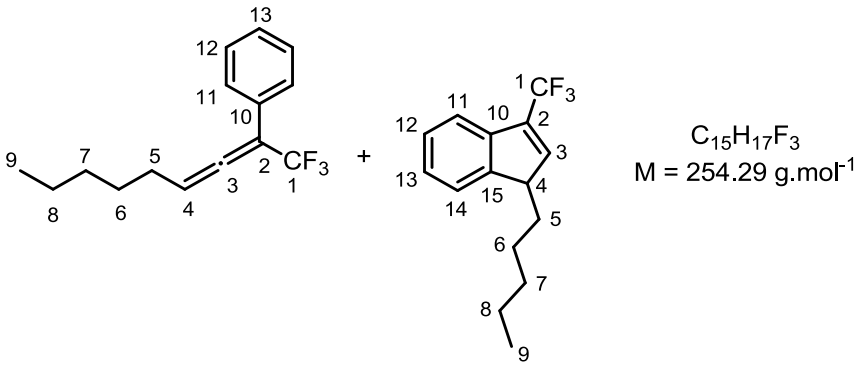
Following general procedure D starting with **III.13ai** (0.20 mmol, reaction time: 2 h).

Flash chromatography: PE/EtOAc 95 : 5.

Yield: 18 mg (20% yield) of a colorless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.78 (d, *J* = 8.3 Hz, 2H, H_7), 7.63 – 7.62 (m, 1H, H_{Ar}), 7.38 (d, J = 8.2 Hz, 2H, H_6), 7.22 – 7.07 (m, 7H, H_{Ar}), 6.62 (d, J = 6.8 Hz, 2H, H_{Ar}), 4.60 (d, J = 15.0 Hz, 1H, H_{10}), 3.98 (d, J = 15.0 Hz, 1H, $H_{10'}$), 2.48 (s, 3H, H_9)	
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	197.5 (C_3), 144.7 (C_8), 135.1 ($C_{Ar\text{-}q}$), 134.5 ($C_{Ar\text{-}q}$), 130.2 (C_{Ar}), 129.1 ($C_{Ar\text{-}q}$), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 127.8 (C_{Ar}), 127.1 (C_{Ar}), 127.3 (C_{Ar}), 127.1 (C_{Ar}), 107.6 (C_{Ar}), 51.3 (C_{10}), 21.8 (C_9) (C_1 and C_2 were not observed because of the low intensity of the quadruplets)	
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-62.0	
MS (HRMS EI)	Calcd for $C_{24}H_{21}F_3NO_2S$: 444.1244 [*M*+H^+]	Found: 444.1244

(1,1,1-trifluorononona-2,3-dien-2-yl)benzene (III.14aj) & 1-pentyl-3-(trifluoromethyl)-1H-indene (III.20aj)



Following general procedure D starting with **III.13aj** (0.1 mmol).

Flash chromatography: PE.

Yield: Using catalyst **III.12** at 60 °C during 16 h led to the formation of a mixture of 18% of allene and 81% of indene (NMR yields). Using catalyst **III.9** at room temperature during 24 h led to an isolated yield of 81% (mixture allene / indene 5 : 1).

Characterization: Due to the difficulty to separate an allene from the corresponding indene, they were characterized together. A pure sample of the indene could be obtained by adding an excess of gold catalyst to an allene/indene mixture until complete conversion of the allene into the indene. A sample of the allene could be obtained by adding an excess of NaH to an allene/indene mixture (in order to deprotonate the indene) and by quenching it with an electrophile (benzaldehyde). In both cases, purification by flash chromatography with pure PE was carried out.

Allene III.14aj:

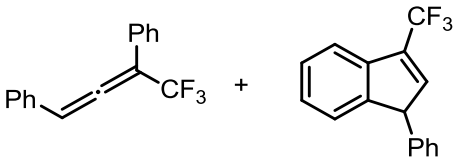
^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.45 – 7.42 (m, 2H, H_{Ar}), 7.39 – 7.34 (m, 2H, H_{Ar}), 7.31 – 7.28 (m, 1H, H_{13}), 5.95 (tq, *J* = 6.6, 3.2 Hz, 1H, H_4), 2.25 – 2.19 (m, 2H, H_5), 1.54 – 1.48 (m, 2H, H_6), 1.39 – 1.25 (m, 4H, H_{7+8}), 0.90 – 0.86 (m, 3H, H_9)

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	204.4 (q, *J* = 4.1 Hz, C_3), 130.5 (C_{10}), 128.8 (C_{Ar}), 128.0 (C_{Ar}), 127.4 (q, *J* = 1.5 Hz, C_{11}), 123.6 (q, *J* = 273.9 Hz, C_1), 101.9 (q, *J* = 34.2 Hz, C_2), 100.2 (C_4), 31.3 (C_{7or8}), 28.4 (C_6), 28.2 (C_5), 22.5 (C_{7or8}), 14.1 (C_9)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-61.4
IR (cm^{-1}, CCl_4)	3066 (w), 3038 (w), 2959 (m), 2930 (m), 2860 (m), 1960 (w), 1602 (w), 1498 (w), 1467 (w), 1403 (w), 1304 (s), 1173 (s), 1128 (s), 934 (m)
MS (HRMS EI)	Calcd for $C_{15}H_{17}F_3$: 254.1282 Found: 254.1282

Indene III.20aj:

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.50 – 7.44 (m, 2H, H_{Ar}), 7.36 – 7.26 (m, 2H, H_{Ar}), 6.99 – 6.98 (m, 1H, H_3), 3.62 – 3.55 (m, 1H, H_4), 1.99 – 1.91 (m, 1H, H_5), 1.60 – 1.51 (m, 1H, $H_{5'}$), 1.50 – 1.26 (m, 6H, H_{6+7+8}), 0.91 – 0.87 (m, 3H, H_9)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	147.9 (C_5), 141.1 (q, *J* = 5.0 Hz, C_3), 138.3 (C_{10}), 133.9 (q, *J* = 34.2 Hz, C_2), 127.1 (C_{Ar}), 126.3 (C_{Ar}), 123.4 (C_{Ar}), 122.6 (q, *J* = 269.8 Hz, C_1), 120.7 (C_{Ar}), 49.8 (C_4), 32.1 (C_{aliph}), 30.9 (C_{11}), 27.3 (C_{aliph}), 22.6 (C_{aliph}), 14.2 (C_{15})
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-65.0
IR (cm^{-1}, CCl_4)	3074 (w), 3049 (w), 3025 (w), 2959 (m), 2932 (s), 2860 (m), 1626 (w), 1466 (m), 1383 (m), 1317 (m), 1268 (m), 1216 (m), 1168 (s), 1131 (s), 971 (m)
MS (HRMS EI)	Calcd for $C_{15}H_{17}F_3$: 254.1282 Found: 254.1286

(1,1,1-trifluorononona-2,3-dien-2-yl)benzene (III.14ak) & 1-pentyl-3-(trifluoromethyl)-1H-indene (III.20ak)



$C_{15}H_{17}F_3$
M = 260.25 g.mol^{-1}

Following general procedure D starting with **III.13ak** (0.2 mmol).

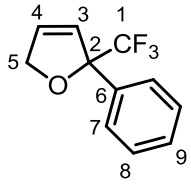
Due to the instability of the indene on silica, the mixture could not be purified. NMR yields could be obtained by using characteristic signals.

Yield: Using catalyst **III.12** at 60 °C during 20 h led to the formation of a mixture of 21% of allene and 72% of indene (NMR yields).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): Characteristic peaks: 6.94 (q, *J* = 3.1 Hz, 1H, allene), 4.74 – 4.71 (m, 1H, indene)

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$): -61.0 (allene), -65.0 (indene)

(3-(benzyloxy)-4,4,4-trifluoro-3-methylbut-1-yn-1-yl)benzene (III.21al)



$C_{11}H_9F_3O$
M = 214.18 g.mol^{-1}

Following general procedure D starting with **III.13al** (0.20 mmol, reaction time: 1 h).

Flash chromatography: PE/EtOAc 98 : 2.

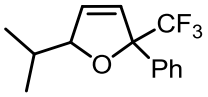
Yield: 35.2 mg (82 %) of colorless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$): 7.55 – 7.53 (m, 2H, H_{Ar}), 7.43 – 7.33 (m, 3H, H_{Ar}), 6.25 (d, *J* = 6.1 Hz, 1H, H_3), 6.16 (dt, *J* = 6.1, 2.4 Hz, 1H, H_4), 4.97 (ddd, *J* = 13.4, 2.4, 1.6 Hz, 1H, H_5), 4.85 – 4.81 (d, *J* = 13.4 Hz, 1H, $H_{5'}$)

^{13}C NMR (δ, ppm): 137.1 (C_6), 131.7 (C_3), 128.7 (C_{Ar}), 128.5 (C_{Ar}),

(75 MHz, $CDCl_3$)	126.4 (C_{Ar}), 125.2 (C_4), 124.8 (q, J = 285.9 Hz, C_1), 92.2 (q, J = 30.2 Hz, C_2), 77.1 (C_5)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-79.4
IR (cm^{-1}, neat)	2957 (m), 2924 (s), 2851 (s), 2357 (w), 1647 (w), 1458 (m), 1377 (w), 1275 (w), 1180 (w), 1132 (w), 1078 (m), 945 (w)
MS (HRMS APCI)	Calcd for $C_{11}H_{10}F_3$: 145.0648 [M-CF_3^+] Found: 145.0648

5-isopropyl-2-phenyl-2-(trifluoromethyl)-2,5-dihydrofuran (III.21am)



$C_{14}H_{15}F_3O$
M = 256.26 g.mol^{-1}

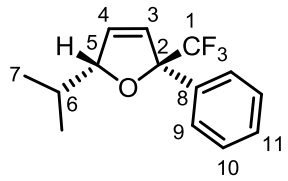
Following general procedure D starting with **III.13am** (0.20 mmol, reaction time: 2 h).

Flash chromatography: PE/EtOAc 99 : 1.

Yield: 45.1 mg (88 %) of a colorless oil as a 1 : 1 mixture of two diastereoisomers.

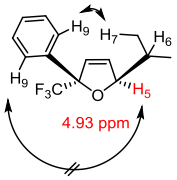
The diastereoisomers were separated by HPLC using a XBridge C18 10x100mm 5µm column (H_2O/CH_3CN 40/60, 5 mL/min, 210 nm, tR_{trans} = 3.999 min, tR_{cis} = 4.664 min).

trans-5-isopropyl-2-phenyl-2-(trifluoromethyl)-2,5-dihydrofuran (trans-III.21am)



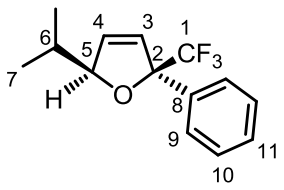
^{1}H NMR (δ, ppm) 7.55 – 7.53 (m, 2H, H_9), 7.42 – 7.31 (m, 3H,

(300 MHz, $CDCl_3$)	H_{10+11}), 6.22 – 6.16 (m, 2H, H_{3+4}), 4.95 – 4.93 (m, 1H, H_5), 1.87 – 1.72 (m, 1H, H_6), 0.92 (d, J = 6.8 Hz, 3H, H_7), 0.84 (d, J = 6.8 Hz, 3H, $H_{7'}$)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	137.5 (C_8), 134.1 (C_3), 128.5 (C_{11}), 128.4 (C_{10}), 126.5 (C_9), 125.6 (C_4), 125.0 (q, J = 286.6 Hz, C_1), 93.8 (C_5), 91.7 (q, J = 29.8 Hz, C_2), 33.2 (C_6), 18.4 (C_7), 18.3 ($C_{7'}$)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-79.8
IR (cm^{-1}, neat)	2954 (m), 2922 (s), 2854 (m), 2359 (w), 2334 (w), 1717 (m), 1458 (m), 1377 (w), 1277 (m), 1261 (w), 1169 (m), 1068 (w), 1058 (w), 947 (w)
MS (HRMS APCI)	Calcd for $C_{14}H_{14}F_3O$: 255.0991 [M-H^+] Found: 255.0990



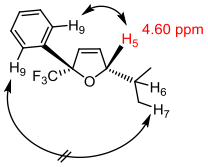
The stereochemistry was determined by H-H NOESY correlation. The NOESY spectrum showed NOE between H_7 and H_9. Furthermore, no NOE between H_6 and H_9 was observed. This product was assigned to the *trans*-isomer.

cis-5-isopropyl-2-phenyl-2-(trifluoromethyl)-2,5-dihydrofuran (cis-III.21am)



^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.53 – 7.51 (m, 2H, H_9), 7.40 – 7.33 (m, 3H, H_{10+11}), 6.21 – 6.14 (m, 2H, H_{3+4}), 4.60 – 4.58 (m, 1H, H_5),

	1.99 – 1.87 (m, 1H, H_6), 1.08 (d, *J* = 6.8 Hz, 3H, H_7), 0.97 (d, *J* = 6.8 Hz, 3H, $H_{7'}$)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	137.5 (C_8), 133.3 (C_3), 128.4 (C_{11}), 128.2 (C_{10}), 126.4 (C_9), 125.8 (C_4), 124.1 (q, *J* = 286.6 Hz, C_1), 92.9 (C_5), 91.2 (q, *J* = 30.5 Hz, C_2), 33.1 (C_6), 19.0 (C_7), 18.2 ($C_{7'}$)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-78.5
IR (cm^{-1}, neat)	2955 (m), 2923 (s), 2853 (s), 2359 (s), 2330 (w), 1660 (m), 1456 (m), 1377 (m), 1277 (m), 1180 (m), 1169 (m), 1132 (m), 1097 (m), 1070 (m), 947 (m), 912 (w)
MS (HRMS APCI)	Calcd for $C_{14}H_{14}F_3O$: 255.0991 [*M*-H$^+$] Found: 255.0990



The stereochemistry was determined by H-H NOESY correlation. The NOESY spectrum showed NOE between H_5 and H_9. Furthermore, no NOE between H_7 and H_9 was observed. This product was assigned to the *cis*-isomer.

Post-functionalization of the CF_3-allenes

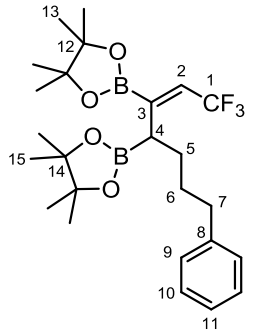
Palladium-catalyzed diboration

This reaction was carried out inspired from a literature procedure.[222] $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 2.9 mg) and $P(NMe_2)_3$ (stock solution 0.06 mol.L^{-1} in toluene) (0.06 equiv, 0.006 mmol, 0.1 mL of solution) were

[222] Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D., Morker, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 16328–16329

dissolved in toluene (0.9 mL). After 30 min stirring at room temperature, bispinacolatodiboron (1.4 equiv, 0.14 mmol, 35.6 mg) was added, followed by allene **III.14g** (1.0 equiv, 0.10 mmol, 22.6 mg) dissolved in toluene (0.25 mL). The mixture was stirred 5 h at room temperature and filtered on silica (eluting with Et_2O). The crude mixture was purified by flash column chromatography (PE/Et_2O 95 : 5) to furnish the diborated product as two isomers (colourless oil, 29 mg, 60% global yield, Z/E 2 : 1 ratio). Both isomers could be separated by column chromatography and characterized individually.

(Z)-2,2'-(1,1,1-trifluoro-7-phenylhept-2-ene-3,4-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) ((Z)-III.25g) (major isomer)

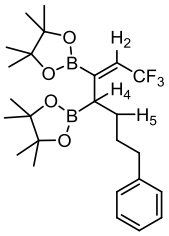


$C_{25}H_{37}B_2F_3O_4$
M = 480.18 g.mol^{-1}

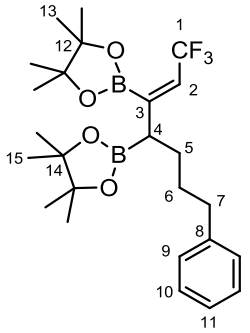
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.27 – 7.22 (m, 3H, H_{Ar}), 7.16 – 7.12 (m, 2H, H_{Ar}), 6.24 (q, *J* = 8.8 Hz, 1H, H_2), 2.69 – 2.45 (m, 3H, H_{4+7}), 1.80 – 1.72 (m, 2H, H_6), 1.57 – 1.47 (m, 2H, H_5), 1.22 – 1.20 (m, 24H, H_{14+15})
^{13}C NMR (δ, ppm) (125 MHz, $CDCl_3$)	143.0 (C_8), 128.6 (C_{9or10}), 128.3 (C_{9or10}), 128.0 (q, *J* = 32.2 Hz, C_2), 125.6 (C_{11}), 36.1 (C_7), 31.4 (C_5), 29.1 (C_6), 25.0 (C_{14or15}), 24.9 (C_{14or15}), 24.7 (C_{14or15}), 24.6 (C_{14or15}) (C_3 and C_4 were not observed due to quadrupolar coupling effects of ^{11}B ; C_1 was not observed because of the low intensity of the quadruplet)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-57.8

IR (cm^{-1}, neat)	2978 (m), 2928 (m), 2854 (m), 2359 (w), 2330 (w), 1684 (w), 1636 (w), 1558 (w), 1541 (w), 1506 (w), 1456 (w), 1373 (m), 1339 (m), 1325 (m), 1263 (s), 1215 (m), 1140 (s), 1117 (s), 1088 (m), 968 (m), 864 (m)	
MS (HRMS APCI)	Calcd for $C_{25}H_{38}B_2F_3O_4$: 481.2904 [M+H^+]	Found: 481.2907

The stereochemistry was determined by H-H NOESY correlation. No significant correlation was observed on this isomer. The NOESY correlations of the other isomer are needed to confirm the stereochemistry of each compound.



(E)-2,2'-(1,1,1-trifluoro-7-phenylhept-2-ene-3,4-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) ((E)- III.25g) (minor isomer)

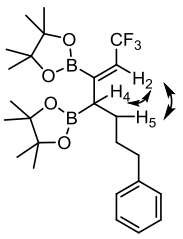


$C_{25}H_{37}B_2F_3O_4$
M = 480.18 $g.mol^{-1}$

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.29 – 7.24 (m, 2H, H_{Ar}), 7.19 – 7.14 (3H, H_{Ar}), 5.81 (q, J = 7.8 Hz, 1H, H_2), 2.60 (t, J = 6.5 Hz, 2H, H_7), 2.02 – 1.98 (m, 1H, H_4), 1.71 – 1.56 (m, 4H, H_{5+6}), 1.27 – 1.22 (m, 24H, H_{13+15})

^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	142.6 (C_8), 128.6 (C_{9or10}), 128.4 (C_{9or10}), 125.8 (C_{11}), 36.0 (C_7), 31.0 (C_5), 29.6 (C_6), 25.0 (C_{14or15}), 24.9 (C_{14or15}), 24.8 (C_{14or15}), 24.8 (C_{14or15}) (C_3 and C_4 were observed due to quadrupolar coupling effects of ^{11}B ; C_1 and C_2 not observed because of the low intensity of the quadruplets)	
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-60.3	
IR (cm^{-1}, neat)	2976 (m), 2924 (m), 2851 (m), 2359 (w), 2330 (w), 1734 (w), 1647 (w), 1541 (w), 1456 (w), 1362 (m), 1325 (m), 1292 (m), 1275 (m), 1132 (s), 1117 (s), 966 (w), 856 (m)	
MS (HRMS APCI)	Calcd for $C_{25}H_{38}B_2F_3O_4$: 481.2904 [M+H^+]	Found: 481.2907

The stereochemistry was determined by H-H NOESY correlation. The NOESY spectrum showed NOE between H_2 and H_4 as well as between H_2 and H_5. This product was assigned to the *(E)*-isomer.

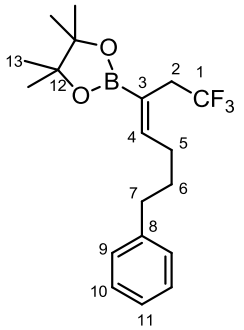


Copper-catalyzed hydroboration

IMesCuDBM (0.05 equiv, 0.005 mmol, 3.0 mg) and bispinacolatodiboron (1.1 equiv, 0.11 mmol, 27.9 mg) were dissolved in THF (0.5 mL) and stirred 5 minutes at room temperature. Allene **III.14g** (1.0 equiv, 0.1 mmol, 22.6 mg) and MeOH (7.4 equiv, 0.74 mmol, 23.8 mg, 30 μL) were dissolved in THF (0.2 mL) and add to the reaction. The mixture was stirred 15 h at room temperature and filtered on silica (eluting with Et_2O). The crude mixture was purified by flash column chromatography (PE/Et_2O 97 : 3) to furnish the

hydroborated product as two isomers (colourless oil, 20.7 mg, 58% global yield, Z/E 6 : 1 ratio). Both isomers could be separated by column chromatography and characterized individually.

(Z)-4,4,5,5-tetramethyl-2-(1,1,1-trifluoro-7-phenylhept-3-en-3-yl)-1,3,2-dioxaborolane ((Z)-III.23g) (major isomer)

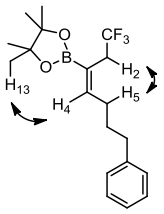


$C_{19}H_{26}BF_3O_2$
M = 354.21 g.mol^{-1}

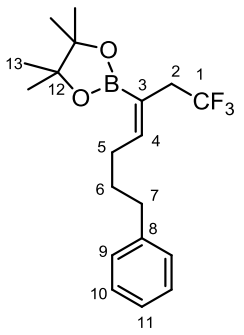
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.31 – 7.25 (m, 2H, H_{10}), 7.20 – 7.16 (m, 3H, H_{9+11}), 6.63 (t, *J* = 7.1 Hz, 1H, H_4), 2.93 (q, *J* = 11.0 Hz, 2H, H_2), 2.67 – 2.62 (m, 2H, H_7), 2.26 – 2.18 (m, 2H, H_5), 1.82 – 1.72 (m, 2H, H_6), 1.26 (s, 12H, H_{13})
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	152.4 (C_4), 141.9 (C_8), 128.4 (C_{9or10}), 128.4 (C_{9or10}), 126.4 (q, *J* = 277.2 Hz, C_1), 125.8 (C_{11}), 83.6 (C_{12}), 35.5 (C_7), 32.5 (q, *J* = 29.3 Hz, C_2), 30.2 (C_6), 28.7 7 (C_5), 24.6 (C_{13}) (C_3 was not observed due to quadrupolar coupling effects of ^{11}B)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-65.8
IR (cm^{-1}, neat)	2978 (m), 2930 (m), 2856 (m), 2357 (w), 2330 (w), 1734 (w), 1636 (m), 1605 (w), 1497 (m), 1454 (m), 1416 (m), 1381 (s), 1346 (s), 1315 (s), 1277 (s), 1252 (s), 1215 (m), 1167 (s), 1117 (br s), 1030 (m), 962 (m), 924 (m), 864 (m)
MS (HRMS APCI)	Calcd for $C_{19}H_{26}O_2BF_3Na$: 377.1870 [*M*+Na^+] Found: 377.1872

The stereochemistry was determined by H-H NOESY correlation. The NOESY spectrum showed NOE between H_2 and H_5 as well as between H_4 and

H_{13}. Furthermore, no NOE between H_2 and H_4 or between H_5 and H_{13} was observed. This product was assigned to the *(Z)*-isomer.



(E)-4,4,5,5-tetramethyl-2-(1,1,1-trifluoro-7-phenylhept-3-en-3-yl)-1,3,2-dioxaborolane ((E)- III.23g) (minor isomer)

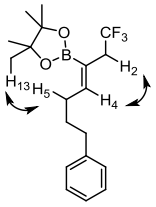


$C_{19}H_{26}BF_3O_2$
M = 354.21 g.mol^{-1}

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.30 – 7.25 (m, 2H, H_{10}), 7.19 – 7.16 (m, 3H, H_{9+11}), 6.30 (t, *J* = 7.5 Hz, 1H, H_4), 2.85 (q, *J* = 11.1 Hz, 2H, H_2), 2.64 – 2.59 (m, 2H, H_7), 2.48 – 2.40 (m, 2H, H_5), 1.76 – 1.46 (m, 2H, H_6), 1.23 (s, 12H, H_{13})
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	154.2 (C_4), 142.6 (C_8), 128.6 (C_{9or10}), 128.4 (C_{9or10}), 125.8 (C_{11}), 83.6 (C_{12}), 40.3 (q, *J* = 28.6 Hz, C_2), 35.6 (C_7), 31.4 (C_{5or6}), 31.1 (C_{5or6}), 24.8 (C_{13}) (C_3 was not observed due to quadrupolar coupling effects of ^{11}B, C_1 was not observed because of the low intensity of the quadruplet)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-67.0
IR (cm^{-1}, neat)	2957 (m), 2922 (s), 2854 (m), 2359 (w), 2324 (w), 1456 (w), 1275 (m), 1259 (m), 1134 (m), 1121 (m), 1086 (w)

MS (HRMS APCI)	Calcd for $C_{19}H_{27}O_2BF_3$: 355.2051 [M+H^+]	Found: 355.2050

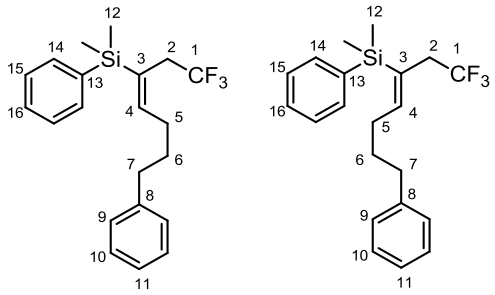
The stereochemistry was determined by H-H NOESY correlation. The NOESY spectrum showed NOE between H_2 and H_4 as well as between H_5 and H_{13}. Furthermore, no NOE between H_2 and H_5 or between H_4 and H_{13} was observed. This product was assigned to the *(E)*-isomer.



Copper-catalyzed hydrosilylation

IMesCuDBM (0.05 equiv, 0.009 mmol, 5.1 mg) was dissolved in THF (0.5 mL) and stirred 5 minutes at room temperature. Allene **III.14g** (1.0 equiv, 0.17 mmol, 39.0 mg) was dissolved in THF (0.2 mL) and add to the reaction, followed by Suginome's reagent $PhMe_2Si$–B(Pin) (1.1 equiv, 0.19 mmol, 49.7 mg, 52 µL) and MeOH (6.0 equiv, 1.02 mmol, 32.7 mg, 41 µL). The mixture was stirred 4 h at room temperature and filtered on silica (eluting with Et_2O). The crude mixture was purified by flash column chromatography (PE/EtOAc 98 : 2) to furnish the hydrosilylated product as two isomers (yellow oil, 41.0 mg, 67% global yield, Z/E 7 : 1 ratio). Both isomers could not be separated by column chromatography and were characterized together.

Dimethyl(phenyl)(1,1,1-trifluoro-7-phenylhept-3-en-3-yl)silane (III.24g)



((*E*)-III.24g)
major isomer

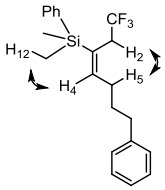
((*Z*)-III.24g)
minor isomer

$C_{21}H_{25}F_3Si$
M = 362.50 g.mol^{-1}

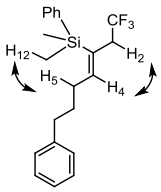
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.52 – 7.49 (m, 2H, H_{Ar}), 7.38 – 7.03 (m, 8H, H_{Ar}), 6.37 (t, *J* = 7.2 Hz, 1H, H_4, minor isomer), 6.16 (t, *J* = 6.9 Hz, 1H, H_4, major isomer), 2.87 (q, *J* = 11.3 Hz, 2H, H_2), 2.65 – 2.60 (m, 2H, H_7, major isomer), 2.40 – 2.35 (m, 2H, H_7, minor isomer), 2.23 (q, *J* = 7.3 Hz, 2H, H_5, major isomer), 2.02 (q, *J* = 7.06 Hz, 2H, H_5, minor isomer), 1.79 – 1.69 (m, 2H, H_6, major isomer), 1.57 – 1.49 (m, 2H, H_6, minor isomer), 0.40 (s, 6H, H_{12})
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	Major isomer: 150.3 (C_4), 142.2 (C_8), 138.0 (C_{Ar}), 134.1 (C_{Ar}), 129.2 (C_{Ar}), 128.5 (C_{9or10}), 128.5 (C_{9or10}), 128.2 (C_{3orAr}), 128.0 (C_{3orAr}), 126.4 (q, *J* = 277.4 Hz, C_1), 126.0 (C_{11}), 35.6 (C_7), 33.6 (q, *J* = 29.0 Hz, C_2), 30.8 (C_6), 29.1 (C_5), -2.5 (C_{12})
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-64.5 (major isomer), -66.3 (minor isomer)
IR (cm^{-1}, neat)	3024 (w), 3005 (w), 2930 (m), 2854 (m), 2353 (w), 1614 (m), 1497 (m), 1454 (m), 1427 (m), 1344 (m), 1279 (m), 1250 (s), 1128 (s), 1111 (s), 1092 (m), 1018 (m), 937 (w), 922 (w), 835 (s), 818 (s)
MS (HRMS ESI)	Calcd for $C_{21}H_{25}F_3NaSi$: 385.1570 [*M*+Na^+] Found: 385.1571

The stereochemistry was determined by H-H NOESY correlation.

For the major isomer, the NOESY spectrum showed NOE between H_2 and H_5 as well as between H_4 and H_{12}. Furthermore, no NOE between H_2 and H_4 or between H_5 and H_{12} was observed. This product was assigned to the *(E)*-isomer.



For the minor isomer, the NOESY spectrum showed NOE between H_2 and H_4 as well as between H_5 and H_{12}. Furthermore, no NOE between H_2 and H_5 or between H_4 and H_{12} was observed. This product was assigned to the *(Z)*-isomer.



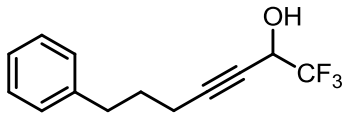
Typical procedure for the enzymatic kinetic resolution of propargyl acetates

A solution of propargyl acetate (1.00, 1.75 mmol equiv) in THF (0.5 mL) was added to water (20 mL). Lipase acrylic resin from Candida Antartica (CALB, supplier: Sigma-Aldrich, 5000 U/g, 500 mg) was added and the mixture was stirred at 40 °C for 2 hours. The mixture was filtrated to remove the acrylic resin, extracted with Et_2O (x3), dried over Na_2SO_4, filtered over silica (Et_2O) and concentrated under reduced pressure. Purification by flash column chromatography (typically PE/EtOAc 95 : 5 to 9 : 1) afforded the pure alcohol and remaining acetate. The enantiomeric excesses were determined using chiral HPLC.

HPLC conditions for the separation of enantiomers in the study of central-to-axial chirality conversion

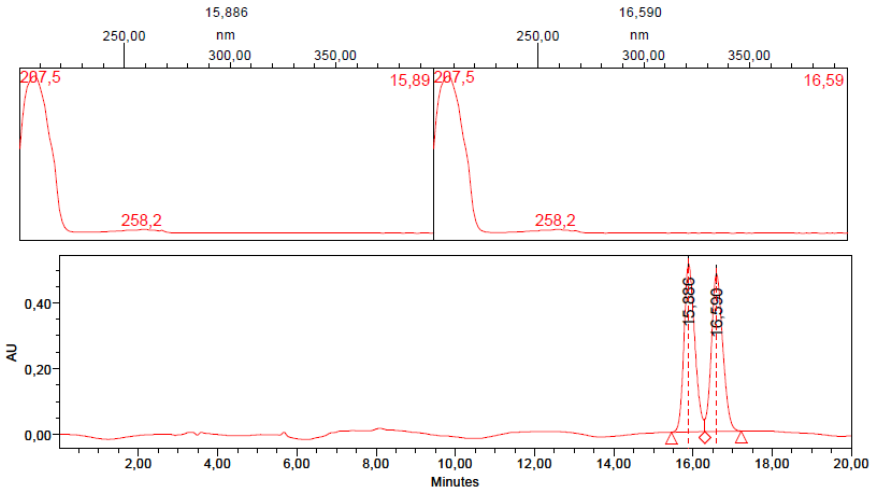
All compounds studied in this section have been separated using a chiral HPLC. The conditions and the retention times are given for the racemic mixtures of compounds. Due to the delay between the measures, some retention time might have shifted in the enantiopure versions. The match between the peaks on the chromatograms is ensured by the UV pattern of the compounds.

1,1,1-trifluoro-7-phenylhept-3-yn-2-ol III.18g

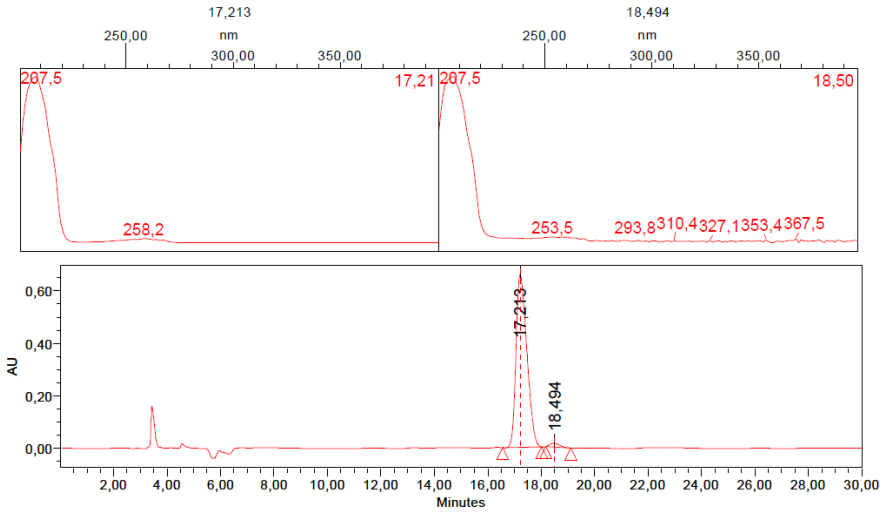


The enantiomers were separated by HPLC using a Chiralcel OJ-H column (isohexane/*i*PrOH 95 : 5, 1 mL/min, 206 nm, tR_a = 15.886 min, tR_b = 16.590 min).

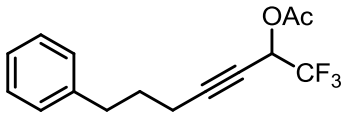
Racemic version:



Enantioenriched version: *ee* = 96%

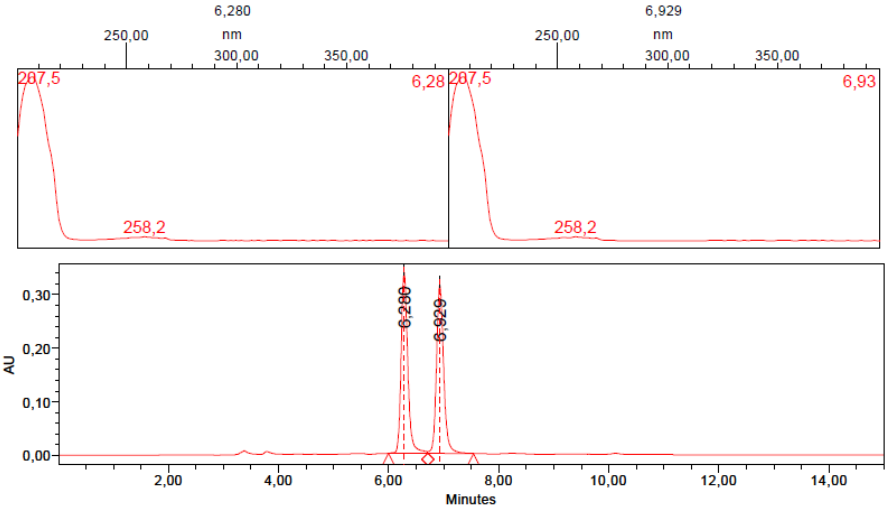


1,1,1-trifluoro-7-phenylhept-3-yn-2-yl acetate III.28g



The enantiomers were separated by HPLC using a Chiralcel OJ-H column (isohexane/*i*PrOH 95 : 5, 1 mL/min, 210 nm, tR_a = 6.280 min, tR_b = 6.929 min).

Racemic version:

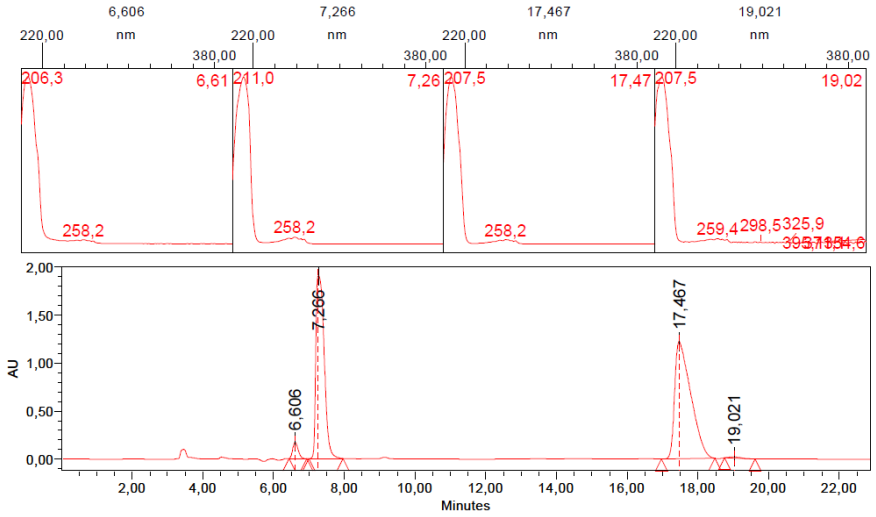


359

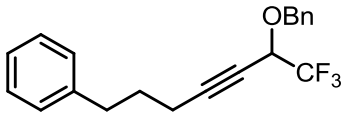
Crude mixture of the enzymatic hydrolysis using the procedure reported (CALB in water).

Peaks 1&2: acetate: *ee* = 89%

Peaks 3&4: alcohol: ee = 98%

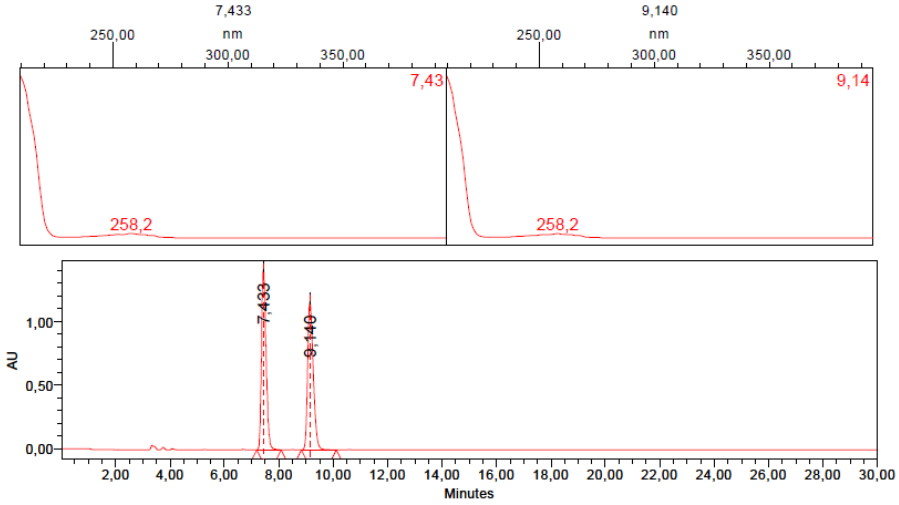


(6-(benzyloxy)-7,7,7-trifluorohept-4-yn-1-yl)benzene III.13g

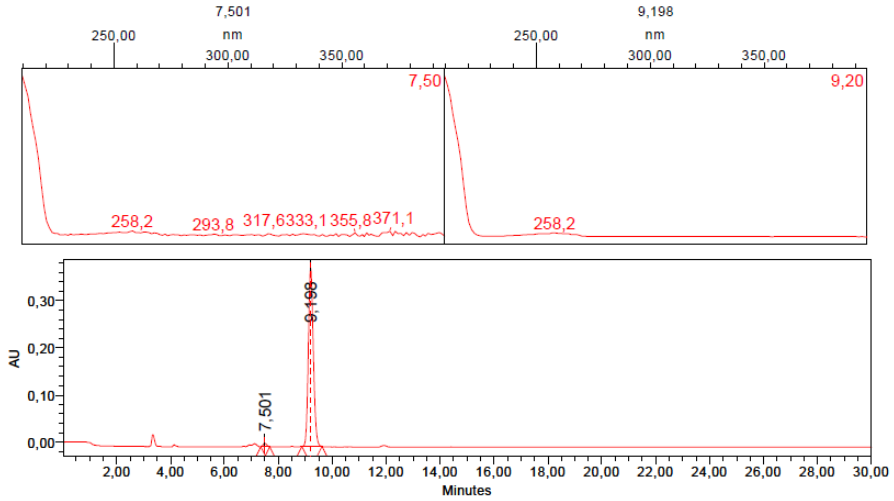


The enantiomers were separated by HPLC using a Chiralcel OJ-H column (isohexane/*i*PrOH 90 : 10, 1 mL/min, 210 nm, tR_a = 7.433 min, tR_b = 9.140 min).

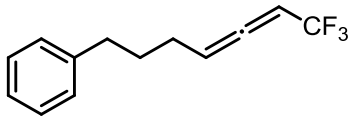
Racemic version:



Enantioenriched version: ee = 97%



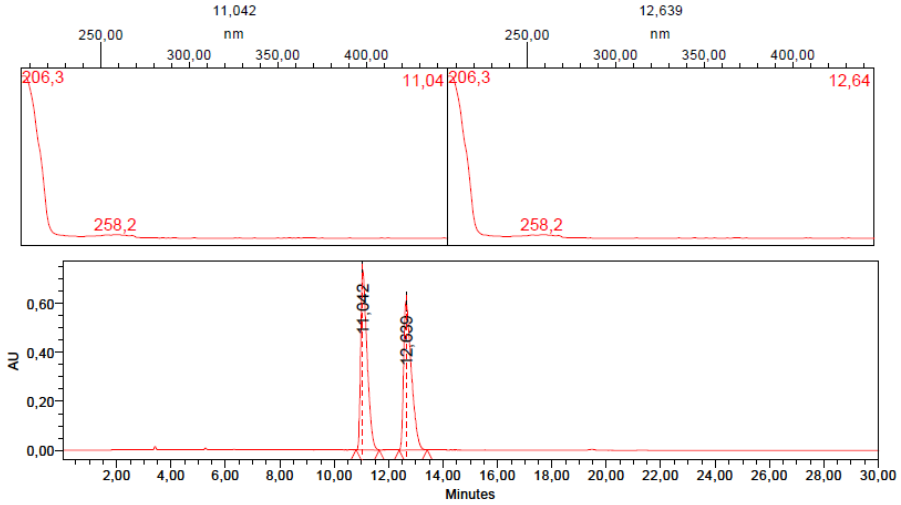
(7,7,7-trifluorohepta-4,5-dien-1-yl)benzene III.14g



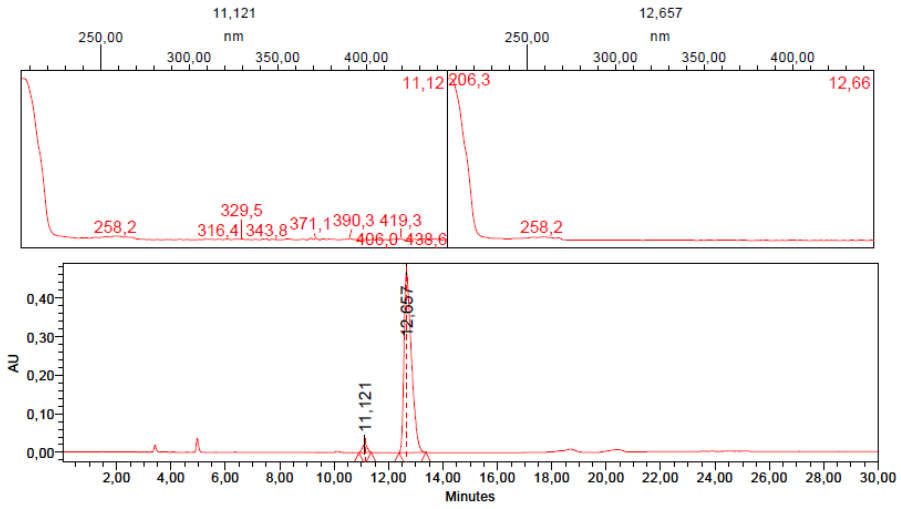
The enantiomers were separated by HPLC using a Chiralcel OJ-H column (isohexane, 1 mL/min, 205 nm, tR_a = 11.042 min, tR_b = 12.639 min).

Racemic version:

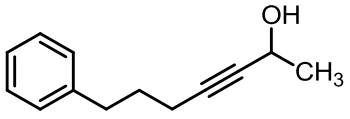
361



Enantioenriched version: *ee* = 94%

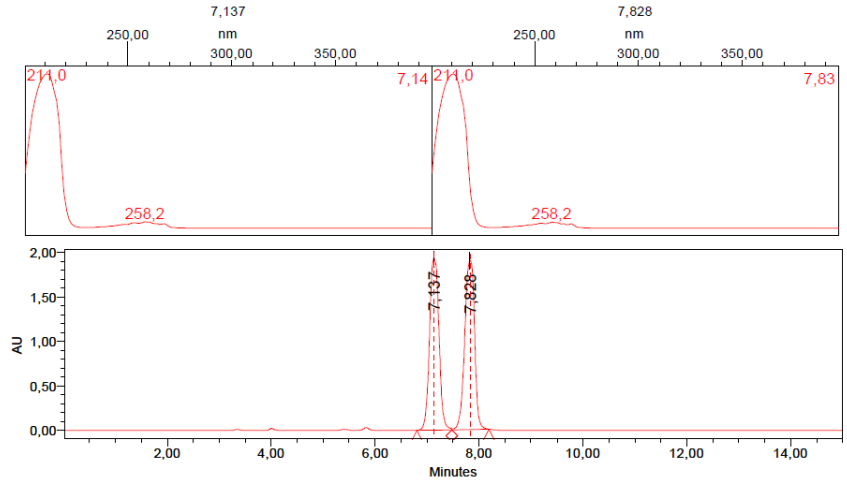


7-phenylhept-3-yn-2-ol

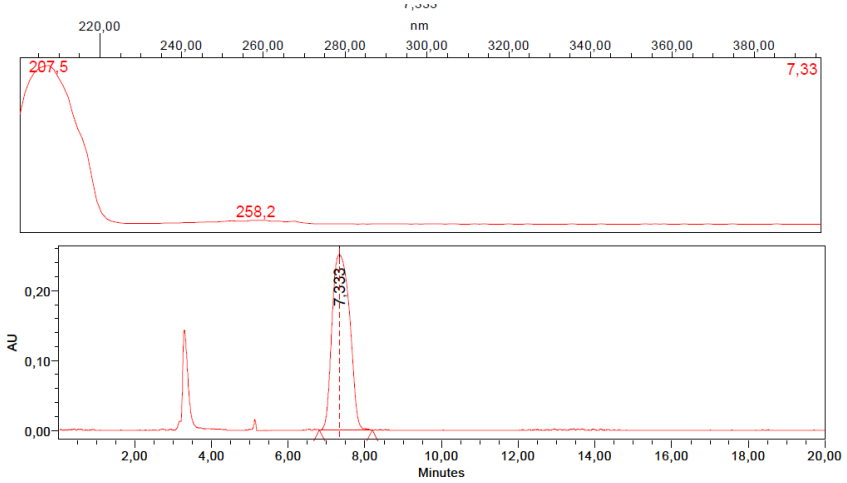


The enantiomers were separated by HPLC using a Chiralpak IB column (isohexane/*i*PrOH 95 : 5, 1 mL/min, 210 nm, tR_a = 7.137 min, tR_b = 7.828 min).

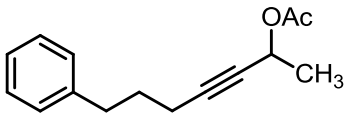
Racemic version:



Enantioenriched version: *ee* > 99%

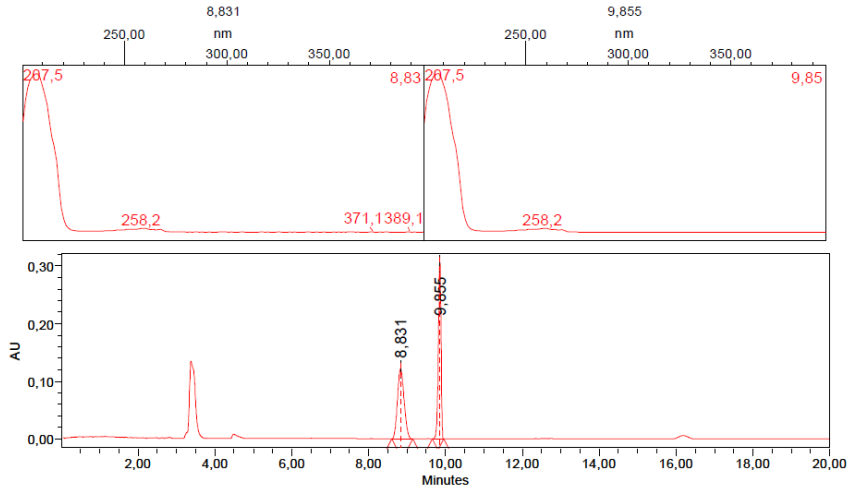


7-phenylhept-3-yn-2-yl acetate

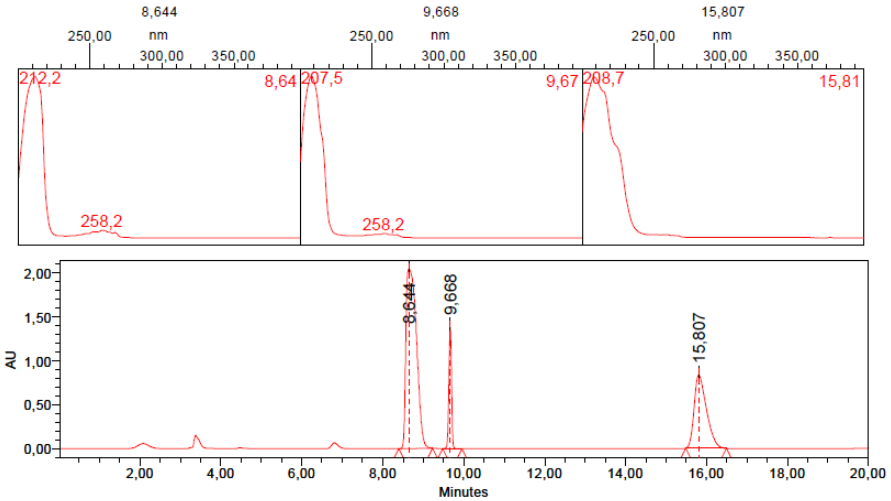


The enantiomers were separated by HPLC using a Chiralcel OJ-H column (isohexane/*i*PrOH 95 : 5, 1 mL/min, 200 nm, tR_a = 8.831 min, tR_b = 9.855 min).

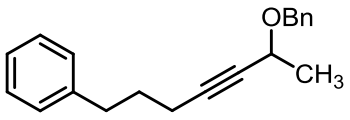
Racemic version:



Enantioenriched version: *ee* = 50%

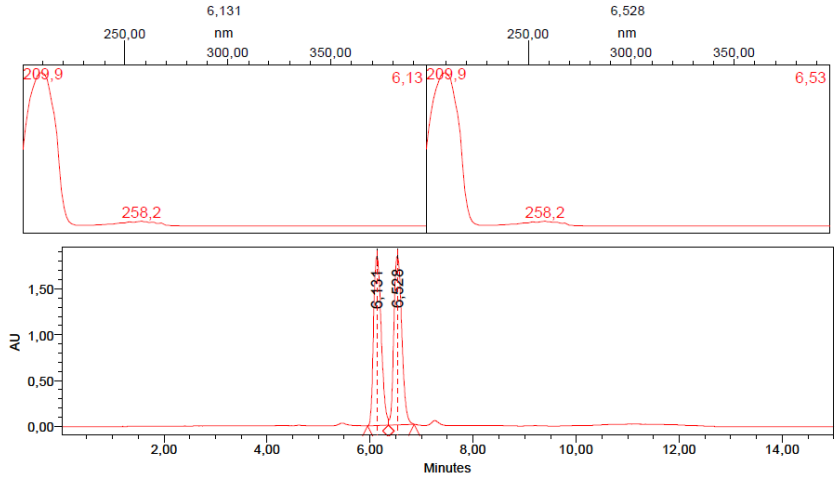


(6-(benzyloxy)hept-4-yn-1-yl)benzene III.29

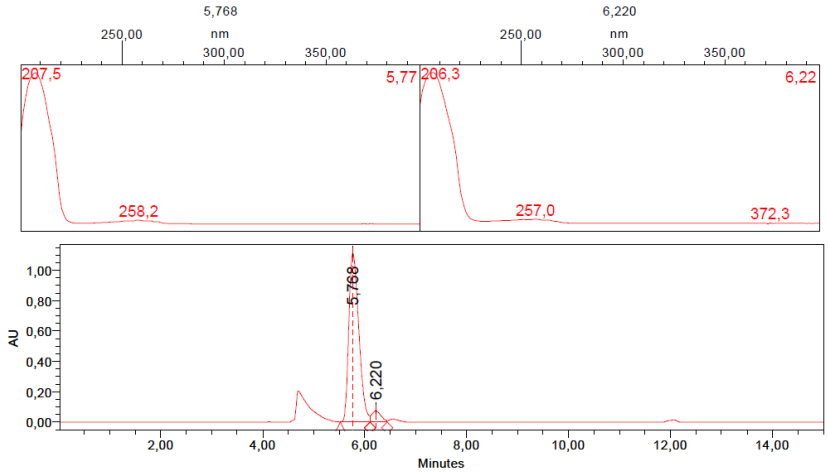


The enantiomers were separated by HPLC using a Chiralpak IA column (isohexane/*i*PrOH 98 : 2, 1 mL/min, 200 nm, tR_a = 6.131 min, tR_b = 6.528 min).

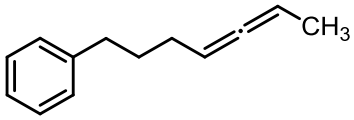
Racemic version:



Enantioenriched version: *ee* = 87%



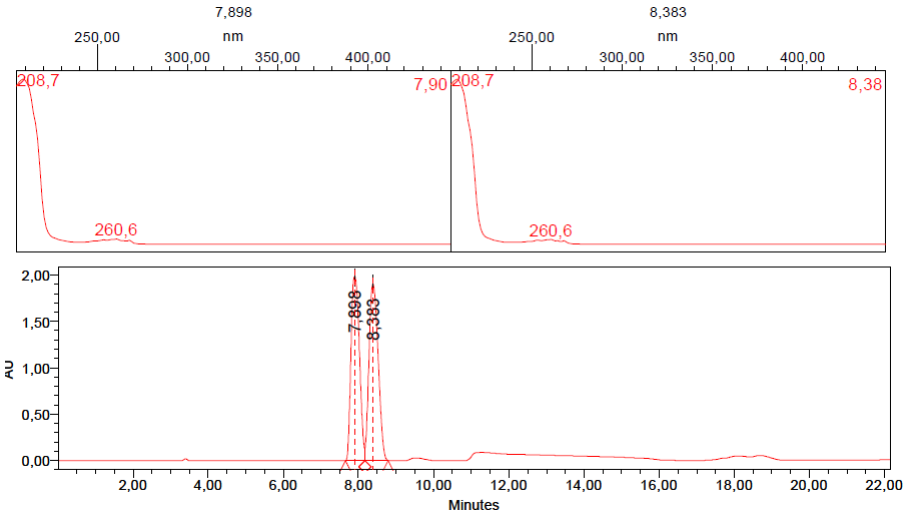
hepta-4,5-dien-1-ylbenzene III.30



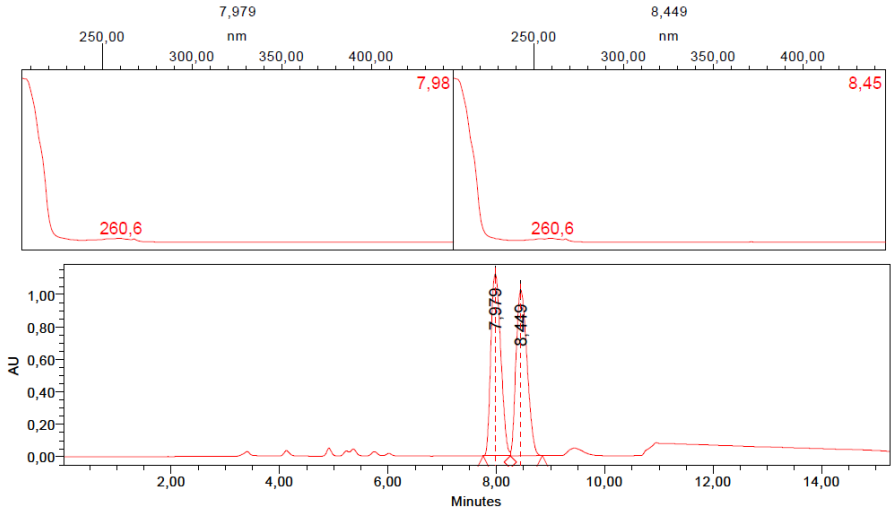
The enantiomers were separated by HPLC using a Chiralcel OJ-H column (isohexane, 1 mL/min, 205 nm, tR_a = 7.898 min, tR_b = 8.383 min)

Racemic version:

365



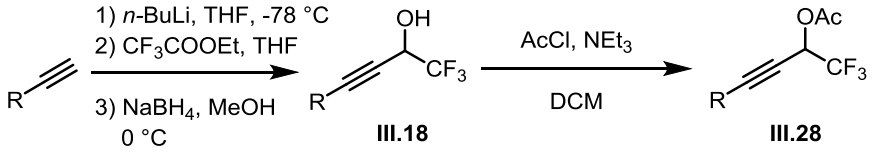
"Enantioenriched" version: *ee* < 1%



III. Chapter I.III: Synthesis of CF_3-Enones by Gold-Catalyzed Acetate Rearrangement

Preparation of the starting materials

Procedure E for the preparation of α-trifluoromethyl secondary propargylic acetates:

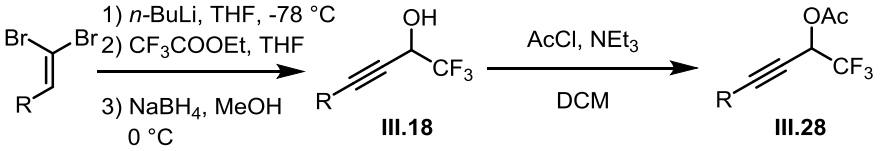


To a solution of alkyne (1.0 eq) in THF (0.5 M) was added dropwise *n*-BuLi (1.1 eq) at -78 °C. The mixture was stirred for 1 h at -78 °C and ethyl trifluoroacetate (1.5 eq) was added. After the complete consumption of the alkyne (TLC), the mixture was diluted with MeOH (same volume than THF). The mixture was allowed to warm up to 0 °C and $NaBH_4$ (1.0 eq) was added. The mixture was stirred overnight while warming up to room temperature. The reaction was then quenched with a saturated solution of NH_4Cl, extracted with Et_2O (x3), washed with water (x3) and brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the α-trifluoromethyl secondary propargylic alcohol. If necessary, the crude alcohol was purified by flash column chromatography.

To a solution of the alcohol dissolved in DCM (0.25 M) was added triethylamine (1.5 eq) and the mixture was cooled to 0 °C. Acetyl chloride (1.2 eq) was then added dropwise and the mixture was stirred while warming up to room temperature until complete conversion of the alcohol. Water and DCM were added, the layers were separated and the aqueous layer was extracted

three times with DCM. The organic layers were then washed successively with a saturated solution of NH_4Cl, water, a saturated solution of $NaHCO_3$ and were dried over $MgSO_4$. The crude acetate was then purified using flash column chromatography.

Procedure F for the preparation of α-trifluoromethyl secondary propargylic acetates from dibromovinyl compounds (Corey Fuchs reaction)

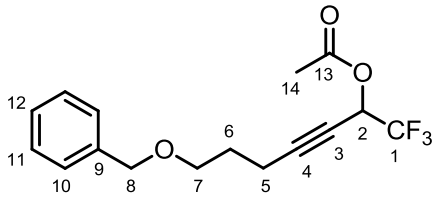


To a solution of 2,2-dibromovinyl derivative (1 equiv) in dry THF (0.5 M) was added *n*-BuLi in solution in hexanes (2.2 equiv) at -78 °C. After 30 min stirring at -78 °C, ethyl trifluoroacetate (1.3 equiv) was added. After 30 minutes stirring at -78 °C, methanol (same volume than THF) was added and the mixture was allowed to warm up to 0 °C. $NaBH_4$ (1.0 equiv) was added and the mixture was stirred overnight while warming up to room temperature. Ethyl acetate and water were added, the mixture was extracted with ethyl acetate (x3) and the organic layers were dried over $MgSO_4$. The crude product was purified by flash column chromatography to afford the desired alcohol.

To a solution of the alcohol dissolved in DCM (0.25 M) was added dropwise NEt_3 (1.5 equiv) at 0 °C, followed by AcCl (1.2 equiv). The solution was stirred while warming up to room temperature. After complete conversion of the alcohol (TLC), water and DCM were added. The layers were separated, extracted with DCM (x3), washed successively with $NH_4Cl_{(sat)}$, H_2O and $NaHCO_{3(sat)}$ and dried over $MgSO_4$. The crude product was then filtrated over silica (eluting with

DCM or Et_2O). If necessary, the product was purified by flash chromatography to afford the pure α-trifluoromethyl secondary propargylic acetate.

7-(benzyloxy)-1,1,1-trifluorohept-3-yn-2-yl acetate (III.28a)



$C_{16}H_{17}F_3O_3$
M = 314.30 g.mol^{-1}

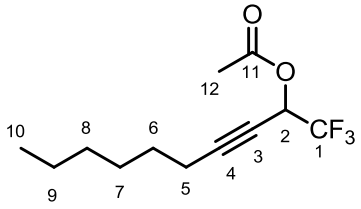
Following procedure E starting with benzylated 4-pentyn-1-ol.

Flash chromatography: PE / EtOAc 98 : 2

Overall yield: 80% of a yellow oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.38 – 7.28 (m, 5H, H_{Ar}), 5.84 – 5.77 (m, 1H, H_2), 4.51 (s, 2H, H_8), 3.55 (t, *J* = 6.0 Hz, 2H, H_7), 2.39 (td, *J* = 7.0, 1.8 Hz, 2H, H_5), 2.17 (s, 3H, H_{14}), 1.88 – 1.79 (m, 2H, H_6)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	168.6 (C_{13}), 138.5 (C_9), 128.5 (C_{Ar}), 127.7 (x2) (C_{Ar}), 122.0 (q, *J* = 280.3 Hz, C_1), 89.3 (C_4), 73.2 (C_8), 69.7 (C_3), 68.5 (C_7), 61.9 (q, *J* = 37.3 Hz, C_2), 28.2 (C_6), 20.6 (C_{14}), 15.6 (C_5)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-78.0
IR (cm^{-1}, CCl_4)	3089 (w), 3067 (w), 3033 (w), 2946 (m, br), 2864 (m, br), 2798 (w), 2307 (w), 2258 (m), 2250 (m), 1954 (w), 1761 (s), 1496 (w), 1455 (m), 1430 (m), 1373 (m), 1274 (s), 1219 (s), 1194 (s), 1165 (s), 1141 (s), 1104 (m), 1078 (m), 1037 (s)
MS (HRMS EI)	Calcd for $C_{16}H_{17}F_3O_3$: 314.1130 Found: 314.1114

1,1,1-trifluorodec-3-yn-2-yl acetate (III.28b)



$C_{12}H_{17}F_3O_2$
M = 250.26 g.mol^{-1}

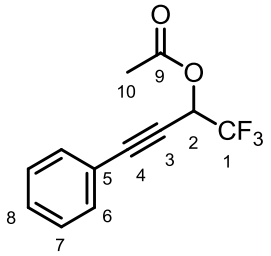
Following procedure E starting with *n*-octyne.

Flash chromatography: PE / EtOAc 95 : 5

Overall yield: 68% of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	5.82 (qt, *J* = 5.8, 2.1 Hz, 1H, H_2), 2.23 (td, *J* = 7.2, 2.1 Hz, 2H, H_5), 2.18 (s, H_{12}), 1.56 – 1.49 (m, 2H, H_6), 1.38 – 1.24 (m, 6H, H_{Aliph}), 0.88 (t, *J* = 6.9 Hz, 3H, H_{10})
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	168.6 (C_{11}), 122.0 (q, *J* = 280.2 Hz, C_1), 90.1 (C_4), 69.3 (C_3), 61.7 (q, *J* = 37.2 Hz, C_2), 31.3 (C_{Aliph}), 28.5 (C_{Aliph}), 28.0 (C_6), 22.6 (C_{Aliph}), 20.5 (C_{12}), 18.7 (C_5), 14.1 (C_{10})
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-78.1
IR (cm^{-1}, CCl_4)	2958 (s), 2933 (s), 2861 (m), 2260 (m), 2249 (m), 1759 (s), 1711 (s), 1602 (w), 1458 (w), 1430 (w), 1373 (s), 1362 (s), 1327 (w), 1275 (s), 1222 (s), 1194 (s), 1166 (s), 1141 (s), 1036 (s), 994 (w)
MS (HRMS EI)	Calcd for $C_{10}H_{13}F_3$: 190.0969 Found: 190.0977 [*M*-AcOH]

1,1,1-trifluoro-4-phenylbut-3-yn-2-yl acetate (III.28c)



$C_{12}H_9F_3O_2$
M = 242.19 g.mol^{-1}

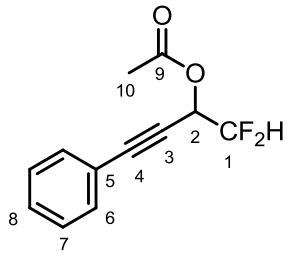
Following procedure E starting with phenylacetylene.

Pure product obtained after filtration on silica (Et_2O)

Overall yield: 410 mg (69%) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.51 – 7.48 (m, 2H, H_{Ar}), 7.41 – 7.32 (m, 3H, H_{Ar}), 6.08 (q, *J* = 5.8 Hz, 1H, H_2), 2.22 (s, 3H, C_{10})
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	168.6 (C_9), 132.4 (C_{Ar}), 129.8 (C_8), 128.6 (C_{Ar}), 122.0 (q, *J* = 280.3 Hz, C_1), 120.9 (C_5), 88.2 (C_4), 77.8 (q, *J* = 2.5 Hz, C_3), 62.0 (q, *J* = 37.6 Hz, C_2), 20.6 (C_{10})
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-77.6
IR (cm^{-1}, CCl_4)	3085 (w), 3061 (w), 3026 (w), 2944 (m), 2259 (m), 2242 (m), 1955 (w), 1887 (w), 1759 (s), 1600 (w), 1492 (m), 1445 (m), 1361 (m), 1326 (m), 1276 (s), 1256 (s), 1217 (s, br), 1148 (s), 1053 (s), 985 (m)
MS (HRMS EI)	Calcd for $C_{12}H_9F_3O_2$: 242.0555 Found: 242.0554

1,1-difluoro-4-phenylbut-3-yn-2-yl acetate (III.28d)



$C_{12}H_{10}F_2O_2$
M = 224.20 g.mol^{-1}

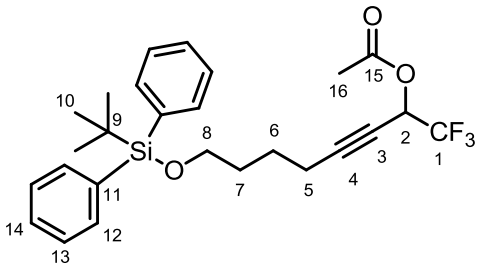
Following procedure E starting with phenylacetylene and using ethyl difluoroacetate instead of ethyl trifluoroacetate.

Pure product obtained after filtration on silica (Et_2O)

Overall yield: 441 mg (45 %) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.50 – 7.47 (m, 2H, H_{Ar}), 7.39 – 7.30 (m, 3H, H_{Ar}), 5.90 (td, *J* = 55.3, 4.0 Hz, 1H, H_1), 5.84 (td, *J* = 9.6, 4.0 Hz, 1H, H_2), 2.19 (s, 3H, H_{10})
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	169.1 (C_9), 132.3 (C_{Ar}), 129.5 (C_8), 128.5 (C_{Ar}), 121.3 (C_5), 112.3 (t, *J* = 247.7 Hz, C_1), 88.2 (C_4), 79.5 (C_3), 63.4 (t, *J* = 28.7 Hz, C_2), 20.8 (C_{10})
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-128.6 (dd, *J* = 55.4, 10.3 Hz), -128.9 (dd, *J* = 55.3, 9.8 Hz)
IR (cm^{-1}, CCl_4)	3085 (w), 3061 (w), 3038 (w), 2985 (m), 2941 (m), 2258 (s), 2251 (s), 2238 (m), 1755 (s), 1600 (w), 1491 (m), 1444 (m), 1373 (s), 1322 (m), 1223 (s, br), 1152 (s), 1087 (s), 1051 (s)
MS (HRMS EI)	Calcd for $C_{12}H_{10}F_2O_2$: 224.0649 Found: 224.0656

8-((tert-butyldiphenylsilyl)oxy)-1,1,1-trifluorooct-3-yn-2-yl acetate (III.28e)



$C_{26}H_{31}F_3O_3Si$
M = 476.60 g.mol^{-1}

Following procedure E starting with *O*-TBDPS-5-hexyn-1-ol.

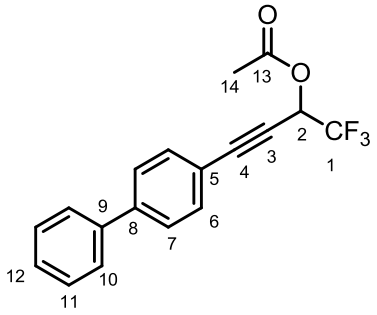
Flash chromatography: PE / EtOAc 95 : 5

Overall yield: 4.94 g (63%) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.68 – 7.65 (m, 4H, H_{12}), 7.45 – 7.36 (m, 6H, H_{13+14}), 5.85 – 5.80 (m, 1H, H_2), 3.69 – 3.66 (m, 2H, H_8),

	2.27 – 2.24 (m, 2H, H_5), 2.17 (s, 3H, H_{16}), 1.66 – 1.63 (m, 4H, H_{6+7}), 1.05 (s, 9H, H_{10})
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	168.6 (C_{15}), 135.7 (C_{12}), 134.1 (C_{11}), 129.7 (C_{14}), 127.8 (C_{13}), 122.0 (q, *J* = 280.3 Hz, C_1), 89.9 (C_4), 69.6 (C_3), 63.4 (C_8), 61.8 (q, *J* = 37.1 Hz, C_2), 31.6 (C_7), 27.0 (C_{10}), 24.7 (C_6), 20.6 (C_{16}), 19.4 (C_9), 18.5 (C_5)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-78.0
IR (cm^{-1}, CCl_4)	3073 (w), 3055 (w), 2953 (m), 2933 (m), 2860 (m), 2252 (m), 1758 (s), 1602 (m), 1472 (w), 1428 (m), 1373 (m), 1274 (m), 1220 (s), 1193 (s), 1165 (s), 1141 (s), 1111 (s), 1037 (s)
MS (HRMS EI)	Calcd for $C_{22}H_{22}F_3O_3Si$: 419.1290 [*M*-*t*Bu] Found: 419.1303

4-([1,1'-biphenyl]-4-yl)-1,1,1-trifluorobut-3-yn-2-yl acetate (III.28f)



$C_{18}H_{13}F_3O_2$
M = 318.29 g.mol^{-1}

Following procedure E starting with 4-ethynylbiphenyl.

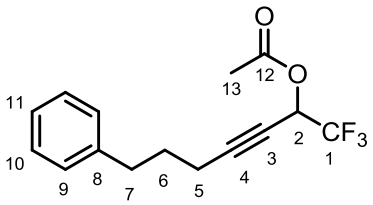
Flash chromatography: PE / EtOAc 95 : 5

Overall yield: 207 mg (57 %) of a white solid.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.60 – 7.57 (m, 6H, H_{Ar}), 7.48 – 7.37 (m, 3H, H_{Ar}), 6.13 – 6.08 (m, 1H, H_2), 2.24 (s, 3H, H_{14})
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	168.6 (C_{13}), 142.6 (C_{8or9}), 140.1 (C_{8or9}), 132.8 (C_{Ar}), 129.0 (C_{Ar}), 128.1 (C_{12}), 127.2 (C_{Ar}), 127.2 (C_{Ar}), 122.0 (q, *J* = 280.4 Hz, C_1), 119.6 (C_5), 88.1 (C_4), 78.4 (C_3), 62.0 (q, *J* = 37.6 Hz, C_2), 20.6 (C_{14})

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-77.5
IR (cm^{-1}, CCl_4)	3081 (w), 3064 (w), 3034 (w), 2944 (w), 2260 (m), 2248 (m), 1759 (s), 1602 (w), 1520 (w), 1486 (m), 1448 (w), 1374 (m), 1325 (m), 1276 (m), 1259 (m), 1216 (s), 1196 (s), 1148 (s), 1053 (s)
MS (HRMS EI)	Calcd for $C_{18}H_{13}F_3O_2$: 318.0868 Found: 318.0860

1,1,1-trifluoro-7-phenylhept-3-yn-2-yl acetate (III.28g)



$C_{15}H_{15}F_3O_2$
M = 284.27 g.mol^{-1}

Following procedure E starting with 5-phenylpent-1-yne

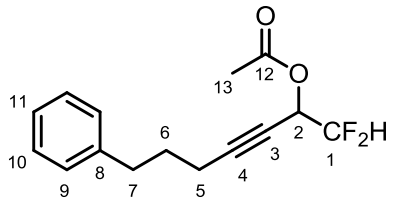
Pure product obtained after filtration on silica (Et_2O)

Overall yield: 2.7 g (89%) of a yellow oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.31 – 7.27 (m, 2H, H_{10}), 7.22 – 7.16 (m, 3H, H_{9+11}), 5.84 (tq, *J* = 5.9, 2.0 Hz, 1H, H_2), 2.71 (t, *J* = 7.6 Hz, 2H, H_7), 2.25 (td, *J* = 7.1, 2.1 Hz, 2H, H_5), 2.19 (s, 3H, H_{13}), 1.90 – 1.82 (m, 2H, H_6)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	168.6 (C_{12}), 141.3 (C_8), 128.6 (C_{Ar}), 128.6 (C_{Ar}), 126.2 (C_{11}), 122.0 (q, *J* = 280.2 Hz, C_1), 89.6 (C_4), 70.1 (q, *J* = 2.7 Hz, C_3), 61.8 (q, *J* = 37.4 Hz, C_2), 34.7 (C_7), 29.7 (C_6), 20.6 (C_{13}), 18.1 (C_5)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-78.0
IR (cm^{-1}, CCl_4)	3086 (w), 3065 (w), 3029 (m), 2948 (m), 2865 (m), 2260 (m), 2249 (m), 1759 (s), 1603 (m), 1496 (m), 1455 (m), 1430 (m), 1373 (m), 1361 (m), 1327 (m), 1274 (s), 1220 (s), 1194 (s), 1168 (s), 1141 (s), 1037 (s)

MS (HRMS EI)	Calcd for $C_{15}H_{15}F_3O_2$: 284.1024	Found: 284.1012

1,1-difluoro-7-phenylhept-3-yn-2-yl acetate (III.28h)



$C_{15}H_{16}F_2O_2$
M = 266.28 g.mol^{-1}

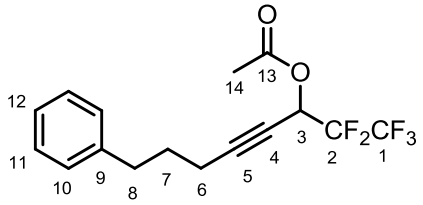
Following procedure E starting with 5-phenylpent-1-yne and using ethyl difluoroacetate instead of ethyl trifluoroacetate

Pure product obtained after filtration on silica (Et_2O)

Overall yield: 514 mg (66%) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.31 – 7.27 (m, 2H, H_{10}), 7.22 – 7.17 (m, 3H, H_{9+11}), 5.79 (td, *J* = 55.3 Hz, *J* = 3.9 Hz, 1H, H_1), 5.63 – 5.56 (m, 1H, H_2), 2.71 (t, *J* = 7.6 Hz, 2H, H_7), 2.25 (td, *J* = 7.1, 2.1 Hz, 2H, H_5), 2.16 (s, 3H, H_{13}), 1.89 – 1.82 (m, 2H, H_6)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	169.2, (C_{12}), 141.4 (C_8), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 126.2 (C_{11}), 112.4 (t, *J* = 247.2 Hz, C_1), 89.4 (C_4), 71.5 (t, *J* = 4.9 Hz, C_3), 63.2 (t, *J* = 28.5 Hz, C_2), 34.8 (C_7), 29.8 (C_6), 20.8 (C_{13}), 18.2 (C_5)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-127.2 (ddd, *J* = 284.8, 55.3 Hz, 10.1 Hz), -128.7 (ddd, *J* = 284.8, 55.2, 10.1 Hz)
IR (cm^{-1}, CCl_4)	3086 (w), 3065 (w), 3029 (m), 2947 (m), 2864 (w), 2253 (m), 1752 (s), 1603 (w), 1496 (m), 1455 (m), 1430 (w), 1373 (m), 1328 (w), 1227 (s), 1176 (m), 1163 (m), 1148 (m), 1124 (m), 1092 (s), 1031 (s)
MS (HRMS EI)	Calcd for $C_{13}H_{12}F_3$: 206.0907 [*M*-AcOH]	Found: 206.0900

1,1,1,2,2-pentafluoro-8-phenyloct-4-yn-3-yl acetate (III.28i)



$C_{16}H_{15}F_5O_2$
M = 334.28 g.mol^{-1}

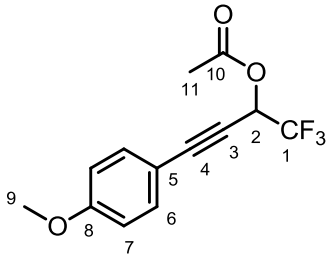
Following procedure E starting with 5-phenylpentyne and using ethyl pentafluoropropionate instead of ethyl trifluoroacetate

Flash chromatography: PE / EtOAc 95 : 5

Overall yield: 480.5 mg (46 %) of a slightly yellow oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.31 – 7.27 (m, 2H, H_{11}), 7.22 – 7.16 (m, 3H, H_{Ar}), 5.97 (tt, *J* = 11.2, 2.1 Hz, 1H, H_3), 2.71 (t, *J* = 7.6 Hz, 2H, H_8), 2.26 (td, *J* = 7.1, 2.1 Hz, 2H, H_6), 2.18 (s, 3H, H_{14}), 1.89 – 1.82 (m, 2H, H_7)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	168.5 (C_{13}), 141.3 (C_9), 128.6 (C_{Ar}), 128.6 (C_{Ar}), 126.2 (C_{12}), 118.6 (qt, *J* = 286.9, 34.9 Hz, C_1), 111.2 (ddq, *J* = 260.7, 258.6 Hz, 36.8 Hz, C_2), 90.4 (C_5), 69.4 (C_4), 60.9 (dd, *J* = 29.4, 27.0 Hz, C_3), 34.7 (C_8), 29.6 (C_7), 20.5 (C_{14}), 18.1 (C_6)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-81.4 (F_1), -121.7 (dd, *J* = 272.5, 8.3 Hz, F_2), -124.2 (dd, *J* = 272.4, 10.4 Hz, F_2)
IR (cm^{-1}, CCl_4)	3086 (w), 3065 (w), 3029 (w), 2948 (m, br), 2865 (w), 2260 (m), 2249 (m), 1763 (s), 1603 (w), 1496 (w), 1455 (w), 1429 (w), 1373 (m), 1315 (m), 1215 (s, br), 1159 (m), 1091 (w), 1045 (m), 1030 (m), 985 (w)
MS (HRMS EI)	Calcd for $C_{14}H_{11}F_5$: 274.0781 [*M*-AcOH] Found: 274.0781

1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-yn-2-yl acetate (III.28j)



$C_{13}H_{11}F_3O_3$
M = 272.22 g.mol^{-1}

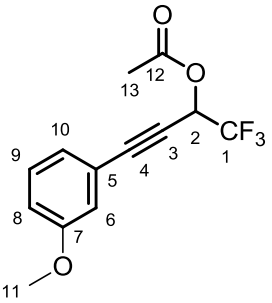
Following procedure F starting with 1-(2,2-dibromovinyl)-4-methoxybenzene.

Pure product obtained after filtration on silica (Et_2O)

Overall yield: 437 mg (55%) of a slightly yellow oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.45 – 7.41 (m, 2H, H_6), 6.87 – 6.83 (m, 2H, H_7), 6.07 (q, *J* = 5.8 Hz, 1H, H_2), 3.82 (s, 1H, H_9), 2.21 (s, 1H, H_{11})
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	168.6 (C_{10}), 160.8 (C_8), 134.0 (C_{Ar}), 122.0 (q, *J* = 280.0 Hz, C_1), 114.2, (C_{Ar}), 112.9 (C_5), 88.4 (C_4), 76.6 (C_3), 62.2 (q, *J* = 37.6 Hz, C_2), 55.5 (C_9), 20.6 (C_{11})
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-77.6
IR (cm^{-1}, CCl_4)	3085 (w), 3061 (w), 3026 (w), 2944 (m), 2259 (m), 2242 (m), 1955 (w), 1887 (w), 1759 (s), 1600 (w), 1492 (m), 1445 (m), 1361 (m), 1326 (m), 1276 (s), 1256 (s), 1217 (s, br), 1148 (s), 1053 (s), 985 (m)
MS (HRMS EI)	Calcd for $C_{13}H_{11}F_3O_3$: 272.0296 Found: 272.0303

1,1,1-trifluoro-4-(3-methoxyphenyl)but-3-yn-2-yl acetate (III.28k)



$C_{13}H_{11}F_3O_3$
M = 272.22 g.mol^{-1}

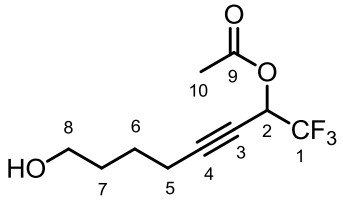
Following procedure F starting with 1-(2,2-dibromovinyl)-3-methoxybenzene.

Pure product obtained after filtration on silica (Et_2O)

Overall yield: 101.5 mg (34%) of a yellow oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.26 – 7.22 (m, 1H, H_9), 7.10 – 7.08 (m, 1H, H_{Ar}), 7.01 – 7.00 (m, 1H, H_6), 6.94 (ddd, *J* = 8.4, 2.6, 1.0 Hz, 1H, H_{Ar}), 6.08 (q, *J* = 5.8 Hz, 1H, H_2), 3.81 (3H, H_{11}), 2.22 (3H, H_{13})
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	168.6 (C_{12}), 159.5 (C_7), 129.7 (C_{Ar}), 124.9 (C_{Ar}), 122.0 (q, *J* = 280.4 Hz, C_1), 121.8 (C_5), 117.0 (C_{Ar}), 116.6 (C_{Ar}), 88.1 (C_4), 77.6 (C_3), 62.0 (q, *J* = 37.6 Hz, C_2), 55.5 (C_{11}), 20.6 (C_{13})
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-77.5
IR (cm^{-1}, CCl_4)	3009 (w), 2943 (m), 2838 (w), 2260 (m), 2248 (m), 1759 (s), 1599 (m), 1577 (m), 1490 (m), 1466 (m), 1423 (m), 1374 (m), 1360 (m), 1326 (m), 1288 (m), 1273 (m), 1210 (s), 1178 (m), 1148 (s), 1054 (s)
MS (HRMS EI)	Calcd for $C_{13}H_{11}F_3O_3$: 272.0296 Found: 272.0296

1,1,1-trifluoro-8-hydroxyoct-3-yn-2-yl acetate (III.16l)

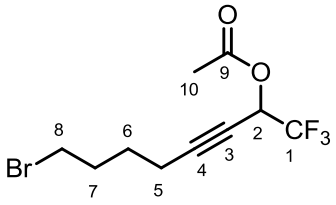


$C_{10}H_{13}F_3O_3$
M = 238.20 g.mol^{-1}

To a solution of 8-((tert-butyldiphenylsilyl)oxy)-1,1,1-trifluorooct-3-yn-2-yl acetate (1 equiv, 4.2 mmol, 2.00 g) **III.28e** in THF (8 mL) was added TBAF (1M in THF, 1.5 equiv, 6.3 mmol, 6.3 mL) dropwise at room temperature. After 1 h 30, water and ethyl acetate were added. The layers were separated and the aqueous phase was extracted with ethyl acetate (x3). The organic layers were washed with brine and dried over $MgSO_4$. Purification by flash column chromatography (PE / EtOAc 1 : 1) afforded the desired alcohol as a yellow oil (687 mg, 2.88 mmol, 69% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	5.84 – 5.77 (m, 1H, H_2), 3.69 – 3.65 (m, 2H, H_8), 2.31 – 2.28 (m, 2H, H_5), 2.18 (s, 3H, H_{10}), 1.66 – 1.62 (m, 4H, H_{6+7}), 1.31 (br s, 1H, OH)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	168.7 (C_9), 121.9 (q, J = 280.3 Hz, C_1), 89.6 (C_4), 69.7 (q, J = 2.3 Hz, C_3), 62.3 (C_8), 61.7 (q, J = 37.4 Hz, C_2), 31.7 (C_7), 24.3 (C_6), 20.6 (C_{10}), 18.5 (C_5)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-78.0
IR (cm^{-1}, CCl_4)	3625 (s), 2946 (s), 2882 (m), 2307 (w), 2260 (s), 2249 (s), 2135 (w), 1962 (w), 1760 (s), 1602 (m), 1456 (s), 1430 (s), 1374 (s), 1360 (s), 1328 (sm), 1275 (s), 1220 (s), 1194 (s), 1166 (s), 1141 (s), 1037 (s), 994 (m)
MS (HRMS EI)	Calcd for $C_8H_9F_3O$: 178.0605 [*M*-AcOH] Found: 178.0598
MS (HRMS EI)	Calcd for $C_{18}H_{16}F_3NO_4$: 367.1031 Found: 367.1024

8-bromo-1,1,1-trifluorooct-3-yn-2-yl acetate (III.16m)

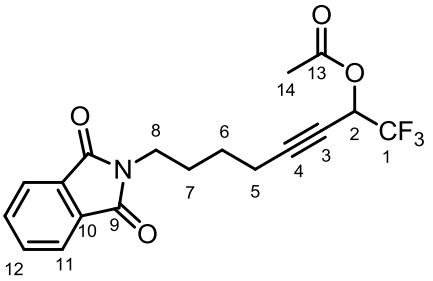


$C_{10}H_{12}BrF_3O_2$
M = 301.10 g.mol^{-1}

To a solution of 1,1,1-trifluoro-8-hydroxyoct-3-yn-2-yl acetate (1 equiv, 0.80 mmol, 191 mg) **III.16l** in DCM (2.0 mL) was added carbon tetrabromide (1.1 equiv, 0.88 mmol, 292 mg). Triphenylphosphine (1.1 equiv, 0.88 mmol, 231 mg) in solution in DCM (2 mL) was then added dropwise and the mixture was stirred overnight at room temperature. DCM and water were added and the mixture was extracted with DCM (x3) and dried over $MgSO_4$. Purification by flash column chromatography (PE/EtOAc 95 : 5) afforded the desired product as a colorless oil (158 mg, 0.525 mmol, 66% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	5.81 (qt, *J* = 5.8, 2.1 Hz, 1H, H_2), 3.43 (t, *J* = 6.6 Hz, 2H, H_8), 2.30 (td, *J* = 7.0, 2.1 Hz, 2H, H_5), 2.18 (s, 3H, H_{10}), 1.99 – 1.92 (m, 2H, H_7), 1.74 – 1.69 (m, 2H, H_6)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	168.6 (C_9), 121.9 (q, *J* = 280.2 Hz, C_1), 88.9 (C_4), 70.2 (q, *J* = 2.4 Hz, C_3), 61.7 (q, *J* = 37.3 Hz, C_2), 33.0 (C_8), 31.6 (C_7), 26.4 (C_6), 20.6 (C_{10}), 18.0 (C_5)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-78.0
IR (cm^{-1}, CCl_4)	2947 (m), 2869 (w), 2842 (w), 2308 (w), 2259 (m), 2249 (m), 1760 (s), 1602 (w), 1454 (m), 1433 (m), 1374 (m), 1360 (m), 1329 (m), 1275 (s), 1219 (s), 1194 (s), 1167 (s), 1142 (s), 1038 (s), 994 (m)
MS (HRMS EI)	Calcd for $C_{10}H_{12}BrF_3O_2$: 299.9973 Found: 299.9970

8-(1,3-dioxoisoindolin-2-yl)-1,1,1-trifluorooct-3-yn-2-yl acetate (III.16n)

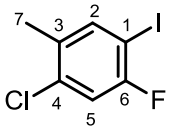


$C_{18}H_{16}F_3NO_4$
M = 367.32 g.mol^{-1}

To a solution of 1,1,1-trifluoro-8-hydroxyoct-3-yn-2-yl acetate (1 equiv, 0.80 mmol, 191 mg) **III.16l** in THF (2.5 mL) were added successively triphenylphosphine (1.95 equiv, 1.56 mmol, 409 mg) and phtalimide (1 equiv, 0.80 mmol, 118 mg). Diethyl azodicarboxylate (1.95 equiv, 1.56 mmol, 272 mg, 0.25 mL) was then added dropwise to the reaction mixture. After 4 h stirring at room temperature, methanol was added and the solvents were evaporated. Purification by flash column chromatography (PE/EtOAc 8 : 2) afforded the desired product as a colorless oil (140 mg, 0.381 mmol, 48% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.85 – 7.83 (m, 2H, H_{Ar}), 7.73 –7.70 (m, 2H, H_{Ar}), 5.80 (qt, *J* = 5.9, 2.0 Hz, 1H, H_2), 3.71 (t, *J* = 7.0 Hz, 2H, H_8), 2.31 (td, *J* = 7.1, 2.0 Hz, 2H, H_5), 2.17 (s, 3H, H_{14}), 1.82 – 1.75 (m, 2H, H_7), 1.62 – 1.55 (m, 2H, H_6)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	168.5 (C_{13}), 134.1 (C_{Ar}), 132.2 (C_{Ar}), 123.4 (C_{Ar}), 121.9 (q, *J* = 279.6 Hz, C_1), 89.1 (C_4), 70.0 (C_3), 61.6 (q, *J* = 37.2 Hz, C_2), 37.4 (C_8), 27.7 (C_7), 25.2 (C_6), 20.6 (C_{14}), 18.3 (C_5)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-78.0
IR (cm^{-1}, CCl_4)	2948 (m, br), 2868 (w), 2260 (m), 1763 (s), 1712 (s), 1469 (w), 1440 (m), 1397 (s), 1375 (s), 1331 (m), 1275 (m), 1219 (s), 1193 (s), 1166 (s), 1142 (s), 1119 (w), 1038 (s)

1-chloro-5-fluoro-4-iodo-2-methylbenzene (III.39)



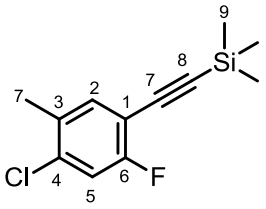
C_7H_5ClFI
M = 270.47 g.mol^{-1}

To a mixture of 2-chloro-4-fluorotoluene **III.38** (1 equiv, 17.09 mmol, 2.47 g, 2.06 mL) with trifluoroacetic acid (10 mL) was added *N*-iodosuccinimide (1.1 equiv, 18.8 mmol, 4.23 g). The mixture was stirred overnight at room temperature and was then diluted with ethyl acetate and water. A saturated solution of $NaHCO_3$ in water was added slowly to the mixture under stirring in order to neutralize the trifluoroacetic acid. When the bubbling of carbon dioxide stopped, the layers were separated and the aqueous layer was extracted with ethyl acetate (x3). The organic layers were washed with water and with NaS_2O_3(aq), dried over $MgSO_4$ and the solvents were evaporated. The crude product was filtrated over silica (PE : EtOAc 95 : 5) to afford the desired product as a white solid (4.20 g, 15.5 mmol, 91% yield). A minor regioisomer was detected (5%) but could not be separated on this step.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.60 (d, *J* = 6.7 Hz, 1H, H_{Ar}), 7.08 (d, *J* = 7.6 Hz, 1H, H_{Ar}), 2.30 (s, 3H, H_7)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	160.1 (d, *J* = 245.9 Hz, C_6), 140.4 (d, *J* = 2.1 Hz, C_2), 135.2 (d, *J* = 8.8 Hz, C_{3or4}), 134.4 (d, *J* = 3.8 Hz, C_{3or4}), 116.6 (d, *J* = 27.1 Hz, C_5), 78.6 (d, *J* = 25.3 Hz, C_1), 19.2 (C_7)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-97.5
IR (cm^{-1}, CCl_4)	3096 (w), 2986 (w), 2959 (w), 2927 (w), 2862 (w), 2248 (w), 1730 (w), 1594 (m), 1569 (m), 1481 (s), 1461 (s), 1384 (m), 1356 (s), 1270 (w), 1252 (s), 1175 (s), 1066 (s), 1037 (w), 1006 (s)
MS	Calcd for C_7H_5ClFI: 269.9108 Found: 269.9104

(HRMS EI)

((4-chloro-2-fluoro-5-methylphenyl)ethynyl)trimethylsilane (III.40)



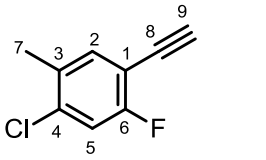
$C_{12}H_{14}ClFSi$
$M = 240.78\ g.mol^{-1}$

To a solution of 1-chloro-5-fluoro-4-iodo-2-methylbenzene (1 equiv, 10 mmol, 2.70 g) **III.39** in triethylamine (50 mL) was added ethynyltrimethylsilane (1.13 equiv, 11.3 mmol, 1.11 g, 1.60 mL). Bis(triphenylphosphine)palladium(II) dichloride (0.04 equiv, 0.4 mmol, 280.8 mg) and copper iodide (0.02 equiv, 0.2 mmol, 38.1 mg) were added and the mixture was stirred at room temperature until full conversion of the starting material (1 h). The volatiles were removed under reduced pressure and the crude mixture was filtered over silica (PE/EtOAc 95 : 5) to afford the desired product as a yellow oil (2.27 g, 9.45 mmol, 94% yield). A minor regioisomer was detected (5%) but could not be separated on this step.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$) 7.31 (d, *J* = 7.5 Hz, 1H, H_{Ar}), 7.09 (d, *J* = 8.8 Hz, 1H, H_{Ar}), 2.29 (s, 3H, H_7), 0.25 (s, 9H, H_9)

MS (HRMS EI) Calcd for $C_{12}H_{14}ClFSi$: 240.0537 Found: 240.0533

1-chloro-4-ethynyl-5-fluoro-2-methylbenzene (III.36o)



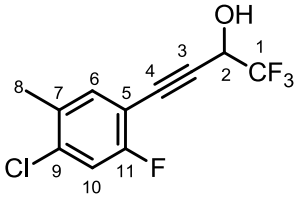
C_9H_6ClF
$M = 168.60\ g.mol^{-1}$

To a solution of ((4-chloro-2-fluoro-5-methylphenyl)ethynyl)trimethylsilane **III.40** (1.0 equiv, 12.4 mmol, 3.00 g) in methanol (50 mL) was added K_2CO_3 (0.11 equiv, 1.36 mmol, 186 mg) and the mixture was stirred 1 h at room

temperature. The volatiles were removed under reduced pressure and DCM and water were added. The mixture was extracted with DCM (x3) and dried under $MgSO_4$. Purification by flash column chromatography (PE to PE/EtOAc 95 : 5) afforded the desired product as a white solid (1.308 g, 7.76 mmol, 63% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.33 (d, *J* = 7.4 Hz, 1H, H_2), 7.12 (d, *J* = 8.8 Hz, 1H, H_5), 3.30 (s, 1H, H_8), 2.31 (s, 3H, H_7)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	161.4 (d, *J* = 253.1 Hz, C_6), 135.7 (d, *J* = 9.7 Hz, C_{Ar}), 135.3 (d, *J* = 1.8 Hz, C_2), 132.2 (d, *J* = 3.8 Hz, C_{Ar}), 116.7 (d, *J* = 24.2 Hz, C_5), 109.2 (d, *J* = 15.6 Hz, C_{Ar}), 82.9 (d, *J* = 3.3 Hz, C_9), 76.4 (C_8), 19.3 (C_7)
IR (cm^{-1}, CCl_4)	3305 (s), 3077 (s), 2959 (w), 2929 (w), 2251 (w), 2114 (w), 1611 (m), 1566 (w), 1498 (m), 1481 (s), 1453 (m), 1386 (m), 1374 (m), 1280 (m), 1269 (m), 1194 (m), 1175 (m), 1140 (m), 1039 (w), 1006 (w), 993 (s)
MS (HRMS EI)	Calcd for $C_{12}H_{14}ClFSi$: 240.0537 Found: 240.0533

4-(4-chloro-2-fluoro-5-methylphenyl)-1,1,1-trifluorobut-3-yn-2-ol (III.18o)



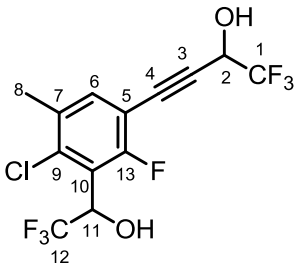
$C_{11}H_7ClF_4O$
M = 266.62 g.mol^{-1}

To a solution of 1-chloro-4-ethynyl-5-fluoro-2-methylbenzene **III.36o** (1.0 equiv, 1.78 mmol, 300 mg) in THF (2.2 mL) was added dropwise NaHMDS (2M in THF, 1.2 equiv, 2.14 mmol, 1.1 mL) at -78 °C. After 20 minutes stirring at -78 °C, ethyl trifluoroacetate (1.3 equiv, 2.31 mmol, 323 mg, 0.28 mL) was added. After 30 minutes stirring at -78 °C, the mixture was diluted with MeOH (2.2 mL). The mixture was allowed to warm up to 0 °C and $NaBH_4$ (1.0 equiv, 1.78 mmol, 67 mg) was added. The mixture was stirred 1

h while warming up to room temperature. The reaction was then quenched with a saturated solution of NH_4Cl, extracted with EtOAc (x3), washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the α-trifluoromethyl secondary propargylic alcohol. Purification by flash column chromatography (PE/EtOAc 9 : 1 to 85 : 15) afforded the desired pure alcohol (370 mg, 1.39 mmol, 78% yield) as a yellow oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.32 (d, *J* = 7.3 Hz, 1H, H_6), 7.13 (d, *J* = 8.8 Hz, 1H, H_{10}), 4.94 (q, *J* = 8.8 Hz, 1H, H_2), 2.61 (br s, 1H, OH), 2.31 (s, 3H, H_8)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	161.0 (d, *J* = 254.3 Hz, C_{11}), 136.5 (d, *J* = 9.6 Hz, C_9), 134.9 (d, *J* = 3.8 Hz, C_6), 132.3 (d, *J* = 3.8 Hz, C_7), 122.6 (q, *J* = 282.0 Hz, C_1), 116.7, (d, *J* = 23.9 Hz, C_{10}), 107.9 (d, *J* = 15.4 Hz, C_5), 85.7 (C_3), 80.9 (C_4), 63.0 (q, *J* = 36.5 Hz, C_2), 19.2 (C_8)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-80.2 (d, *J* = 7.1 Hz, F_1), -112.9 (F_{11})
IR (cm^{-1}, CCl_4)	3589 (m, br), 3079 (w), 2985 (w), 2960 (w), 2929 (w), 2863 (w), 2260 (m), 1611 (m), 1569 (m), 1499 (m), 1484 (s), 1454 (m), 1388 (m), 1351 (m), 1273 (s), 1249 (m), 1190 (s), 1145 (s), 1079 (m), 1022 (m), 1006 (m)
MS (HRMS EI)	Calcd for $C_{11}H_7ClF_4O$: 266.0122 Found: 266.0127

4-(4-chloro-2-fluoro-5-methyl-3-(2,2,2-trifluoro-1-hydroxyethyl)phenyl)-1,1,1-trifluorobut-3-yn-2-ol (III.41)

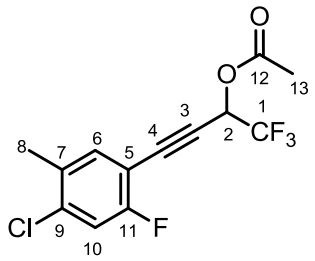


$C_{13}H_8ClF_7O_2$
M = 364.64 g.mol^{-1}

When procedure E was used on 1-chloro-4-ethynyl-5-fluoro-2-methylbenzene **III.36o** with LDA as the base, the double deprotonation product was formed in a mixture with the desired product **III.18o**. It could be isolated by flash column chromatography (PE/AcOEt 85 : 15).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.42 (d, *J* = 7.4 Hz, 1H, H_6), 5.68 (q, *J* = 7.0 Hz, 1H, H), 4.94 (q, *J* = 5.6 Hz, 1H, H_2), 3.47 (br s, 1H, OH), 2.74 (br s, 1H, OH), 2.37 (s, 3H, H_8)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	160.7 (d, *J* = 254.4 Hz, C_{13}), 136.6 (C_9), 135.7 (C_6), 133.9 (C_7), 124.1 (q, *J* = 283.8 Hz, C_{12}), 122.7 (q, *J* = 282.0 Hz, C_1), 120.8, (d, *J* = 12.9 Hz, C_{10}), 109.3 (d, *J* = 17.5 Hz, C_5), 87.1 (C_3), 79.9 (C_4), 70.0 (q, *J* = 33.4 Hz, C_{11}), 63.1 (q, *J* = 36.6 Hz, C_2), 20.4 (C_8)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-78.06 (F_{1or12}), -80.14 (F_{1or12}), -114.01 (F_{13})
IR (cm^{-1}, CCl_4)	3602 (m, br), 2960 (w), 2930 (w), 2858 (w), 2258 (m), 1731 (w), 1605 (m), 1575 (w), 1467 (m), 1413 (m), 1385 (m), 1317 (w), 1265 (m), 1221 (m), 1187 (s), 1141 (s), 1091 (m), 1045 (m), 1022 (w), 982 (w)
MS (HRMS EI)	Calcd for $C_{13}H_8ClF_7O_2$: 364.0101 Found: 364.0097

4-(4-chloro-2-fluoro-5-methylphenyl)-1,1,1-trifluorobut-3-yn-2-yl acetate (III.28o)



$C_{13}H_9ClF_4O_2$
M = 308.66 g.mol^{-1}

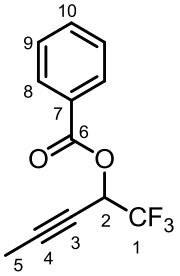
Following the acetylation part of procedure E starting with 0.5 mmol (133 mg) of 4-(4-chloro-2-fluoro-5-methylphenyl)-1,1,1-trifluorobut-3-yn-2-ol **III.18o**.

Pure product obtained after filtration on silica (Et_2O)

Yield: 138 mg (94%) of a slightly yellow oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.34 (d, *J* = 7.3 Hz, 1H, H_6), 7.13 (d, *J* = 8.8 Hz, 1H, H_{10}), 6.09 (q, *J* = 5.8 Hz, 1H, H_2), 2.31 (s, 3H, H_8), 2.22 (s, 3H, H_{13})
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	168.5 (C_{12}), 161.2 (d, *J* = 254.8 Hz, C_{11}), 136.8 (d, *J* = 9.6 Hz, C_9), 135.2 (d, *J* = 3.8 Hz, C_6), 132.4 (d, *J* = 3.8 Hz, C_7), 121.8 (q, *J* = 282.0 Hz, C_1), 116.8, (d, *J* = 23.9 Hz, C_{10}), 107.9 (d, *J* = 15.4 Hz, C_5), 83.2 (C_3), 81.0 (C_4), 61.9 (q, *J* = 37.6 Hz, C_2), 20.5 (C_{13}), 19.3 (C_8)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-77.4 (F_1), -112.5 (F_{11})
IR (cm^{-1}, CCl_4)	2944 (w), 2262 (w), 2246 (w), 1761 (s), 1611 (m), 1570 (w), 1500 (m), 1484 (m), 1454 (w), 1373 (m), 1355 (m), 1324 (m), 1273 (s), 1215 (s), 1202 (s), 1171 (m), 1148 (s), 1062 (m), 1033 (m), 956 (m)
MS (HRMS EI)	Calcd for $C_{13}H_9ClF_4O_2$: 308.0227 Found: 308.0234

1,1,1-trifluoropent-3-yn-2-yl benzoate (III.42p)



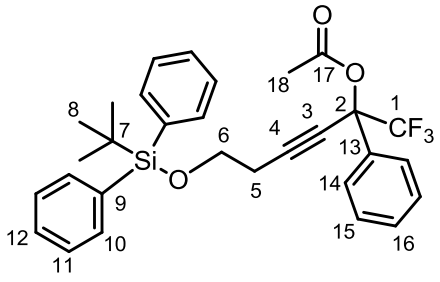
$C_{12}H_9F_3O_2$
M = 242,19 g.mol^{-1}

To a solution of diisopropylamine (3.33 equiv, 34.0 mmol, 3.44 g, 4.78 mL) in THF (40 mL) was added dropwise a solution of *n*BuLi in solution in hexanes (3.30 equiv, 33.0 mmol) at -78 °C. The solution was allowed to warm up a few minutes to 0 °C, and 1,2-dibromopropane (1.1 equiv, 11.0 mmol, 2.22 g, 1.15 mL) was then added dropwise at -78 °C. The solution was allowed to warm up again to 0 °C, before the addition of ethyl trifluoroacetate (1.0 equiv, 10.0 mmol, 1.42 g, 1.19 mL) at -78 °C. After 30 minutes, the mixture was allowed to warm up to 0 °C and methanol (40 mL) was added, followed by $NaBH_4$ (1.0 equiv, 10.0 mmol, 378 mg). The mixture was stirred overnight while warming up to room temperature. A solution of NH_4Cl was added and the mixture was extracted with Et_2O. The organic layers were washed with NH_4Cl(sat) and water and dried over $MgSO_4$. The solvents were evaporated to furnish the crude alcohol.

To a solution of the crude alcohol in DCM (40 mL) at 0 °C were added triethylamine (2.0 equiv, 20 mmol, 2.02 g, 2.79 mL) and benzoyl chloride (1.5 equiv, 15 mmol, 2.11 g, 1.74 mL). The mixture was stirred while warming up to room temperature until full conversion of the alcohol. Water was added, and the mixture was extracted with DCM (x3). The organic layers were washed successively with $NH_4Cl_{(sat)}$, water, $NaHCO_{3(sat)}$ and were dried over $MgSO_4$. The crude compound was purified by flash column chromatography (PE to PE/EtOAc 95 : 5) to afford the desired compound as a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	8.11 – 8.09 (m, 2H, H_8), 7.64 – 7.61 (m, 1H, H_{10}), 7.50 – 7.46 (m, 2H, H_9), 6.06 – 6.00 (m, 1H, H_2), 1.91 (d, *J* = 2.2 Hz, 3H, H_5)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	164.4 (C_6), 134.1 (C_{10}), 130.3 (C_8), 128.8 (C_9), 128.5 (C_7), 122.2 (q, *J* = 280.3 Hz, C_1), 85.9 (C_4), 68.7 (q, *J* = 2.2 Hz, C_3), 62.3 (q, *J* = 37.4 Hz, C_2), 3.8 (C_5)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-77.7
IR (cm^{-1}, CCl_4)	3067 (m), 2948 (m), 2926 (m), 2260 (m), 1737 (s), 1602 (m), 1586 (w), 1493 (w), 1453 (m), 1359 (s), 1329 (s), 1278 (s), 1259 (s), 1194 (s), 1171 (s), 1141 (s), 1103 (s), 1091 (s), 1069 (s), 1027 (s), 996 (s)
MS (HRMS EI)	Calcd for [M-HF] $C_{12}H_8F_2O_2$: 222.0492 Found: 222.0495 Calcd for [M-$C_6H_5O_2$]: $C_5H_4F_3$: 121.0265 Found: 121.0268

6-((tert-butyldiphenylsilyl)oxy)-1,1,1-trifluoro-2-phenylhex-3-yn-2-yl acetate (III.28q)



$C_{30}H_{31}F_3O_3Si$
M = 524.65 g.mol^{-1}

To a solution of (but-3-yn-1-yloxy)(tert-butyl)diphenylsilane (1 equiv, 2.0 mmol, 617 mg) in THF (3 mL) was added dropwise *n*-BuLi in solution in hexanes (1.2 equiv, 2.4 mmol) at -78 °C. After 10 minutes stirring at -78 °C, trifluoroacetophenone (1.3 equiv, 2.6 mmol, 453 mg, 0.37 mL) and was added at -78 °C and the mixture was stirred overnight while warming up to room temperature. The reaction was quenched by the addition of $NH_4Cl_{(sat)}$

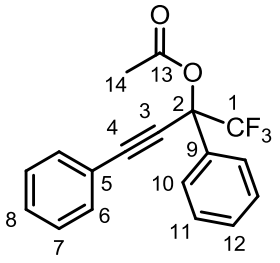
and was then allowed to warm up to room temperature. Et_2O and $NH_4Cl_{(sat)}$ were added and the mixture was extracted with Et_2O (x3) and dried over $MgSO_4$. Purification by flash column chromatography (PE/EtOAc 9 : 1) afforded the desired alcohol ***III.18q*** (579 mg, 60% yield).

The acetylated product was obtained following the acetylation part of procedure E starting with 1.20 mmol (579 mg) of 6-((tert-butyldiphenylsilyl)oxy)-1,1,1-trifluoro-2-phenylhex-3-yn-2-ol ***III.28q***.

Yield: 392 mg (62% yield) as a white solid.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.73 – 7.70 (m, 4H, H_{10}), 7.66 – 7.64 (m, 2H, H_{14or15}), 7.47 – 7.37 (m, 9H, H_{Ar}), 3.87 (t, *J* = 6.5 Hz, 2H, H_6), 2.65 (t, *J* = 6.5 Hz, 2H, H_5), 2.16 (s, 3H, H_{18}), 1.09 (s, 9H, H_8)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	166.9 (C_{17}), 135.7 (C_{10}), 133.5 (C_{9or13}), 133.4 (C_{9or13}), 129.9 (C_{Ar}), 129.6 (C_{16}), 128.5 (C_{Ar}), 127.8 (C_{11}), 127.2 (C_{14or15}), 122.5 (q, *J* = 284.0 Hz, C_1), 89.1 (C_4), 77.6 (q, *J* = 32.0 Hz, C_2), 73.0 (C_3), 61.8 (C_6), 26.8 (C_8), 23.3 (C_5), 21.6 (C_{18}), 19.3 (C_7)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-79.9
Melting point (°C)	88.6 – 90.0
IR (cm^{-1}, CCl_4)	3073 (w), 3054 (w), 2960 (m), 2933 (m), 2882 (w), 2860 (m), 2251 (m), 1770 (s), 1602 (w), 1590 (w), 1473 (w), 1453 (w), 1428 (m), 1385 (w), 1370 (m), 1335 (w), 1270 (s), 1224 (s), 1191 (s), 1163 (m), 1112 (s), 1025 (m), 956 (m)
MS (HRMS EI)	Calcd for $C_{30}H_{31}F_3O_3Si$: 524.1994 Found: 524.1983

1,1,1-trifluoro-2,4-diphenylbut-3-yn-2-yl acetate (III.28r)



$C_{18}H_{13}F_3O_2$
M = 318.29 g.mol^{-1}

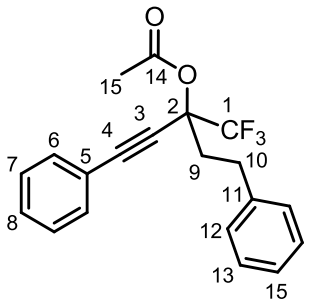
To a solution of phenylacetylene (1.0 equiv, 10 mmol, 1.02 g, 1.10 mL) in THF (10 mL) at -78 °C was added dropwise a solution of *n*-BuLi in hexanes (1.0 equiv, 10.0 mmol). After 10 minutes stirring at -78 °C, trifluoroacetophenone (1.2 equiv, 12.0 mmol, 2.09 g, 1.69 mL) was added dropwise and the mixture was stirred 1 h at -78 °C and 30 minutes at 0 °C. $NH_4Cl_{(sat)}$ and Et_2O were added, and the mixture was extracted with Et_2O (x3), washed with water and dried over $MgSO_4$. Purification by flash column chromatography (PE/EtOAc 9 : 1) afforded the desired alcohol in quantitative yield **III.18r**.

To a solution of the alcohol **III.18r** (1.0 equiv, 2.0 mmol, 552.0 mg) in DCM (8.0 mL) were added successively DMAP (0.1 equiv, 0.2 mmol, 24.4 mg), triethylamine (1.5 equiv, 3.0 mmol, 303.6 mg, 0.42 mL) and acetic anhydride (1.2 equiv, 2.4 mmol, 245.0 mg, 0.23 mL) at room temperature and the mixture was stirred overnight. DCM and $NH_4Cl_{(sat)}$ were added and the mixture was extracted with DCM and dried over $MgSO_4$. Purification by flash column chromatography (PE/EtOAc 95 : 5) afforded the desired product **III.28r** as colorless sticky oil (493.0 mg, 77% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.72 – 7.70 (m, 2H, H_{Ar}), 7.61 – 7.58 (m, 2H, H_{Ar}), 7.45 – 7.35 (m, 6H, H_{Ar}), 2.23 (s, 3H, H_{14})
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	167.0 (C_{13}), 133.2 (C_9), 132.4 (C_{Ar}), 129.8 (C_{8or12}), 129.7 (C_{8or12}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 127.1 (C_{Ar}), 126.8 (C_{Ar}), 122.6 (q, J = 284.2 Hz, C_1), 121.2 (C_5),

	90.1 (C_4), 80.7 (C_3), 77.9 (q, J = 32.3 Hz, C_2), 21.5 (C_{14})
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-79.6
IR (cm^{-1}, CCl_4)	3069 (w), 3036 (w), 2240 (m), 1955 (w), 1888 (w), 1769 (s), 1601 (w), 1491 (m), 1453 (m), 1445 (w), 1370 (m), 1281 (m), 1257 (s), 1223 (s), 1209 (s), 1191 (s), 1094 (m), 1064 (m), 1023 (s), 955 (m)
MS (HRMS EI)	Calcd for $C_{18}H_{13}F_3O_2$: 318.0868 Found: 318.0869

1,5-diphenyl-3-(trifluoromethyl)pent-1-yn-3-yl acetate (III.28s)



$C_{20}H_{17}F_3O_2$
M = 346.34 g.mol^{-1}

To a solution of 1,5-diphenylpent-1-yn-3-one (1.0 equiv, 2.0 mmol, 469 mg) in THF (3 mL) at 0 °C was added trifluoromethyltrimethylsilane (1.2 equiv, 2.4 mmol, 341 mg, 0.35 mL) followed by TBAF (1M in THF, 0.1 equiv, 0.2 mmol, 0.2 mL) which was added over 5 minutes. After 2 h stirring at room temperature, 3 mL HCl (2M) was added and the mixture was stirred 20 minutes. The mixture was extracted with Et_2O, washed with HCl (2M) and dried over $MgSO_4$. Purification by column chromatography (PE/EtOAc 9 : 1) afforded the desired alcohol **III.18s** (500.0 mg, 1.64 mmol, 82% yield) as a bright yellow oil.

To a solution of the alcohol (1.0 equiv, 1.64 mmol, 500.0 mg) in DCM (6.6 mL) were added successively DMAP (0.1 equiv, 0.16 mmol, 20.0 mg), tri-ethylamine (1.5 equiv, 2.46 mmol, 248.9 mg, 0.34 mL) and acetic anhydride

(1.2 equiv, 1.97 mmol, 200.9 mg, 0.19 mL) at room temperature and the mixture was stirred overnight. DCM and $NH_4Cl_{(sat)}$ were added and the mixture was extracted with DCM and dried over $MgSO_4$. Purification by flash column chromatography (PE/EtOAc 95 : 5) afforded the desired product as slightly yellow oil **III.28s** (226 mg, 40% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.52 – 7.50 (m, 2H, H_{Ar}), 7.40 – 7.29 (m, 5H, H_{Ar}), 7.24 – 7.20 (m, 3H, H_{Ar}), 3.01 – 2.93 (m, 1H, H_9), 2.89 – 2.81 (m, 1H, $H_{9'}$), 2.62 – 2.57 (m, 2H, H_{10}), 2.13 (s, 3H, H_{15})
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	167.7 (C_{14}), 140.6 (C_{11}), 132.3 (C_{Ar}), 129.5 (C_8), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 126.4 (C_{15}), 123.3 (q, J = 284.9 Hz, C_1), 121.3 (C_5), 89.7 (C_4), 80.5 (C_3), 76.6 (q, J = 32.0 Hz, C_2), 36.2 (C_{9or10}), 30.5 (C_{9or10}), 21.6 (C_{15})
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-78.4
IR (cm^{-1}, CCl_4)	3087 (w), 3066 (w), 3030 (m), 2949 (w), 2876 (w), 2264 (w), 2249 (m), 1952 (w), 1884 (w), 1759 (s), 1711 (w), 1603 (m), 1491 (m), 1456 (m), 1445 (m), 1370 (m), 1258 (m), 1226 (s), 1206 (s), 1193 (s), 1114 (m), 1100 (m), 1071 (m), 1042 (m), 958 (w)
MS (HRMS EI)	Calcd for $C_{20}H_{17}F_3O_2$: 346.1181 Found: 346.1184

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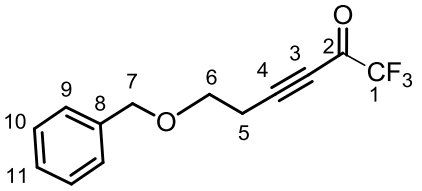
6-(benzyloxy)-1,1,1-trifluorohex-3-yn-2-one

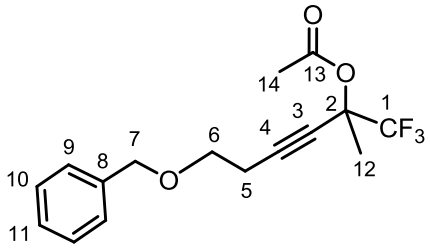


$C_{13}H_{11}F_3O_2$
M = 256.22 g.mol^{-1}

To a solution of ((but-3-yn-1-yloxy)methyl)benzene (1 equiv, 15.0 mmol, 2.40 g) in THF (30 mL) was added dropwise *n*-BuLi in solution in hexanes (1.2 equiv, 18.0 mmol) at -78 °C. After 20 minutes stirring at -78 °C, ethyl trifluoroacetate (1.3 equiv, 19.5 mmol, 2.77 g, 2.32 mL) and $BF_3.Et_2O$ (1.3 equiv, 19.5 mmol, 2.77 g, 2.45 mL) were added successively at -78 °C and the mixture was stirred 90 minutes at -78 °C. The reaction was quenched by the addition of $NH_4Cl_{(sat)}$ and was then allowed to warm up to room temperature. The mixture was extracted with EtOAc (x3), washed with brine and dried over $MgSO_4$. Purification by flash column chromatography (PE/EtOAc 9 : 1) afforded the desired ketone as a yellow oil (2.23 g, 58% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.40 – 7.30 (m, 5H, H_{Ar}), 4.58 (s, 2H, H_7), 3.70 (t, *J* = 6.5 Hz, 2H, H_6), 2.81 (t, *J* = 6.5 Hz, 2H, H_5)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	167.2 (q, *J* = 42.1 Hz, C_2), 137.6 (C_8), 128.7 (C_{9or10}), 128.1 (C_{11}), 127.8 (C_{9or10}), 114.8 (q, *J* = 288.4 Hz, C_1), 101.9 (C_4), 76.6 (C_3), 73.4 (C_7), 66.5 (C_6), 21.2 (C_5)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-79.2
IR (cm^{-1}, CCl_4)	3308 (w), 3089 (w), 3068 (w), 3033 (w), 2870 (br m), 2301 (w), 2251 (m), 2220 (s), 1710 (s), 1600 (w), 1496 (w), 1455 (w), 1410 (w), 1390 (w), 1364 (w), 1338 (w), 1317 (w), 1275 (w), 1219 (s), 1168 (s), 1150 (s), 1100 (s), 1028 (w), 989 (w)
MS (HRMS EI)	Calcd for $C_{13}H_{11}F_3O_2$: 256.0711 Found: 256.0709

6-(benzyloxy)-1,1,1-trifluoro-2-methylhex-3-yn-2-yl acetate (III.28t)



$C_{16}H_{17}F_3O_3$
M = 314.30 g.mol^{-1}

1st procedure for the preparation of the alcohol: To a solution of 6-(benzyloxy)-1,1,1-trifluorohex-3-yn-2-one (1.0 equiv, 1.2 mmol, 307.2 mg) in Et_2O (2.5 mL) at 0 °C was added dropwise a solution of methyllithium in hexanes (1.5 equiv, 1.8 mmol). After 3 h stirring while warming up to room temperature, Et_2O and water were added. The mixture was extracted with Et_2O and dried over $MgSO_4$. Purification by flash column chromatography (PE/EtOAc 9 : 1 to 85 : 15) afforded the pure alcohol **III.18t** (0.61 mmol, 51% yield).

2nd procedure for the preparation of the alcohol: To a solution of 4-(benzyloxy)-2-butanone (1.0 equiv, 5.48 mmol, 1.11 g) in THF (20 mL) at 0 °C was added trifluoromethyltrimethylsilane (1.5 equiv, 8.23 mmol, 1.17 g, 1.22 mL) followed by TBAF (1.2 equiv, 6.58 mmol, 2.08 g). After 1 h 20 stirring while warming up to room temperature, water and EtOAc were added. The mixture was extracted with EtOAc (x3), washed with brine and dried over $MgSO_4$. Purification by column chromatography (PE/EtOAc 9 : 1 to 8 : 2) afforded the desired alcohol **III.18t** (3.42 mmol, 62% yield).

Acetylation procedure: The acetylated product was obtained following the acetylation part of procedure E starting with 3.42 mmol (931.6 mg) of 6-(benzyloxy)-1,1,1-trifluoro-2-methylhex-3-yn-2-ol **III.18t**.

Flash chromatography: PE / EtOAc 9 : 1

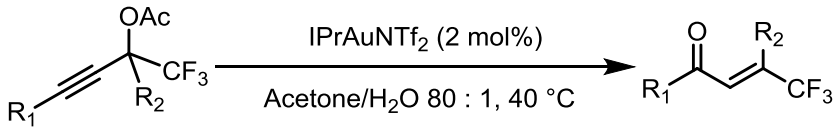
Yield : 699.1 mg (65%) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.38 – 7.26 (m, 5H, H_{Ar}), 4.55 (s, 2H, H_7), 3.61 (t, *J* = 7.0 Hz, 2H, H_6), 2.57 (t, *J* = 7.0 Hz, 2H, H_5), 2.09 (s, 3H, H_{14}), 1.84 (s, 3H, H_{12})*
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	168.0 (C_{13}), 138.2 (C_8), 128.6 (C_{9or10}), 127.8 (C_{11}), 127.7 (C_{9or10}), 123.1 (q, *J* = 283.1 Hz, C_1), 86.1 (C_4), 73.9 (C_3), 73.8 (q, *J* = 32.6 Hz, C_2), 73.2 (C_7), 67.9 (C_6), 21.7 (C_{12or14}), 20.8 (C_{12or14}), 20.4 (C_5)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-82.8
IR (cm^{-1}, CCl_4)	3067 (w), 3033 (w), 3006 (w), 2921 (w), 2869 (m), 2251 (m), 1757 (s), 1603 (w), 1496 (w), 1454 (m), 1432 (w), 1379 (m), 1370 (m), 1310 (m), 1282 (w), 1247 (s), 1228 (s), 1185 (s), 1112 (s), 1015 (w), 953 (w)
MS (HRMS EI)	Calcd for $C_{16}H_{17}F_3O_3$: 314.1130 Found: 314.1126

***** This singlet is broad and can be interpreted as a non-defined quadruplet due to the coupling with the CF_3 group

Catalysis step

General procedure G for the gold-catalyzed acetate rearrangement:

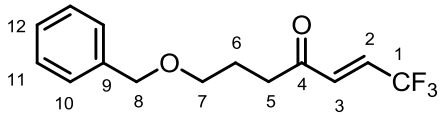


To a solution of propargylic acetate (1 equiv) in acetone/water 80 : 1 (0.5 $mol.L^{-1}$) was added $IPrAuNTf_2$ (2 mol%) and the reaction was heated up to 40 °C. After the indicated time, the solvent was evaporated and purification by flash chromatography gave the pure trifluoromethylated enone.

General procedure H for the one-pot gold-catalyzed rearrangement/Diels-Alder reaction

IPrAuNTf$_2$ (0.05 equiv) was weighted in a vial. A solution of propargyl acetate (1 equiv) in dioxane/water 80 : 1 (0.4-0.5 M) was added. The diene (4 equiv) was added immediately (one-pot with all reagents) or after the specified time of stirring at 80 °C (sequential one-pot). The mixture was then stirred at 80 °C in the saeled vial and the solvents were removed under reduced pressure. Purification by flash column chromatography afforded the pure Diels-Alder adduct.

(E)-7-(benzyloxy)-1,1,1-trifluorohept-2-en-4-one (III.16a)



$C_{14}H_{15}F_3O_2$
M = 272.26 g.mol^{-1}

Following procedure G starting with 0.2 mmol of 7-(benzyloxy)-1,1,1-trifluorohept-3-yn-2-yl acetate **III.28a**.

Reaction time: 3 h

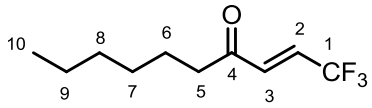
Flash chromatography: PE / EtOAc 95 :5

Yield: 47.8 mg (88 %) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.37 – 7.27 (m, 5H, H_{Ar}), 6.71 (dq, *J* = 16.0, 1.7 Hz, 1H, H_3), 6.58 (dq, *J* = 16.0, 6.3 Hz, 1H, H_2), 4.48 (s, 2H, H_8), 3.51 (t, *J* = 5.9 Hz, 2H, H_7), 2.76 (t, *J* = 7.1 Hz, 2H, H_5), 2.00 – 1.93 (m, 2H, H_6)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	198.0 (C_4), 138.3 (C_9), 134.4 (q, *J* = 5.5 Hz, C_3), 128.7 (C_{11}), 128.5 (q, *J* = 35.2 Hz, C_2), 127.8 (C_{12}), 127.8 (C_{10}), 122.6 (q, *J* = 270.54 Hz, C_1), 73.1 (C_8), 69.0 (C_7), 38.7 (C_5), 23.8 (C_6)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-66.2
IR (cm^{-1}, CCl_4)	3153 (w), 3033 (w), 2936 (w), 2865 (w), 2259 (s), 1793 (w), 1713 (m), 1662 (w), 1602 (w), 1455 (w),

	1363 (w), 1303 (s), 1268 (m), 1141 (s), 1028 (w), 972 (m)
MS (HRMS EI)	Calcd for $C_{14}H_{15}F_3O_2$: 272.1024 Found: 272.1024

(E)-1,1,1-trifluorodec-2-en-4-one (III.16b)



$C_{10}H_{15}F_3O$
M = 208.22 g.mol^{-1}

Following procedure G starting with 0.2 mmol of 1,1,1-trifluorodec-3-yn-2-yl acetate **III.28b**.

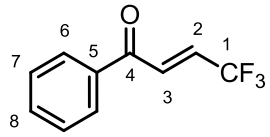
Reaction time: 4 h

Flash chromatography: PE / EtOAc 95 :5

Yield: 31.7 mg (76 %) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	6.71 (dq, *J* = 15.9, 1.7 Hz, 1H, H_3), 6.59 (q, *J* = 15.9, 6.3 Hz, 1H, H_2), 2.62 (t, *J* = 7.4 Hz, 2H, H_5), 1.67 – 1.61 (m, 2H, H_6), 1.35 – 1.24 (m, 6H, H_{7+8+9}), 0.88 (t, *J* = 6.39 Hz, 3H, H_{10})
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	198.4 (C_4), 134.3 (q, *J* = 5.5 Hz, C_3), 128.4 (q, *J* = 35.2 Hz, C_2), 122.6 (q, *J* = 270.3 Hz, C_1), 42.1 (C_5), 31.6 (C_{Aliph}), 28.8 (C_{Aliph}), 23.6 (C_6), 22.6 (C_{Aliph}), 14.1 (C_{10})
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-66.2 (d, *J* = 5.5 Hz)
IR (cm^{-1}, CCl_4)	3071 (w), 2959 (s), 2932 (s), 2873 (m), 2860 (m), 2258 (s), 1711 (s), 1662 (m), 1467 (m), 1460 (m), 1404 (m), 1375 (m), 1303 (s), 1270 (s), 1175 (m), 1142 (s), 1072 (w), 972 (m)
MS (HRMS EI)	Calcd for $C_{10}H_{15}F_3O$: 208.1075 Found: 208.1081

(E)-4,4,4-trifluoro-1-phenylbut-2-en-1-one (III.16c)



$C_{10}H_7F_3O$
M = 200.16 g.mol^{-1}

Following procedure G starting with 0.2 mmol of 1,1,1-trifluoro-4-phenylbut-3-yn-2-yl acetate **III.28c**.

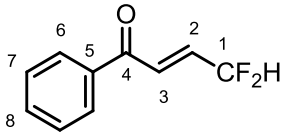
Reaction time: 4 h

Flash chromatography: PE/EtOAc 95 : 5

Yield: 30.0 mg (75 %) of a slightly yellow oil/low melting point solid.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	8.00 – 7.97 (m, 2H, H_{Ar}), 7.68 – 7.63 (m, 1H, H_{Ar}), 7.57 – 7.51 (m, 3H, H_{Ar}), 6.83 (dq, *J* = 15.5, 6.7 Hz, 1H, H_2)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	188.2 (C_4), 136.3 (C_5), 134.3 (C_8), 131.1 (q, *J* = 5.4 Hz, C_3), 130.4 (q, *J* = 35.1 Hz, C_2), 129.2 (C_{Ar}), 129.0 (C_{Ar}), 122.7 (q, *J* = 270.3 Hz, C_1)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-66.1 (d, *J* = 5.6 Hz)
IR (cm^{-1}, CCl_4)	3087 (w), 3063 (w), 3031 (w), 2961 (w), 2926 (w), 2258 (s), 1966 (w), 1904 (w), 1815 (w), 1711 (s), 1688 (s), 1650 (s), 1598 (s), 1581 (m), 1536 (w), 1493 (w), 1450 (m), 1363 (m), 1331 (s), 1306 (s), 1273 (s), 1224 (m), 1181 (m), 1141 (s), 1014 (s), 967 (s)
MS (HRMS EI)	Calcd for $C_{10}H_7F_3O$: 200.0449 Found: 200.0457

(E)-4,4-difluoro-1-phenylbut-2-en-1-one (III.16d)



$C_{10}H_8F_2O$
M = 182.17 g.mol^{-1}

Following procedure C starting with 0.2 mmol of 1,1-difluoro-4-phenylbut-3-yn-2-yl acetate **III.28d**.

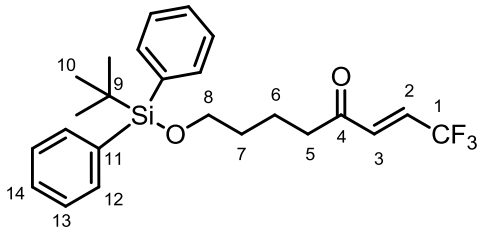
Reaction time: 18 h with 4 mol% catalyst

Flash chromatography: PE/EtOAc 95 : 5

Yield: 32.6 mg (89 %) of a white solid.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.99 – 7.96 (m, 2H, H_{Ar}), 7.65 – 7.61 (m, 1H, H_8), 7.54 – 7.50 (m, 2H, H_{Ar}), 7.34 (dtd, *J* = 15.7, 3.1, 1.1 Hz, 1H, H_3), 6.86 (dtd, *J* = 15.7, 10.6, 3.9 Hz, 1H, H_2), 6.35 (tdd, *J* = 55.0, 3.9, 1.0 Hz, 1H, H_1)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	189.1 (C_4), 136.8 (C_5), 135.7 (t, *J* = 23.5 Hz, C_2), 133.9 (C_8), 130.1 (t, *J* = 9.5 Hz, C_3), 129.0 (C_{Ar}), 128.9 (C_{Ar}), 113.0 (q, *J* = 237.5 Hz, C_1)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-116.8 (dd, *J* = 55.5, 10.3 Hz)
IR (cm^{-1}, CCl_4)	3063 (w), 2969 (w), 2261 (m), 1683 (s), 1644 (s), 1599 (s), 1450 (m), 1380 (s), 1349 (s), 1328 (m), 1280 (s), 1212 (m), 1182 (m), 1138 (s), 1048 (s, br), 1018 (m), 974 (m)
MS (HRMS EI)	Calcd for $C_{10}H_8F_2O$: 182.0543 Found: 182.0563

(E)-8-((tert-butyldiphenylsilyl)oxy)-1,1,1-trifluorooct-2-en-4-one (III.16e)



$C_{24}H_{29}F_3O_2Si$
M = 434.57 g.mol^{-1}

Following procedure G starting with 0.2 mmol of 8-((tert-butyldiphenylsilyl)oxy)-1,1,1-trifluorooct-3-yn-2-yl acetate **III.28e**.

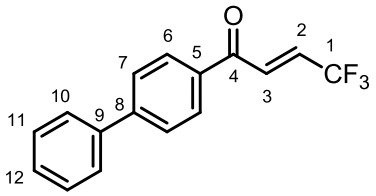
Reaction time: 4 h at room temperature.

Flash chromatography: PE / EtOAc 95 :5

Yield: 70.0 mg (81 %) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.67 – 7.65 (m, 4H, H_{12}), 7.45 – 7.36 (m, 6H, H_{13+14}), 6.68 (dq, *J* = 15.9, 1.7 Hz, 1H, H_3), 6.57 (dq, *J* = 15.9, 6.2 Hz, 1H, H_2), 3.68 (t, *J* = 6.1 Hz, 2H, H_8), 2.59 (t, *J* = 7.2 Hz, 2H, H_5), 1.78 – 1.71 (m, 2H, H_6), 1.60 – 1.55 (m, 2H, H_7), 1.05 (s, 9H, H_{10})
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	198.0 (C_4), 135.7 (C_{12}), 134.3 (q, *J* = 5.4 Hz, C_3), 134.0 (C_{11}), 129.8 (C_{14}), 128.5 (q, *J* = 35.4 Hz, C_2), 127.8 (C_{13}), 122.6 (q, *J* = 270.3 Hz, C_1), 63.4 (C_8), 41.6 (C_5), 31.8 (C_7), 27.0 (C_{10}), 20.1 (C_6), 19.4 (C_9)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-66.2
IR (cm^{-1}, CCl_4)	3073 (w), 3054 (w), 2958 (m), 2933 (m), 2896 (m), 2860 (m), 2259 (s), 1712 (m), 1662 (m), 1602 (w), 1590 (w), 1472 (m), 1463 (m), 1428 (m), 1390 (w), 1362 (w), 1302 (s), 1269 (m), 1142 (s), 1112 (s)
MS (HRMS EI)	Calcd for $C_{20}H_{20}F_3O_2Si$: 377.1185 [*M*-*t*Bu] Found: 377.1188

(E)-1-([1,1'-biphenyl]-4-yl)-4,4,4-trifluorobut-2-en-1-one (III.16f)



$C_{16}H_{11}F_3O$
M = 276.25 g.mol^{-1}

Following procedure G starting with 0.2 mmol of 4-([1,1'-biphenyl]-4-yl)-1,1,1-trifluorobut-3-yn-2-yl acetate **III.28f**.

Reaction time: 3 h

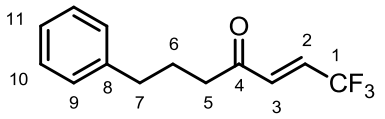
Flash chromatography: PE / EtOAc 95 : 5

Yield : 48.6 mg (88%) of a white solid.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	8.08 – 8.05 (m, 2H, H_6), 7.77 – 7.74 (m, 2H, H_7), 7.66 – 763 (m, 2H, H_{10}), 7.59 (dq, *J* = 15.5, 2.0 Hz, 1H, H_3), 7.52 – 7.47 (m, 2H, H_{11}), 7.45 – 7.41 (m, 1H, H_{12}), 6.86 (dq, *J* = 15.5, 6.6 Hz, 1H, H_2)

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	187.6 (C_4), 147.0 (C_8), 139.6 (C_9), 135.0 (C_5), 131.1 (q, J = 5.6 Hz, C_3), 130.4 (q, J = 35.1 Hz, C_2), 129.6 (C_{Ar}), 129.2 (C_{Ar}), 128.7 (C_{12}), 127.8 (C_{Ar}), 127.5 (C_{Ar}), 122.7 (q, J = 270.2 Hz, C_1)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-66.1
IR (cm^{-1}, CCl_4)	3152 (w), 3062 (w), 3034 (w), 2963 (w), 2259 (m), 1686 (m), 1649 (m), 1603 (m), 1560 (w), 1516 (w), 1487 (w), 1450 (w), 1407 (w), 1331 (m), 1306 (s), 1275 (m), 1226 (w), 1191 (w), 1142 (s), 1027 (w), 1007 (w), 967 (m)
MS (HRMS EI)	Calcd for $C_{16}H_{11}F_3O$: 276.0762 Found: 276.0762

(E)-1,1,1-trifluoro-7-phenylhept-2-en-4-one (III.16g)



$C_{13}H_{13}F_3O$
M = 242.24 g.mol^{-1}

Following procedure G starting with 0.2 mmol of 1,1,1-trifluoro-7-phenylhept-3-yn-2-yl acetate **III.28g**.

Reaction time: 3 h.

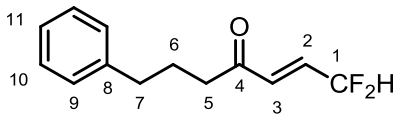
Flash chromatography: pentane to pentane/Et_2O 95 :5

Yield: 38.0 mg (78 %) of a yellow oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.32 – 7.28 (m, 2H, H_{10}), 7.23 – 7.16 (m, 3H, H_{9+11}), 6.68 (dq, J = 15.9, 1.7 Hz, 1H, H_3), 6.55 (dq, J = 15.9, 6.3 Hz, 1H, H_2), 2.69 – 2.61 (m, 4H, H_{5+7}), 2.03 – 1.96 (m, 2H, H_6)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	197.9 (C_4), 141.2 (C_8), 134.3 (q, J = 5.6 Hz, C_3), 128.6 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (q, J = 35.3 Hz, C_2), 126.3 (C_{11}), 122.6 (q, J = 270.4 Hz, C_1), 41.1 (C_5), 35.0 (C_7), 25.0 (C_6)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-66.2

IR (cm^{-1}, CCl_4)	3066 (w), 3029 (m), 2942 (m, br), 2863 (w), 2259 (s), 1712 (m), 1693 (m), 1662 (m), 1603 (m), 1496 (m), 1454 (m), 1405 (w), 1373 (m), 1303 (s), 1269 (m), 1144 (s), 1074 (w), 1030 (w), 972 (m)
MS (HRMS EI)	Calcd for $C_{13}H_{13}F_3O$: 242.0918 Found: 242.0927

(E)-1,1-difluoro-7-phenylhept-2-en-4-one (III.16h)



$C_{13}H_{14}F_2O$
M = 224.25 g.mol^{-1}

Following procedure G starting with 0.2 mmol of 1,1-difluoro-7-phenylhept-3-yn-2-yl acetate **III.28h**.

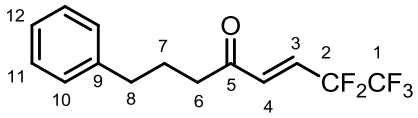
Reaction time: 6 h.

Flash chromatography: pentane/Et_2O 8 : 2

Yield: 39.3 mg (88 %) of a slightly yellow oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.32 – 7.26 (m, 2H, H_{10}), 7.23 – 7.16 (m, 3H, H_{9+11}), 6.59 (dtd, *J* = 16.1, 9.6 Hz, 4.1 Hz, 1H, H_2), 6.47 (dtd, *J* = 16.1, 2.6 Hz, 0.7 Hz, 1H, H_3), 6.21 (tdd, *J* = 54.9, 4.2, 0.8 Hz, 1H, H_1), 2.68 – 2.60 (m, 4H, H_{5+7}), 2.02 – 1.95 (m, 2H, H_6)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	198.8 (C_4), 141.4 (C_8), 133.7 (t, *J* = 23.9 Hz, C_2), 133.6 (t, *J* = 9.6 Hz, C_3), 128.6 (x2) (C_{9+10}), 126.2 (C_{11}), 113.1 (t, *J* = 237.4 Hz, C_1), 40.4 (C_5), 35.1 (C_7), 25.2 (C_6)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-116.4 (dd, *J* = 55.4, 9.5 Hz)
IR (cm^{-1}, CCl_4)	3086 (m), 3065 (m), 3029 (m), 2951 (m, br), 2863 (m), 2254 (s), 1948 (w), 1807 (w), 1707 (s), 1689 (s), 1603 (m), 1496 (m), 1454 (m), 1380 (s), 1349 (m), 1257 (m), 1139 (s), 1126 (s), 1046 (s, br)
MS (HRMS EI)	Calcd for $C_{13}H_{14}F_2O$: 224.1013 Found: 224.1013

(E)-7,7,8,8,8-pentafluoro-1-phenyloct-5-en-4-one (III.16i)



$C_{14}H_{13}F_5O$
M = 292.24 g.mol^{-1}

Following procedure G starting with 0.2 mmol of 1,1,1,2,2-pentafluoro-8-phenyloct-4-yn-3-yl acetate **III.28i**.

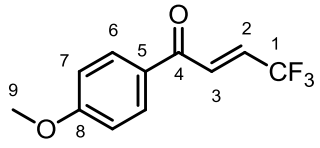
Reaction time: 8 h.

Flash chromatography: PE/EtOAc 96 : 4

Yield: 48.0 mg (82 %) of a colorless oil.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.32 – 7.28 (m, 2H, H_{11}), 7.23 – 7.17 (m, 3H, H_{9+12}), 6.74 (dt, *J* = 16.0, 1.9 Hz, 1H, H_4), 6.59 (dt, *J* = 16.0, 11.5 Hz, 1H, H_3), 2.69 – 2.62 (m, 4H, H_{6+8}), 2.04 – 1.96 (m, 2H, H_7)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	197.5 (C_5), 141.2 (C_9), 136.21 (t, *J* = 6.9 Hz, C_4), 128.6 (C_{10or11}), 128.6 (C_{10or11}), 127.6 (t, *J* = 23.7 Hz, C_3), 126.3 (C_{12}), 118.6 (qt, *J* = 285.9, 36.8 Hz, C_1), 112.0 (tq, *J* = 251.6, 39.3 Hz, C_2), 41.3 (C_6), 34.9 (C_8), 25.0 (C_7)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-85.6 (F_1), -118.0 (d, *J* = 11.9 Hz, F_2)
IR (cm^{-1}, CCl_4)	3086 (w), 3066 (w), 3029 (m), 2942 (m, br), 2863 (w), 2254 (m), 1711 (m), 1653 (m), 1603 (m), 1496 (m), 1454 (m), 1405 (w), 1373 (m), 1341 (m), 1308 (m), 1274 (m), 1247 (m), 1210 (s), 1123 (m), 1043 (m), 974 (m)
MS (HRMS EI)	Calcd for $C_{14}H_{13}F_5O$: 292.0886 Found: 292.0882

(E)-4,4,4-trifluoro-1-(4-methoxyphenyl)but-2-en-1-one (III.16j)



$C_{11}H_9F_3O$
M = 230.18 g.mol^{-1}

Following procedure G starting with 0.2 mmol of 1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-yn-2-yl acetate **III.28j**.

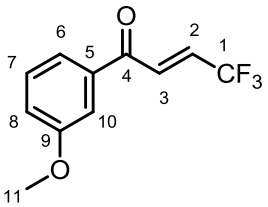
Reaction time: 22 h.

Flash chromatography: PE/EtOAc 9 : 1

Yield : 40.1 mg (87%) of a slightly yellow oil/low melting point solid

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	8.00 – 7.97 (m, 2H, H_6), 7.54 (dq, *J* = 15.5, 2.0 Hz, 1H, H_3), 7.01 – 5.98 (m, 2H, H_7), 6.80 (dq, *J* = 15.5, 6.7 Hz, 1H, H_2), 3.90 (s, 3H, H_9)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	186.3 (C_4), 164.6 (C_8), 131.4 (C_6), 131.2 (q, *J* = 5.6 Hz, C_3), 129.7 (q, *J* = 35.0 Hz, C_2), 129.4 (C_5), 122.8 (q, *J* = 270.1 Hz, C_1), 114.4 (C_7), 55.8 (C_9)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-66.0 (d, $J_{F\text{-}H2}$ = 5.6 Hz)
IR (cm^{-1}, CCl_4)	3063 (w), 3013 (m), 2968 (m), 2939 (m), 2843 (m), 2580 (w), 2258 (s), 1683 (s), 1644 (s), 1599 (s), 1574 (s), 1513 (s), 1465 (m), 1448 (m), 1423 (m), 1335 (s), 1307 (s), 1265 (s), 1234 (s), 1172 (s), 1140 (s), 1033 (m), 1018 (m), 967 (m)
MS (HRMS EI)	Calcd for $C_{11}H_9F_3O_2$: 230.0555 Found: 230.0553

(E)-4,4,4-trifluoro-1-(3-methoxyphenyl)but-2-en-1-one (III.16k)



$C_{11}H_9F_3O$
M = 230.18 g.mol^{-1}

Following procedure G starting with 0.2 mmol of 1,1,1-trifluoro-4-(3-methoxyphenyl)but-3-yn-2-yl acetate **III.28k**.

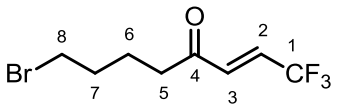
Reaction time: 15 h.

Flash chromatography: PE/EtOAc 95 : 5

Yield : 37.1 mg (80%) of a yellow oil

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.55 – 7.49 (m, 3H, H_{3+Ar}), 7.43 (t, *J* = 7.9 Hz, 1H, H_{Ar}), 7.19 (ddd, *J* = 8.2, 2.7, 0.9 Hz, 1H, H_{Ar}), 6.82 (dq, *J* = 15.6, 6.6 Hz, 1H, H_2), 3.88 (s, 3H, H_{11})
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	187.9 (C_4), 160.23 (C_9), 137.6 (C_5), 131.2 (q, *J* = 5.6 Hz, C_3), 130.4 (q, *J* = 35.1 Hz, C_2), 130.1 (C_{Ar}), 122.7 (q, *J* = 270.2 Hz, C_1), 121.6 (C_{Ar}), 121.0 (C_{Ar}), 112.9 (C_{Ar}), 55.6 (C_{11})
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-66.1
IR (cm^{-1}, CCl_4)	3079 (w), 3010 (w), 2965 (w), 2943 (w), 2839 (w), 2258 (s), 1758 (w), 1688 (m), 1649 (m), 1598 (m), 1582 (m), 1488 (m), 1465 (m), 1454 (m), 1431 (m), 1398 (w), 1306 (s), 1288 (s), 1276 (s), 1260 (s), 1202 (m), 1177 (m), 1141 (s), 1029 (m), 967 (m)
MS (HRMS EI)	Calcd for $C_{11}H_9F_3O_2$: 230.0555 Found: 230.0551

(E)-8-bromo-1,1,1-trifluorooct-2-en-4-one (III.16m)



$C_8H_{10}BrF_3O$
M = 259,06 g.mol^{-1}

Following procedure G starting with 0.2 mmol of 8-bromo-1,1,1-trifluorooct-3-yn-2-yl acetate **III.28m**.

Reaction time: 17 h.

Flash chromatography: PE / Et_2O 9 : 1

Yield : 38.5 mg of a 1 : 0.07 molar mixture of the desired product with remaining starting material (yellow oil), which corresponds to 69% yield.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	6.72 (dq, *J* = 15.9, 1.6 Hz, 1H, H_3), 6.61 (q, *J* = 15.9, 6.2 Hz, 1H, H_2), 3.42 (t, *J* = 6.4 Hz, 2H, H_8), 2.68 (t, *J* = 7.0 Hz, 2H, H_5), 1.93 – 1.86 (m, 2H, H_7), 1.85 – 1.77 (m, 2H, H_6)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	197.4 (C_4), 134.0 (q, *J* = 5.6 Hz, C_3), 128.8 (q, *J* = 35.3 Hz, C_2), 122.5 (q, *J* = 270.4 Hz, C_1), 40.9 (C_5),

33.1 (C_8), 31.9 (C_7), 22.0 (C_6)

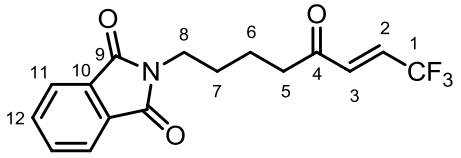
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$): -66.3

IR (cm^{-1}, CCl_4): 3072 (w), 3009 (w), 2945 (br m), 2259 (s), 1759 (m), 1713 (s), 1697 (m), 1662 (m), 1602 (w), 1438 (w), 1405 (m), 1374 (m), 1361 (m), 1303 (s), 1271 (s), 1223 (m), 1193 (m), 1143 (s), 1037 (w), 972 (m)

MS (HRMS EI): Calcd for $C_8H_{10}BrF_3O$: 257.9867 Found: 257.9878

Calcd for $C_8H_{10}F_3O$: 179.0684 [*M*-Br] Found: 179.0679

(E)-2-(8,8,8-trifluoro-5-oxooct-6-en-1-yl)isoindoline-1,3-dione (III.16n)



$C_{16}H_{14}F_3NO_3$
M = 325.28 g.mol^{-1}

Following procedure G starting with 0.2 mmol of 8-(1,3-dioxoisoindolin-2-yl)-1,1,1-trifluorooct-3-yn-2-yl acetate **III.28n**.

Reaction time: 18 h.

Flash chromatography: PE/EtOAc 8 : 2

Yield : 57.0 mg (80%) of a white solid.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$): 7.85 – 7.80 (m, 2H, H_{12}), 7.73 – 7.69 (m, 2H, H_{11}), 6.70 (dq, *J* = 16.0, 1.6 Hz, 1H, H_3), 6.59 (dq, *J* = 16.0, 6.1 Hz, 1H, H_2), 3.70 (t, *J* = 6.7 Hz, 2H, H_8), 2.70 (t, *J* = 7.0 Hz, 2H, H_5), 1.74 – 1.65 (m, 2H, H_{6+7})

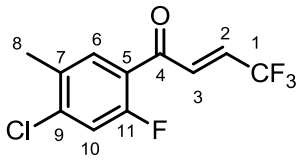
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$): 197.6 (C_4), 168.5 (C_9), 134.1 (q, *J* = 5.6 Hz, C_3), 134.1 (C_{11}), 132.1 (C_{10}), 128.6 (q, *J* = 35.2 Hz, C_2), 123.4 (C_{12}), 122.5 (q, *J* = 270.5 Hz, C_1), 41.1 (C_5), 37.4 (C_8), 27.9 (C_7), 20.5 (C_6)

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$): -66.3

IR (cm^{-1}, CCl_4)	3691 (w), 3466 (w), 3064 (w), 2947 (m), 2872 (w), 2258 (s), 1772 (s), 1712 (br s), 1662 (m), 1616 (m), 1469 (m), 1440 (s), 1898 (s), 1376 (s), 1302 (s), 1269 (s), 1172 (s), 1143 (br s), 1088 (m), 1037 (s), 972 (s).

MS (HRMS EI)	Calcd for $C_{16}H_{14}F_3NO_3$: 325.0926	Found: 325.0921

(E)-1-(4-chloro-2-fluoro-5-methylphenyl)-4,4,4-trifluorobut-2-en-1-one (III.16o)



$C_{11}H_7ClF_4O$
M = 266.62 g.mol^{-1}

Following procedure G starting with 0.105 mmol of 4-(4-chloro-2-fluoro-5-methylphenyl)-1,1,1-trifluorobut-3-yn-2-yl acetate **III.28o**.

Reaction time: 10 h with 5 mol% catalyst

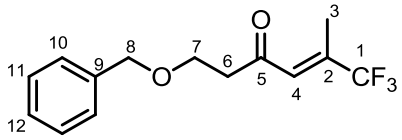
Flash chromatography: PE / EtOAc 95 : 5

Yield : 20.1 mg (72%) of a white solid

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.74 (dd, *J* = 7.8, 0.4 Hz, 1H, H_6), 7.43 – 7.37 (m, 1H, H_3), 7.23 (d, *J* = 10.5 Hz, H_{10}), 6.79 (dqd, *J* = 14.8, 6.6, 1.5 Hz, 1H, H_2), 2.39 (s, 3H, H_8)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	185.4 (d, *J* = 3.4 Hz, C_4), 160.0 (d, *J* = 255.9 Hz, C_{11}), 141.5 (d, *J* = 10.6 Hz, $C_{Ar\text{-}q}$), 134.0 (dq, *J* = 11.6, 5.8 Hz, C_3), 133.5 (d, *J* = 3.5 Hz, $C_{Ar\text{-}q}$), 132.7 (d, *J* = 2.6 Hz, C_6), 130.2 (qd, *J* = 35.2, 1.0 Hz, C_2), 123.3 (d, *J* = 12.1 Hz, $C_{Ar\text{-}q}$), 122.6 (q, *J* = 270.2 Hz, C_1), 117.8 (d, *J* = 26.7 Hz, C_{10}), 19.4 (C_8)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-65.6 (d, *J* = 4.8 Hz, F_1), -112.4 (d, *J* = 7.7 Hz, F_{11})
IR	2928 (w), 2856 (w), 2259 (m), 1684 (m), 1650 (m),

(cm^{-1}, CCl_4)	1606 (m), 1570 (w), 1478 (m), 1453 (w), 1391 (m), 1381 (w), 1319 (m), 1304 (s), 1195 (w), 1141 (s), 1064 (m), 1035 (w), 1007 (m), 971 (m)
MS (HRMS EI)	Calcd for $C_{11}H_7ClF_4O$: 266.0122 Found: 266.0121

(E)-1-(benzyloxy)-6,6,6-trifluoro-5-methylhex-4-en-3-one (III.16t)



$C_{14}H_{15}F_3O_2$
M = 272.26 g.mol^{-1}

Following procedure G starting with 0.048 mmol of 6-(benzyloxy)-1,1,1-trifluoro-2-methylhex-3-yn-2-yl acetate **III.28t**.

Reaction time: 24 h with 5 mol% catalyst

Flash chromatography: PE / EtOAc 95 : 5

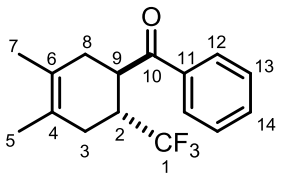
Yield : 11.2 mg (86%) of a slightly yellow oil

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.36 – 7.29 (m, 5H, $H_{10\text{-}12}$), 6.64 (dt, *J* = 2.9, 1.4 Hz, 1H, H_4), 4.52 (s, 2H, H_8), 3.78 (t, *J* = 6.1 Hz, 2H, H_7), 2.83 (t, *J* = 6.1 Hz, 2H, H_6), 2.17 (d, *J* = 1.5 Hz, 3H, H_3)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	198.9 (C_5), 139.6 (q, *J* = 30.1 Hz, C_2), 138.0 (C_9), 128.6 (C_{10or11}), 127.9 (C_{12}), 127.8 (C_{10or11}), 126.7 (q, *J* = 5.3 Hz, C_4), 123.4 (q, *J* = 274.3 Hz, C_1), 73.5 (C_8), 65.1 (C_7), 44.9 (C_6), 12.7 (q, *J* = 1.3 Hz, C_3)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-72.2
IR (cm^{-1}, CCl_4)	3033 (w), 2868 (w), 2256 (s), 1704 (m), 1651 (w), 1496 (w), 1455 (w), 1365 (w), 1293 (s), 1185 (s), 1136 (s), 1101 (m), 1050 (w), 1029 (w), 981 (w)
MS	Calcd for $C_{14}H_{15}F_3O_2$: 272.1024 Found: 272.1035

(HRMS EI)

Post-functionalizations of CF_3-enones

(trans-3,4-dimethyl-6-(trifluoromethyl)cyclohex-3-en-1-yl)(phenyl)methanone (III.45a)



$C_{16}H_{17}F_3O$
M = 282.31 g.mol^{-1}

Following procedure H starting with 0.2 mmol of 1,1,1-trifluoro-4-phenylbut-3-yn-2-yl acetate **III.28c** and 0.8 mmol of 2,3-dimethylbutadiene.

Reaction time: 15 h

Flash chromatography: PE/EtOAc 97.5 : 2.5

Yield: 39.3 mg (70 %) of a white solid.

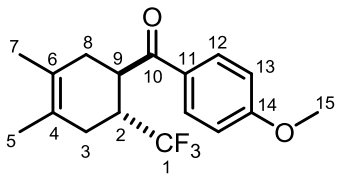
A slightly modified procedure where the acetate **III.28c** and the gold catalyst were stirred at 40 °C for 2 h 40 before the addition of the diene and 16 h stirring at 80 °C was also used. In this case, 49.3 mg (87% yield) of the desired product were isolated.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.97 – 7.95 (m, 2H, H_{13}), 7.61 – 7.57 (m, 1H, H_{14}), 7.50 – 7.46 (m, 2H, H_{12}), 3.77 (td, *J* = 10.1, 5.8 Hz, 1H, H_9), 3.05 – 2.92 (m, 1H, H_2), 2.35 – 2.14 (m, 4H, H_{3+8}), 1.69 (s, 3H, H_{5or7}), 1.63 (s, 3H, H_{5or7})
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	202.3 (C_{10}), 136.7 (C_{11}), 133.5 (C_{14}), 128.9 (C_{12or13}), 128.4 (C_{12or13}), 127.7 (q, *J* = 280.2 Hz, C_1), 124.2 (C_{4or6}), 122.8 (C_{4or6}), 40.6 (q, *J* = 25.6 Hz, C_2), 40.2 (q, *J* = 1.6 Hz, C_9), 35.5 (C_8), 29.9 (q, *J* = 2.9 Hz, C_3), 18.8 (C_{5or7}), 18.7 (C_{5or7})
^{19}F NMR (δ, ppm)	-70.9

(282 MHz, $CDCl_3$)

IR (cm^{-1}, CCl_4)	3153 (w), 3065 (w), 2918 (m), 2859 (m), 2259 (s), 1817 (w), 1793 (w), 1681 (s), 1597 (w), 1581 (w), 1448 (m), 1390 (m), 1330 (m), 1319 (m), 1300 (m), 1262 (s), 1191 (m), 1183 (m), 1159 (s), 1134 (s), 1106 (s), 1046 (w), 1019 (w), 991 (w)
MS (HRMS EI)	Calcd for $C_{16}H_{17}F_3O$: 282.1231 Found: 282.1224

(trans-3,4-dimethyl-6-(trifluoromethyl)cyclohex-3-en-1-yl)(4-methoxyphenyl)methanone (III.45b)



$C_{17}H_{19}F_3O_2$
M = 312.33 $g.mol^{-1}$

Following procedure H starting with 0.2 mmol of 1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-yn-2-yl acetate **III.28j** and 0.8 mmol of 2,3-dimethylbutadiene.

Reaction time: 18 h

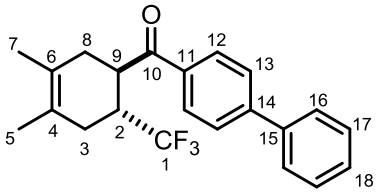
Flash chromatography: PE/EtOAc 97.5 : 2.5

Yield: 47.5 mg (76 %) of a white solid.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.98 – 7.94 (m, 2H, H_{12}), 6.96 – 6.94 (m, 2H, H_{13}), 3.87 (s, 3H, H_{15}), 3.72 (td, *J* = 10.4, 5.6 Hz, 1H, H_9), 3.01 – 2.91 (m, 1H, H_2), 2.33 – 2.04 (m, 4H, H_{3+8}), 1.68 (s, 3H, H_{5or7}), 1.62 (s, 3H, H_{5or7})
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	200.6 (C_{10}), 163.9 (C_{14}), 130.8 (C_{12}), 129.6 (C_{11}), 127.7 (q, *J* = 280.4 Hz, C_1), 124.4 (C_{4or6}), 122.7 (C_{4or6}), 114.0 (C_{13}), 55.6 (C_{15}), 40.7 (q, *J* = 25.5 Hz, C_2), 39.8 (q, *J* = 1.5 Hz, C_9), 35.6 (C_8), 23.0 (q, *J* = 2.9

	Hz, C_3), 18.7 (C_{5or7}), 18.7 (C_{5or7})
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-71.0
Melting point (°C)	91 – 93
IR (cm^{-1}, CCl_4)	2964 (br m), 2917 (br m), 2858 (m), 2844 (m), 2259 (s), 1673 (s), 1601 (s), 1576 (m), 1511 (m), 1459 (), 1443 (m), 1421 (m), 1389 (m), 1370 (m), 1329 (m), 1316 (m), 1301 (m), 1260 (s), 1203 (m), 1172 (s), 1158 (s), 1133 (s), 1106 (m), 1033 (m)
MS (HRMS EI)	Calcd for $C_{17}H_{19}F_3O_2$: 312.1337 Found: 312.1340

[1,1'-biphenyl]-4-yl(trans-3,4-dimethyl-6-(trifluoromethyl)cyclohex-3-en-1-yl)methanone (III.45c)



$C_{22}H_{21}F_3O$
M = 358.40 g.mol^{-1}

Following procedure H starting with 0.133 mmol of 4-([1,1'-biphenyl]-4-yl)-1,1,1-trifluorobut-3-yn-2-yl acetate **III.16f** and 0.53 mmol of 2,3-dimethylbutadiene.

Reaction time: 15 h

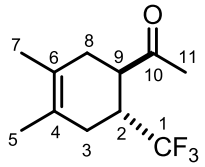
Flash chromatography: PE/EtOAc 97.5 : 2.5

Yield: 32.2 mg (68 %) of a white solid.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	8.06 – 8.04 (m, 2H, H_{12}), 7.72 – 7.69 (m, 2H, H_{13}), 7.65 – 7.62 (m, 2H, H_{16}), 7.50 – 7.46 (m, 2H, H_{17}), 7.43 – 7.39 (m, 1H, H_{18}), 3.81 (td, *J* = 10.3, 5.8 Hz, 1H, H_9), 3.07 – 2.95 (m, 1H, H_2), 2.36 – 2.17 (m, 4H,

	H_{3+8}), 1.70 (s, 3H, H_{5or7}), 1.65 (s, 3H, H_{5or7})
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	201.8 (C_{10}), 146.2 (C_{14}), 139.9 (C_{15}), 135.3 (C_{11}), 129.1 (C_{Ar}), 129.1 (C_{Ar}), 128.4 (C_{18}), 127.6 (C_{Ar}), 127.4 (C_{Ar}), 124.3 (C_{4or6}), 122.8 (C_{4or6}), 40.7 (q, *J* = 25.7 Hz, C_2), 40.2 (q, *J* = 2.1 Hz, C_9), 35.6 (C_8), 30.0 (q, *J* = 3.0 Hz, C_3), 18.8 (C_{5or7}), 18.7 (C_{5or7}) (C_1 was not observed due to the overlapping of the small quadruplet with other peaks)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-70.9
Melting point (°C)	164.5 – 165.8
IR (cm^{-1}, CCl_4)	3061 (w), 3034 (w), 2919 (m), 2859 (w), 2259 (s), 1678 (s), 1605 (s), 1560 (w), 1516 (w), 1487 (w), 1448 (w), 1407 (m), 1389 (m), 1330 (m), 1317 (m), 1301 (m), 1262 (s), 1246 (m), 1188 (s), 1159 (s), 1134 (s), 1105 (s), 1007 (m)
MS (HRMS EI)	Calcd for $C_{22}H_{21}F_3O$: 358.1544 Found: 358.1540

1-(trans-3,4-dimethyl-6-(trifluoromethyl)cyclohex-3-en-1-yl)ethanone (III.45d)



Following procedure H starting with 0.5 mmol of 1,1,1-trifluoropent-3-yn-2-yl benzoate **III.42p** and 2.0 mmol of 2,3-dimethylbutadiene.

Reaction time: 14 h 30

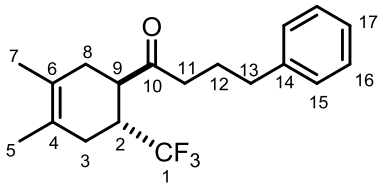
Flash chromatography: PE to PE/Et_2O 95 : 5

Yield: 82% (NMR yield)

^{1}H NMR (δ, ppm) 2.84 (td, *J* = 9.3, 5.9 Hz, 1H, H_9), 2.78 – 2.69 (m, 1H,

(400 MHz, $CDCl_3$)	H_2), 2.27 – 2.06 (m, 4H, H_{3+8}), 2.23 (s, 3H, H_{11}), 1.63 (s, 6H, H_{5+7})
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	210.1 (C_{10}), 127.6 (q, *J* = 279.9 Hz, C_1), 123.8 (C_{4or6}), 122.9 (C_{4or6}), 46.4 (q, *J* = 1.6 Hz, C_9), 40.4 (q, *J* = 25.9 Hz, C_2), 33.7 (C_8), 29.8 (q, *J* = 0.9 Hz, C_{11}), 29.7 (q, *J* = 2.8 Hz, C_3), 18.7 (C_5), 18.7 (C_7)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-71.2 (d, *J* = 7.4 Hz)
IR (cm^{-1}, CCl_4)	2964 (m), 2920 (br m), 2861 (m), 2258 (s), 1716 (s), 1602 (w), 1444 (m), 1387 (m), 1358 (m), 1327 (m), 1309 (m), 1283 (m), 1260 (s), 1238 (m), 1217 (m), 1190 (s), 1160 (s), 1108 (s), 1052 (w), 1026 (w)
MS (HRMS EI)	Calcd for $C_{11}H_{15}F_3O$: 220.1075 Found: 220.1070

1-(trans-3,4-dimethyl-6-(trifluoromethyl)cyclohex-3-en-1-yl)-4-phenylbutan-1-one (III.45f)



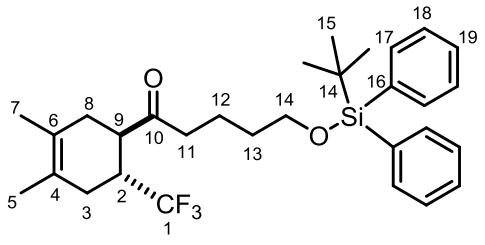
$C_{19}H_{23}F_3O$
M = 324.39 g.mol^{-1}

A modified procedure of procedure H was used. IPrAuNTf$_2$ (0.05 equiv, 0.01 mmol, 8.7 mg) was weighted in a vial. A solution of 1,1,1-trifluoro-7-phenylhept-3-yn-2-yl acetate **III.28g** (1 equiv, 0.2 mmol, 56.8 mg) in dioxane/water 80 : 1 (0.5 mL) was added. The mixture was stirred 1 h at 80 °C in the sealed vial and 2,3-dimethylbutadiene (4 equiv, 0.8 mmol, 65.8 mg, 90 µL) was added. The mixture was stirred 13 h 30 at 80 °C in the sealed vial. The solvents were evaporated and purification by flash column chromatography (PE/EtOAc 97.5 : 2.5) afforded the desired product as a white solid (50.1 mg, 65% yield).

^{1}H NMR (δ, ppm)	7.31 – 7.26 (m, 2H, H_{16}), 7.21 – 7.17 (m, 3H, H_{15+17}),

(400 MHz, $CDCl_3$)	2.83 – 2.74 (m, 2H, H_{2+9}), 2.68 – 2.58 (m, 2H, H_{13}), 2.53 (td, *J* = 7.1, 3.4 Hz, 2H, H_{11}), 2.23 – 2.01 (m, 4H, H_{3+8}), 1.91 (p, *J* = 7.4 Hz, 2H, H_{12}), 1.63 (s, 3H, H_5), 1.61 (s, 3H, H_6)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	211.9 (C_{10}), 141.8 (C_{14}), 128.6 (C_{15}), 128.5 (C_{16}), 127.7 (q, *J* = 280.2 Hz, C_1), 126.1 (C_{17}), 124.0 (C_{4or7}), 122.8 (C_{4or7}), 45.6 (q, *J* = 1.4 Hz, C_9), 42.4 (C_{11}), 40.4 (q, *J* = 25.8 Hz, C_2), 35.1 (C_{13}), 34.3 (C_8), 29.8 (q, *J* = 2.8 Hz, C_3), 24.9 (C_{12}), 18.7 (C_5), 18.7 (C_7)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-71.0 (d, *J* = 6.6 Hz)
Melting point (°C)	55.5 – 56.6
IR (cm^{-1}, CCl_4)	3086 (w), 3065 (w), 3029 (m), 2994 (w), 2920 (br s), 2860 (m), 2259 (s), 1948 (w), 1716 (s), 1603 (w), 1496 (m), 1454 (m), 1444 (m), 1388 (m), 1378 (m), 1327 (m), 1259 (s), 1235 (m), 1190 (s), 1158 (s), 1134 (s), 1106 (s), 1075 (m), 1052 (m), 1030 (w)
MS (HRMS EI)	Calcd for $C_{19}H_{23}F_3O$: 324.1701 Found: 324.1715

5-((tert-butyldiphenylsilyl)oxy)-1-((1R,6R)-3,4-dimethyl-6-(trifluoromethyl)cyclohex-3-en-1-yl)pentan-1-one (III.45h)



$C_{30}H_{39}F_3O_2Si$
M = 516.72 g.mol^{-1}

Following procedure H starting with 0.133 mmol of 8-((tert-butyldiphenylsilyl)oxy)-1,1,1-trifluorooct-3-yn-2-yl acetate (**III.28e**) and 0.53 mmol of 2,3-dimethylbutadiene.

415

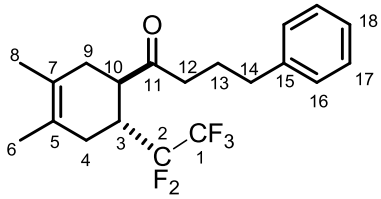
Reaction time: 19 h

Flash chromatography: PE to PE/EtOAc 97.5 : 2.5

Yield: 65.4 mg of a 95 : 5 molar mixture (colourless oil) of the desired product with remaining enone, which corresponds to 60% yield (with 4% yield enone).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.69 – 7.65 (m, 4H, H_{Ar}), 7.47 – 7.35 (m, 6H, H_{Ar}), 3.67 (t, J = 6.1 Hz, 2H, H_{14}), 2.82 – 2.72 (m, 2H, H_{2+9}), 2.52 (t, J = 7.2 Hz, H_{11}), 2.26 – 2.03 (m, 4H, H_{3+8}), 1.72 – 1.54 (m, 10H, $H_{5+7+12+13}$), 1.06 (s, 9H, H_{15})
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	212.0 (C_{10}), 135.7 (C_{17or18}), 134.1 (C_{16}), 129.7 (C_{19}), 127.8 (C_{17or18}), 124.0 (C_{4or6}), 122.8 (C_{4or6}), 63.7 (C_{14}), 45.5 (C_9), 42.9 (C_{11}), 40.5 (q, *J* = 25.7 Hz, C_2), 34.3 (C_8), 31.2 (C_{13}), 29.9 (C_3), 27.0 (C_{15}), 20.0 (C_{12}), 19.4 (C_{14}), 18.7 (C_{5+7}) (C_1 was not observed because of the low intensity of the quadruplet)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-73.2
IR (cm^{-1}, CCl_4)	3061 (w), 2932 (s), 2860 (s), 1718 (s), 1442 (m), 1427 (s), 1389 (s), 1362 (m), 1327 (m), 1302 (s), 1257 (s), 1234 (m), 1188 (s), 1155 (s), 1132 (s), 1101 (s), 1007 (m), 972 (m), 937 (m), 908 (m), 824 (s)

1-trans-3,4-dimethyl-6-(perfluoroethyl)cyclohex-3-en-1-yl)-4-phenylbutan-1-one (III.45j)

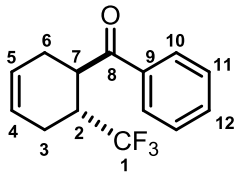


A modified procedure of procedure H was used. $IPrAuNTf_2$ (0.05 equiv, 0.01 mmol, 8.7 mg) was weighted in a vial. A solution of 1,1,1,2,2-

pentafluoro-8-phenyloct-4-yn-3-yl acetate **III.28i** (1 equiv, 0.2 mmol, 66.8 mg) in dioxane/water 80 : 1 (0.5 mL) was added. The mixture was stirred 6 h at 80 °C in the sealed vial and 2,3-dimethylbutadiene (5 equiv, 1.0 mmol, 82.2 mg, 0.11 mL) was added. The mixture was stirred 17 h at 80 °C in the sealed vial. The solvents were evaporated and purification by flash column chromatography (PE/Et_2O 95 : 5) afforded a 94 : 6 mixture of the desired product with the starting enone as a colorless oil (62.6 mg). This corresponded to 59.5 mg of the desired product (79% yield) after correction.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.31 – 7.27 (m, 2H, H_{17}), 7.21 – 7.18 (m, 3H, H_{16+18}), 2.89 – 2.87 (m, 2H, H_{3+10}), 2.70 – 2.48 (m, 4H, H_{12+14}), 2.18 – 2.10 (m, 4H, H_{4+9}), 1.93 (p, *J* = 7.3 Hz, 2H, H_{13}), 1.62 (s, 6H, H_{6+8})
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	211.7 (C_{11}), 141.8 (C_{15}), 128.6 (C_{16or17}), 128.5 (C_{16or17}), 126.1 (C_{18}), 123.8 (C_{5or7}), 122.8 (C_{5or7}), 119.3 (qt, *J* = 286.9, 36.8 Hz, C_1), 116.8 (ddq, *J* = 257.4, 255.1, 36.8 Hz, C_2), 44.6 (C_{10}), 41.8 (d, *J* = 2.4 Hz, C_{12}), 37.9 (dd, *J* = 20.3, 18.6 Hz, C_3), 35.1 (C_{14}), 34.2 (C_9), 29.4 – 29.3 (m, C_4), 24.9 (C_{13}), 18.7 (C_6), 18.7 (C_8)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-83.0 (F_1), -111.1 (d, *J* = 267.8 Hz, F_2), -125.6 (dd, *J* = 268.2, 24.5 Hz, $F_{2'}$)
IR (cm^{-1}, CCl_4)	3086 (m), 3065 (m), 3029 (s), 2992 (m), 2923 (br s), 2861 (s), 2255 (s), 1948 (w), 1874 (w), 1807 (w), 1716 (s), 1603 (m), 1496 (s), 1454 (s), 1402 (m), 1376 (s), 1343 (s), 1297 (s), 1261 (s), 1201 (br s), 1132 (s), 1100 (s), 1057 (s), 1029 (s)
MS (HRMS EI)	Calcd for $C_{20}H_{23}F_5O$: 374.1669 Found: 374.1665

phenyl(trans)-6-(trifluoromethyl)cyclohex-3-en-1-yl)methanone (III.45k)



$C_{14}H_{13}F_3O$
M = 254.25 g.mol^{-1}

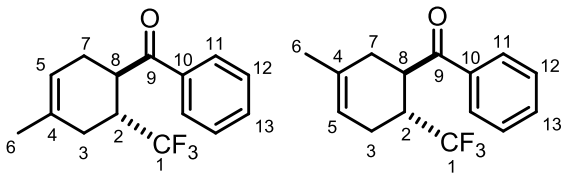
A modified procedure of procedure H was used. IPrAuNTf$_2$ (0.05 equiv, 0.01 mmol, 8.7 mg) was weighted in a vial. A solution of 1,1,1-trifluoro-4-phenylbut-3-yn-2-yl acetate **III.28c** (1 equiv, 0.2 mmol, 48.4 mg) and sulfolene (4 equiv, 0.8 mmol, 94.5 mg) in dioxane/water 80 : 1 (0.5 mL) was added. The mixture was stirred 1 h at 80 °C and then 18 h 30 at 120 °C in the sealed vial. The solvents were evaporated and purification by flash column chromatography (PE/EtOAc 97.5 : 2.5) afforded the desired product as a white solid (38.4 mg, 76% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.98 – 7.96 (m, 2H, H_{11}), 7.61 – 7.57 (m, 1H, H_{12}), 7.51 – 7.47 (m, 2H, H_{10}), 5.80 – 5.72 (m, 2H, $_{H4+5}$), 3.80 (ddd, *J* = 9.9, 8.5, 6.8 Hz, 1H, H_2), 3.04 – 2.98 (m, 1H, H_7), 2.52 – 2.25 (m, 4H, $_{H3+6}$)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	202.0 (C_8), 136.5 (C_9), 133.6 (C_{12}), 128.9 (C_{10or11}), 128.5 (C_{10or11}), 127.7 (q, *J* = 280.3 Hz, C_1), 125.0 (C_{4or5}), 123.8 (C_{4or5}), 39.8 (q, *J* = 25.8 Hz, C_2), 39.2 (q, *J* = 1.9 Hz, C_7), 28.8 (C_6), 23.6 (q, *J* = 3.1 Hz, C_3)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-70.9
Melting point (°C)	52.3 – 53.8
IR (cm^{-1}, CCl_4)	3153 (w), 3039 (w), 2926 (w), 2855 (w), 2251 (s), 1818 (w), 1683 (s), 1598 (m), 1581 (m), 1449 (m), 1441 (m), 1391 (m), 1381 (m), 1363 (w), 1320 (m), 1298 (m), 1260 (s), 1240 (m), 1203 (s), 1181 (s), 1156

(s), 1120 (s), 1084 (w), 1012 (w)

MS (HRMS EI)	Calcd for $C_{14}H_{13}F_3O$: 254.0918	Found: 254.0912

(trans-3/4-methyl-6-(trifluoromethyl)cyclohex-3-en-1-yl)(phenyl)methanone (III.45m)



$C_{15}H_{15}F_3O$
M = 268.28 g.mol^{-1}

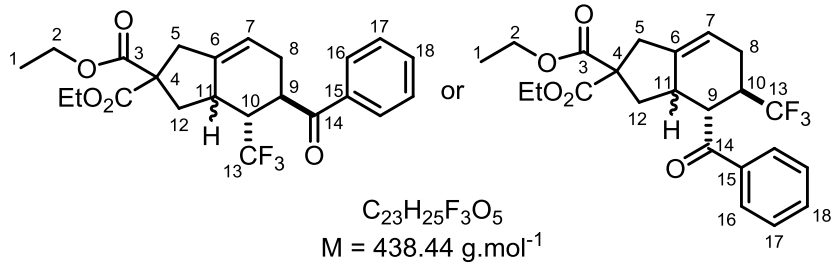
Regioisomer ratio
4 : 3

A modified procedure of procedure H was used. IPrAuNTf$_2$ (0.05 equiv, 0.01 mmol, 8.7 mg) was weighted in a vial. A solution of 1,1,1-trifluoro-4-phenylbut-3-yn-2-yl acetate **III.28c** (1 equiv, 0.2 mmol, 48.4 mg) in dioxane/water 80 : 1 (0.5 mL) was added. The mixture was stirred 3 h at 80 °C in the sealed vial and isoprene (4 equiv, 0.8 mmol, 54.5 mg, 80 µL) was added. The mixture was stirred 15 h at 80 °C in the sealed vial. The solvents were evaporated and purification by flash column chromatography (PE/EtOAc 97.5 : 2.5) afforded a mixture 4 : 3 of regioisomers of the desired product as a slightly yellow oil (35.1 mg, 65% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.98 – 7.95 (m, 2H, H_{12}), 7.62 – 7.57 (m, 1H, H_{13}), 7.51 – 7.46 (m, 2H, H_{11}), 5.47 – 5.44 (m, 1H, H_5), 3.82 (td, *J* = 9.8, 6.1 Hz, 1H, H_2 (regio 2)), 3.76 – 3.69 (m, 1H, H_2 (regio 1)), 3.08 – 2.99 (m, 1H, H_8 (regio 1)), 2.97 – 2.88 (m, 1H, H_8 (regio 2)), 2.41 – 2.18 (m, 4H, H_{3+7}), 1.74 (s, 3H, H_6 (regio 1)), 1.68 (s, 3H, H_6 (regio 2))

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	202.2* (C_9), 136.6 (C_{10}), 133.5* (C_{13}), 132.4 (C_4 (regio 2)), 131.2 (C_4 (regio 1)), 128.9* (C_{11or12}), 128.5* (C_{11or12}), 119.1 (C_5 (regio 1)), 117.6 (C_5 (regio 2)), 40.4 (q, *J* = 25.7 Hz, C_2 (regio 1)), 39.8 (q, *J* = 25.7 Hz, C_2 (regio 2)), 39.8 (q, *J* = 1.6 Hz, C_8 (regio 1)), 39.3 (q, *J* = 1.7 Hz, C_8 (regio 1)), 33.6 (C_7 (regio 2)), 29.3 (C_7 (regio 1)), 28.3 (q, *J* = 2.9 Hz, C_3 (regio 1)), 23.9 (q, *J* = 3.1 Hz, C_3 (regio 2)), 23.2 (C_6 (regio 1)), 23.1 (C_6 (regio 2))
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-71.0 (d, *J* = 9.3 Hz, regio 2), -71.7 (d, *J* = 8.1 Hz, regio 1)
IR (cm^{-1}, CCl_4)	3153 (w), 2974 (w), 2916 (w), 2855 (w), 2251 (s), 1818 (w), 1793 (w), 1682 (s), 1597 (w), 1581 (w), 1472 (w), 1449 (m), 1387 (m), 1345 (w), 1307 (m), 1297 (m), 1261 (s), 1190 (s), 1159 (s), 1121 (s), 1070 (w), 1048 (w), 1015 (w), 1003 (w)
MS (HRMS EI)	Calcd for $C_{15}H_{15}F_3O$: 268.1075 Found: 268.1069

Diethyl 5-benzoyl-4-(trifluoromethyl)-1,3,3a,4,5,6-hexahydro-2H-indene-2,2-dicarboxylate or diethyl 4-benzoyl-5-(trifluoromethyl)-1,3,3a,4,5,6-hexahydro-2H-indene-2,2-dicarboxylate (III.45m)



Following procedure H starting with 0.2 mmol of 1,1,1-trifluoro-4-phenylbut-3-yn-2-yl acetate **III.28c** and 0.4 mmol (2 equiv) of diethyl 3-vinylcyclopent-3-ene-1,1-dicarboxylate.

Reaction time: 18 h 30

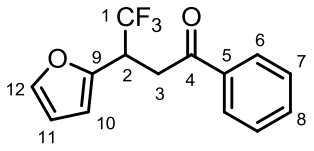
Flash chromatography: PE to PE/EtOAc 97.5 : 2.5

Yield: 59.7 mg of a yellow oil. Several isomers are assumed to be present as a mixture.

The two major isomers are present in a 2.6 : 1 ration. Only characteristic peaks are presented for ^{13}C NMR below due to the complexity of the spectrum.

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	8.01 – 7.94 (m, 2H, H_{16}), 7.62 – 7.58 (m, 1H, H_{18}), 7.52 – 7.47 (m, 2H, H_{17}), 5.62 (p, J = 2.8 Hz, 1H, isomer 1, H_7), 5.53 (s, 1H, isomer 2, H_7), 4.28 – 4.07 (m, 4H, H_2), 349 – 3.42 (m, 1H), 3.15 – 2.75 (m, 4H), 2.58 – 2.45 (m, 1H), 2.37 – 2.17 (m, 2H), 1.87 – 1.67 (m, 1H), 1.28 – 1.14 (m, 6H, H_1)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	202.2 (C_{14}, isomer 1), 199.1 (C_{14}, isomer 2), 172.0 (C_2, isomer 2), 171.7 (C_2, isomer 1), 171.4 (C_2, isomer 1), 171.2 (C_2, isomer 2), 139.9 (C_6), 133.7 (C_{15}, isomer 1), 133.7 (C_{15}, isomer 2), 129.1 (C_{16or17}, isomer 2), 128.9 (C_{16or17}, isomer 1), 128.5 (C_{16or17}, isomer 1), 128.3 (C_{16or17}, isomer 2), 116.0 (C_7, isomer 2), 115.8 (C_7, isomer 1), 41.7 (q, *J* = 25.6 Hz, isomer 1, C_{10}), 39.0 (q, *J* = 25.8 Hz, isomer 2, C_{10})
IR (cm^{-1}, CCl_4)	3152 (w), 3063 (w), 2984 (m), 2939 (m), 2909 (m), 2873 (w), 2254 (s), 1815 (w), 1793 (w), 1726 (s), 1681 (s), 1597 (m), 1581 (m), 1466 (w), 1449 (m), 1384 (m), 1369 (m), 1297 (s), 1258 (s), 1180 (s), 1146 (m), 1127 (m), 1098 (m), 1063 (m)
MS (HRMS EI)	Calcd for $C_{23}H_{25}F_3O_5$: 438.1654 Found: 438.1655

4,4,4-trifluoro-3-(furan-2-yl)-1-phenylbutan-1-one (III.51)



$C_{14}H_{11}F_3O_2$
M = 268.23 g.mol^{-1}

A modified procedure of procedure H was used. IPrAuNTf$_2$ (0.05 equiv, 0.01 mmol, 8.8 mg) was weighted in a vial. A solution of 1,1,1-trifluoro-4-phenylbut-3-yn-2-yl acetate **III.28c** (1 equiv, 0.2 mmol, 48.4 mg) in dioxane/water 80 : 1 (0.5 mL) was added. The mixture was stirred 3 h at 40 °C in the sealed vial and furan (10 equiv, 2.0 mmol, 136.1 mg, 0.14 mL) was added. The mixture was stirred 18 h 30 at 80 °C in the sealed vial. The solvents were evaporated and purification by flash column chromatography (PE/EtOAc 97.5 : 2.5) afforded the Michael addition product as yellow oil (35.7 mg, 67% yield).

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$)	7.99 – 7.96 (m, 2H, H_6), 7.62 – 7.58 (m, 1H, H_8), 7.51 – 7.47 (m, 2H, H_7), 7.36 – 7.35 (m, 1H, H_{12}), 6.36 (d, *J* = 3.3 Hz, 1H, H_{10}), 6.33 (dd, *J* = 3.3, 1.8 Hz, 1H, H_{11}), 4.43 (pd, *J* = 9.2, 3.8 Hz, 1H, H_2), 3.79 (dd, *J* = 17.8, 9.6 Hz, 1H, H_3), 3.48 (dd, *J* = 17.8, 3.7 Hz, 1H, $H_{3'}$)
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$)	195.1 (C_4), 147.6 (q, *J* = 2.5 Hz, C_9), 142.9 (C_{12}), 136.2 (C_5), 133.8 (C_8), 128.9 (C_7), 128.2 (C_6), 125.9 (q, *J* = 279.7 Hz, C_1), 110.7 (C_{10or11}), 109.5 (C_{10or11}), 39.1 (q, *J* = 29.4 Hz, C_2), 36.1 (q, *J* = 1.4 Hz, C_3)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	-71.2 (d, *J* = 8.7 Hz)
IR (cm^{-1}, CCl_4)	3067 (w), 2977 (w), 2927 (w), 2874 (w), 2251 (m), 1693 (s), 1598 (m), 1582 (w), 1504 (m), 1450 (m), 1420 (w), 1367 (m), 1339 (m), 1296 (s), 1266 (s), 1247 (m), 1222 (m), 1213 (m), 1182 (s), 1162 (s),

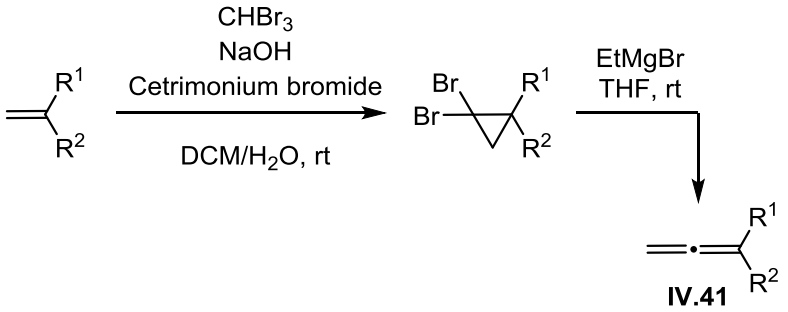
1148 (s), 1114 (s), 1063 (w), 1015 (m), 1002 (w), 990 (w)

MS (HRMS EI) Calcd for $C_{14}H_{11}F_3O_2$: 268.0711 Found: 268.0699

IV. Chapter II: Copper-Catalyzed Boroacylation of Allenes

Preparation of the allenes

Procedure I for the preparation of the allenes:



Step 1: The cyclopropanation of the 1,1-distubstituted alkene was carried out according to literature procedures.[223,224]

To a solution of alkene (1.0 equiv) and cetrimonium bromide (0.12 equiv) in dichloromethane (0.16 mL/mmol alkene) was added dropwise aqueous solution of NaOH (4.6 equiv; 0.5mL water/mmol). After 5 min. $CHBr_3$ (2 equiv) in CH_2Cl_2 (0.08 mL/mmol alkene) was added and left stirring at room temperature for 2-3 days. Water and DCM were added. The aqueous phase was

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[223] A. Edwards, P. Ryabchuk, A. Barkov, M. Rubina, M. Rubin, *Tetrahedron: Asymmetry*, **2014**, *25*, 1537-1549.

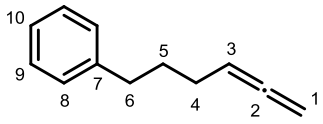
[224] X. Yang, Y. She, Y. Chong, H. Zhai, H. Zhu, B. Chen, G. Huang, R. Yan, *Adv. Synth. Catal*. **2016**, *358*, 3130-3134.

extracted with DCM. The combined organic phases were washed with saturated NaCl solution, dried over Na_2SO_4 and the solvent removed under reduced pressure. Purification by flash chromatography on silica gel afforded the pure cyclopropane products.

Step 2: The preparation of the 1,1-disubstituted allenes was carried out according to a literature procedure.[224]

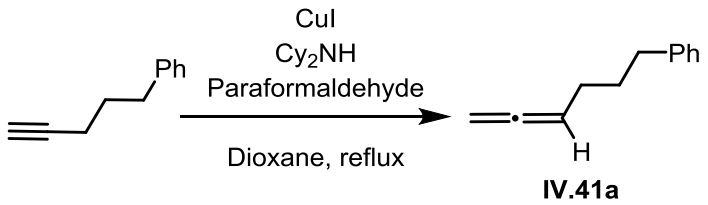
EtMgBr (3.0 M in THF, 1.5 equiv was added dropwise via syringe pump to a solution of cyclopropane (1.0 equiv) in dry THF (2 ml/mmol of cyclopropane) under nitrogen atmosphere at room temperature. The resulting mixture was allowed to stir at room temperature for an additional 30 minutes. Then the reaction was quenched by saturated NH_4Cl solution, and extracted with diethyl ether (15 mL×3). The combined organic layers was washed with brine, and dried with anhydrous Na_2SO_4. After removing the solvent under reduced pressure, the crude product was purified by flash column chromatography on silica gel afforded the desired allenes **IV.41**.

Hexa-4,5-dien-1-ylbenzene (IV.41a)



$C_{12}H_{14}$
$M = 158.24\ g.mol^{-1}$

This substrate was prepared via a Crabbé reaction according to a literature procedure.[225]



IV.41a

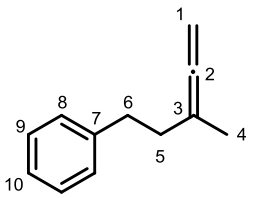
[225] J. Kuang, S. Ma, *J. Org. Chem.* **2009**, *74*, 1763-1765.

Pent-4-yn-1-ylbenzene (1.0 equiv, 34.9 mmol, 5.00 g, 5.3 mL), dicyclohexylamine (1.8 equiv, 62.8 mmol, 11.39 g, 12.5 mL), copper(I) iodide (0.5 equiv, 17.45 mmol, 3.32 g) and paraformaldehyde (2.5 equiv, 87.25 mmol, 2.62 g) were added sequentially in dioxane (150 mL). This mixture was stirred at 100 °C during 17 h. The reaction mixture was cooled down to room temperature and was filtered over silica (eluting with PE). The solvents were removed under reduced pressure. The crude was filtered again over silica (eluting with PE) and the solvents were evaporated.
Purified by flash chromatography (PE) afforded the pure product **IV.41a** as a colourless oil (3.58g, 22.6 mmol, 65% yield).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.30 – 7.25 (m, 2H), 7.19 – 7.15 (m, 3H), 5.12 (p, *J* = 6.7 Hz, 1H), 4.68 (dt, *J* = 6.6, 3.3 Hz, 2H), 2.68 – 2.62 (m, 2H), 2.09 – 1.99 (m, 2H), 1.80 – 1.69 (m, 2H)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	208.7, 142.5, 128.6, 128.4, 125.8, 89.8, 75.0, 35.4, 30.9, 27.8

Spectroscopic data are in agreement with those reported in the literature[226]

(3-methylpenta-3,4-dien-1-yl)benzene (IV.41b)



$C_{12}H_{14}$
M = 158.24 g.mol^{-1}

Following general procedure I starting with (3-methylbut-3-en-1-yl)benzene (36.3 mmol).[227]

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[226] G. Song, B. Wang, M. Nishiura, Z. Hou, *Chem. - Eur. J.* **2015**, *21*, 8394-8398.

425

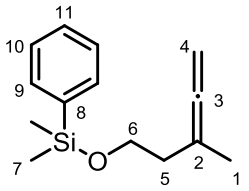
Flash chromatography: PE

Overall yield: 55% of a colourless oil.

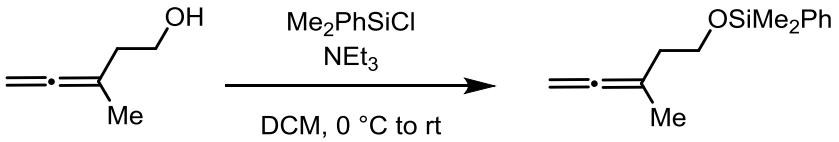
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.32 – 7.17 (m, 5H), 4.62 (hex, *J* = 3.2 Hz, 2H), 2.77 – 2.72 (m, 2H), 2.28 – 2.20 (m, 2H), 1.73 (t, *J* = 3.1 Hz, 3H)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	206.3, 142.3, 128.5, 128.4, 125.9, 98.3, 74.7, 35.3, 34.0, 19.1
MS (HRMS APCI)	Calcd for $[M+H]^+$ $C_{12}H_{15}$: 159.1168 Found: 159.1168

Spectroscopic data are in agreement with those reported in the literature[228]

dimethyl((3-methylpenta-3,4-dien-1-yl)oxy)(phenyl)silane (IV.41c)



$C_{14}H_{20}OSi$
M = 232.40 g.mol^{-1}



IV.41c

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[227] Prepared via a Wittig reaction from the corresponding ketone. Standard Wittig procedure: S. Movahhed, J. Westphal, M. Dindaroğlu, A. Falk, H.-G. Schmalz, *Chem. - Eur. J.* **2016**, *22*, 7381–7384.

[228] J. Takaya, N. Iwasawa, *J. Am. Chem. Soc.* **2008**, *130*, 83, 15254-15255.

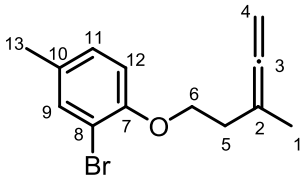
To a solution of 3-methylpenta-3,4-dien-1-ol[229] (1.0 equiv, 5.0 mmol, 491 mg) and triethylamine (2.0 equiv, 10.0 mmol, 1.02 g, 1.40 mL) in DCM (25 mL) at 0 °C was added chloro(dimethyl)phenylsilane (1.5 equiv, 7.5 mmol, 1.28 g, 1.26 mL) dropwise. The mixture was stirred 14 h while warming up at room temperature. The reaction was quenched by the addition of water, extracted with DCM (x3), washed successively with $NH_4Cl_{(sat)}$, water, $NaHCO_{3(sat)}$, dried over Na_2SO_4 and concentrated under reduced pressure.

Purified by flash chromatography on silica gel (eluent: PE/Et_2O 99 : 1 to 97 : 3) afforded the pure product **IV.41c** as a colourless oil (952 mg, 4.10 mmol, 82% yield).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.60 – 7.57 (m, 2H, H_{Ar}), 7.41 – 7.36 (m, 3H, H_{Ar}), 4.56 (hex, *J* = 3.1 Hz, 2H, H_4), 3.70 (t, *J* = 7.1 Hz, 2H, H_6), 2.18 (dq, *J* = 6.9, 3.0 Hz, 2H, H_5), 1.67 (t, *J* = 3.1 Hz, 3H, H_1), 0.38 (s, 6H, H_7)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	206.5 (C_3), 138.1 (C_8), 133.6 (C_{9or10}), 129.7 (C_{11}), 127.9 (C_{9or10}), 95.4 (C_2), 74.2 (C_4), 61.6 (C_6), 36.6 (C_5), 19.2 (C_1), -1.6 (C_7)
IR (cm^{-1}, neat)	2957 (m), 2923 (m), 2868 (m), 2370 (w), 2311 (w), 1959 (m), 1772 (w), 1717 (s), 1591 (w), 1427 (s), 1394 (m), 1369 (m), 1308 (w), 1250 (s), 1215 (w), 1188 (w), 1171 (w), 1117 (s), 1090 (s), 997 (m), 916 (m), 825 (br s), 785 (s)
MS (HRMS APCI)	Calcd for $[M+H]^+$ $C_{14}H_{21}O^{28}Si$: 233.1355 Found: 233.1355

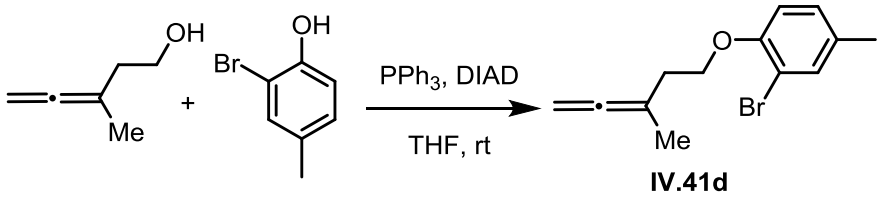
[229] This allenol was prepared according to a literature procedure: A. H. Stoll, S. B. Blakey, *J. Am. Chem. Soc.* **2010**, *132*, 2108-2109.

2-bromo-4-methyl-1-((3-methylpenta-3,4-dien-1-yl)oxy)benzene (IV.41d)



$C_{13}H_{15}BrO$
M = 267.17 g.mol^{-1}

This substrate was prepared via a Mitsunobu reaction according to the literature procedure.[179]



IV.41d

To a solution of 3-methylpenta-3,4-dien-1-ol[229] (1.0 equiv, 5.0 mmol, 491 mg), 2-bromo-4-methylphenol (1.44 equiv, 7.2 mmol, 1.35 g, 0.87 mL) and triphenylphosphine (1.5 equiv, 7.5 mmol, 1.97 g) in THF (15 mL) was added diisopropyl azodicarboxylate (94 M, 1.2 equiv, 6.0 mmol, 1.29 g, 1.257 mL) dropwise at room temperature. The reaction mixture was stirred 14 h and the solvents were evaporated. The crude mixture was dissolved in DCM and filtered on a pad of silica (eluting with PE/Et_2O 97.5:2.5).

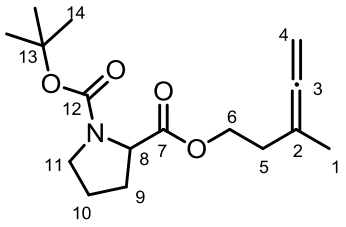
Purified by flash chromatography on silica gel (eluent: PE/Et_2O 99:1 to 98:2 to 97.5:2.5) afforded the pure product **IV.41d** as a colourless oil (385 mg, 1.44 mmol, 29% yield).[230]

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) 7.35 (dd, *J* = 2.1, 0.8 Hz, 1H, H_9), 7.03 (ddd, *J* = 8.2, 2.2, 0.8 Hz, 1H, H_{11}), 6.79 (d, *J* = 8.3 Hz, 1H, H_{12}),

[230] The low yield of this reaction is not due to the reaction itself but to the difficulties in separating the desired product from the other components of the crude mixture.

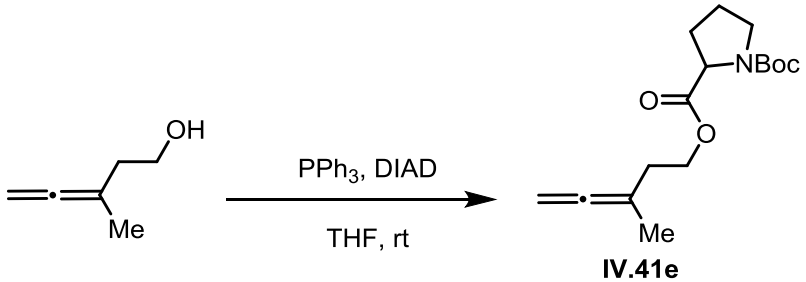
	4.65 (hex, J = 3.2 Hz, 2H, H_4), 4.09 (t, J = 7.0 Hz, 2H, H_6), 2.47 (tt, J = 6.7, 3.1 Hz, 2H, H_5), 2.27 (s, 3H, H_{13}), 1.79 (t, J = 3.2 Hz, 3H, H_1)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	206.4 (C_3), 153.3 (C_7), 133.9 (C_9), 131.6 (C_{10}), 128.9 (C_{11}), 113.5 (C_{12}), 112.1 (C_8), 95.2 (C_2), 74.9 (C_4), 67.9 (C_6), 33.0 (C_5), 20.3 (C_{13}), 19.3 (C_1)
IR (cm^{-1}, neat)	2979 (m), 2930 (m), 2866 (m), 1960 (m), 1732 (w), 1607 (m), 1495 (s), 1470 (s), 1441 (m), 1387 (m), 1284 (s), 1277 (s), 1207 (m), 1153 (m), 1051 (s), 1020 (m), 901 (w), 849 (s), 802 (s)
MS (HRMS APCI)	Calcd for $[M+H]^+$ $C_{13}H_{16}OBr$: 267.0379 Found: 267.0378

1-(tert-butyl) 2-(3-methylpenta-3,4-dien-1-yl) pyrrolidine-1,2-dicarboxylate (IV.41e)



$C_{16}H_{25}NO_4$
M = 295.38 g.mol^{-1}

This substrate was prepared via a Mitsunobu reaction according to the literature procedure.[179]



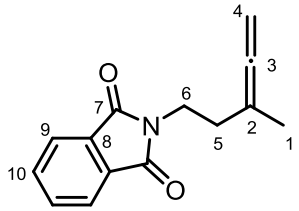
IV.41e

To a solution of 3-methylpenta-3,4-dien-1-ol[229] (1.0 equiv, 3.6 mmol, 354 mg), *N*-Boc-proline (1.5 equiv, 5.4 mmol, 1.16 g) and triphenylphosphine

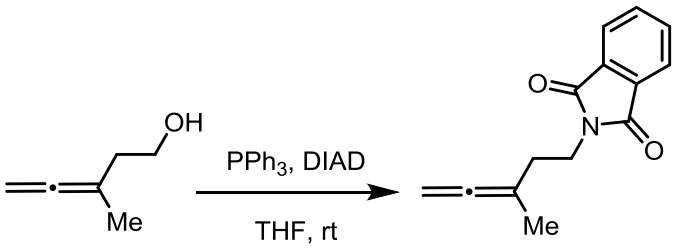
(1.5 equiv, 5.4 mmol, 1.42 g) in THF (10 mL) was added diisopropyl azodicarboxylate (94 %, 1.2 equiv, 4.3 mmol, 0.929 g, 0.91 mL) dropwise at room temperature. The reaction mixture was stirred 6 h and filtered over silica (Et_2O). The solvents were then evaporated and purification by flash chromatography on silica gel (eluent: PE/Et_2O 7:3 to 6:4) afforded the pure product **IV.41e** as a mixture of rotamers (colourless oil, 775 mg, 2.62 mmol, 73 % yield).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	4.68 – 4.60 (m, 2H, H_4), 4.29 – 4.18 (m, 3H, H_{6+8}), 3.59 – 3.35 (m, 2H, H_{11}), 2.30 – 2.15 (m, 3H, H_{Aliph}), 1.99 – 1.82 (m, 3H, H_{Aliph}), 1.72 – 1.69 (m, 3H, H_1), 1.46 (s, 9H, minor rotamer, H_{13}), 1.41 (s, 9H, minor rotamer, H_{14})
^{13}C NMR (δ, ppm) (125 MHz, $CDCl_3$)	206.3 (minor, C_3), 206.3 (major, C_3), 173.2 (major, C_7), 173.0 (minor, C_7), 154.5 (minor, C_{12}), 153.9 (major, C_{12}), 94.8 (minor, C_2), 94.6 (major, C_2), 79.9 (major, C_{13}), 79.8 (minor, C_{13}), 75.0 (major, C_4), 74.9 (minor, C_4), 63.0 (C_6), 59.3 (major, C_8), 59.0 (minor, C_8), 46.6 (minor, C_{11}), 46.4 (major, C_{11}), 32.6 (major, C_{Aliph1}), 32.6 (minor, C_{Aliph1}), 31.0 (major, C_{Aliph2}), 30.0 (minor, C_{Aliph2}), 28.5 – 28.3 (m, C_{14}), 24.4 (minor, C_{Aliph3}), 23.7 (major, C_{Aliph3}), 18.9 (major, C_1), 18.9 (minor, C_1)
IR (cm^{-1}, neat)	2974 (m), 2959 (m), 2881 (m), 1962 (m), 1747 (s), 1697 (s), 1477 (m), 1454 (m), 1396 (s), 1366 (s), 1275 (s), 1256 (s), 1157 (br s), 1119 (s), 1088 (s), 1032 (m), 988 (s), 974 (s), 918 (s), 889 (s), 851 (s)
MS (HRMS APCI)	Calcd for $[M+H]^+$ $C_{16}H_{26}O_4N$: 296.1856 Found: 296.1857

2-(3-methylpenta-3,4-dien-1-yl)isoindoline-1,3-dione (IV.41g)



$C_{14}H_{13}NO_2$
M = 227.26 g.mol^{-1}



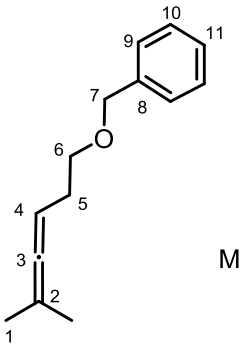
IV.41g

To a solution of 3-methylpenta-3,4-dien-1-ol[229] (1.0 equiv, 3.0 mmol, 295 mg), phthalimide (1.5 equiv, 4.5 mmol, 662 mg) and triphenylphosphine (1.5 equiv, 4.5 mmol, 1.18 g) in THF (10 mL) was added diisopropyl azodicarboxylate (94%, 1.2 equiv, 4.3 mmol, 773 mg, 0.71 mL) dropwise at room temperature. The reaction mixture was stirred 14 h. The solvents were then evaporated and purification by flash chromatography on silica gel (eluent: PE/EtOAc 9 : 1) followed by a washing of the solid obtained with pentane afforded the pure product **IV.41g** as a white solid (248 mg, 1.09 mmol, 36% yield).

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.85 – 7.81 (m, 2H, H_{Ar}), 7.74 – 7.69 (m, 2H, H_{Ar}), 4.71 (h, *J* = 3.1 Hz, 2H, H_4), 3.82 – 3.77 (m, 2H, H_6), 2.34 – 2.27 (m, 2H, H_5), 1.74 (t, *J* = 3.2 Hz, H_1)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	206.6 (C_3), 168.4 (C_7), 134.0 (C_{9or10}), 132.2 (C_8), 123.3 (C_{9or10}), 95.1 (C_2), 74.7 (C_4), 36.2 (C_6), 32.2 (C_5), 18.7 (C_1)
IR (cm^{-1}, neat)	2985 (m), 2939 (m), 2862 (m), 2332 (w), 1959 (m), 1770 (s), 1710 (br s), 1614 (m), 1467 (s), 1435 (s), 1394 (s), 1365 (s), 1308 (s), 1273 (m), 1188 (s), 1173 (s), 1157 (m), 1115 (s), 1086 (s), 1034 (s), 999 (s), 986 (s), 943 (w), 920 (s), 868 (s), 851 (s)

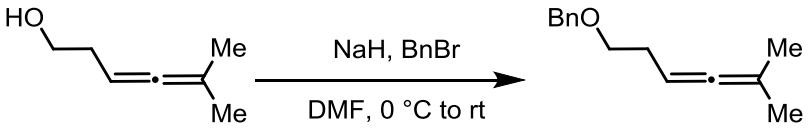
MS (HRMS APCI)	Calcd for $[M+H]^+$ $C_{14}H_{14}O_2N$: 228.1019	Found: 228.1019

(((5-Methylhexa-3,4-dien-1-yl)oxy)methyl)benzene (IV.41h)



$C_{14}H_{18}O$
$M = 202.30\ g.mol^{-1}$

This substrate was prepared according to a literature procedure.[231]



To a solution of NaH (60% in grease, 1.5 equiv, 2.67 mmol, 106.8 mg) in DMF (10 mL) was added 5-methylhexa-3,4-dien-1-ol (1.0 equiv, 1.78 mmol, 200.0 mg, 0.23 mL) dropwise at 0 °C. After stirring 20 min at 0 °C, benzyl bromide (1.5 equiv, 1.78 mmol, 456.7 mg, 0.32 mL) dropwise and the reaction mixture was stirred overnight while warming up to room temperature. The reaction was quenched by saturated NH_4Cl solution, and extracted with diethyl ether (x3). The organic layers were washed with brine (x3) and dried over Na_2SO_4. The solvents were then evaporated and purification by flash chromatography on silica gel (eluent: PE/Et_2O 97.5/2.5) afforded the pure product as a colourless oil (282.8 mg, 1.40 mmol, 79 % yield).

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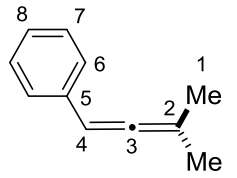
[231] H. Wang, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 7318-7322.

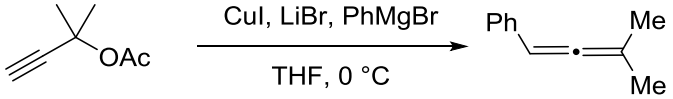
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.36 – 7.26 (s, 5H, H_{Ar}), 5.02 – 4.94 (m, 1H, H_4), 4.52 (s, 2H, H_7), 3.53 (t, *J* = 6.9 Hz, 2H, H_6), 2.28 (q, *J* = 6.8 Hz, 2H, H_5), 1.67 (d, *J* = 2.9 Hz, 6H, H_1)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	202.5 (C_3), 138.7 (C_8), 128.5 (C_{9or10}), 127.8 (C_{9or10}), 127.6 (C_{11}), 95.4 (C_2), 85.4 (C_4), 73.0 (C_7), 70.3 (C_6), 29.9 (C_5), 20.8 (C_1)

Spectroscopic data are in agreement with those reported in the literature.[231]

(3-Methylbuta-1,2-dien-1-yl)benzene (IV.41i)



$C_{11}H_{12}$
M = 144.22 g.mol^{-1}



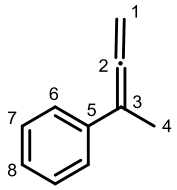
To a solution of CuI (3 equiv, 28 mmol, 5.33 g) and LiBr (3 equiv, 28 mmol, 2.43 g) in THF (60 mL) at 0 °C was added dropwise phenylmagnesium bromide (2.8 mol.L^{-1} in Et_2O, 3 equiv, 28 mmol, 10 mL). After 25 min stirring at 0 °C, 2-methylbut-3-yn-2-yl acetate (1 equiv, 9.33 mmol, 1.18 g) in solution in THF (15 mL) was added dropwise and the reaction mixture was stirred 2 h at the same temperature. The reaction was quenched by saturated NH_4Cl solution, and extracted with diethyl ether (x3). The organic layers were washed successively with HCl 1 mol.L^{-1} and water, and were then dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography on silica gel (eluent: pure PE) followed by Kugelrohr distillation (19 mbar, 120 °C) afforded the desired product as a colourless oil (94% purity (biphenyl as by-product), 736 mg, 5.11 mmol, 55% yield).

^{1}H NMR (δ, 7.28 – 7.24 (m, 4H, H_{Ar}), 7.18 – 7.12 (m, 1H, H_{Ar}), 5.98

ppm) (300 MHz, $CDCl_3$)	(hept, *J* = 2.9 Hz, 1H, H_4), 1.81 (d, *J* = 2.9 Hz, 6H, H_1)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	203.3 (C_3), 136.1 (C_5), 128.6 (C_{Ar}), 126.7 (C_{Ar}), 126.5 (C_8), 99.3 (C_2), 92.7 (C_4), 20.4 (C_1)

Spectroscopic data are in agreement with those reported in the literature.[232]

buta-2,3-dien-2-ylbenzene (IV.41l)



$C_{10}H_{10}$
M = 130.19 g.mol^{-1}

Following general procedure I starting with α-methylstyrene.

Flash chromatography: PE

Overall yield: 69% of a colourless oil.

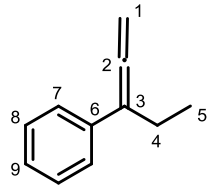
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.43 – 7.40 (m, 2H, H_{Ar}), 7.36 – 7.30 (m, 2H, H_{Ar}), 7.23 – 7.18 (m, 1H, H_{Ar}), 5.03 (q, *J* = 3.2 Hz, 2H, H_1), 2.10 (t, *J* = 3.2 Hz, 3H, H_4)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	209.1 (C_2), 136.8 (C_5), 128.5 (C_{Ar}), 126.7 (C_{Ar}), 125.8 (C_{Ar}), 99.9 (C_3), 77.1 (C_1), 16.8 (C_4)

^{1}H spectroscopic data are in agreement with those reported in the literature[233]

[232] H. Zhang, X. Fu, J. Chen, E. Wang, Y. Liu, Y. Li, *J. Org. Chem.* **2009**, *74*, 9351-9358.

[233] T. Kippo, T. Fukuyama, I. Ryu, *Org. Lett.* **2011**, *13*, 3864

penta-1,2-dien-3-ylbenzene (IV.41m)



$C_{11}H_{12}$
M = 144.22 g.mol^{-1}

Following procedure I starting with α-ethylstyrene.[227]

Flash chromatography: PE

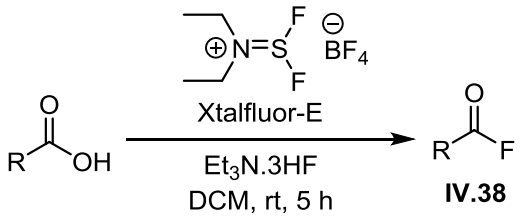
Overall yield: 29% of a colourless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.44 – 7.40 (m, 2H, H_{Ar}), 7.36 – 7.30 (m, 2H, H_{Ar}), 7.23 – 7.18 (m, 1H, H_{Ar}), 5.11 (t, *J* = 3.7 Hz, 2H, H_1), 2.44 (ddt, *J* = 7.4, 6.8, 3.7 Hz, 2H, H_4), 1.16 (td, *J* = 7.4, 0.7 Hz, 3H, H_5)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	208.5 (C_2), 136.7 (C_6), 128.5 (C_{7or8}), 126.7 (C_9), 126.0 (C_{7or8}), 106.8 (C_3), 78.9 (C_1), 22.5 (C_4), 16.2 (C_5)

^{1}H spectroscopic data are in agreement with those reported in the literature.[233]

Preparation of the acyl fluorides

Procedure J for the preparation of acyl fluorides:



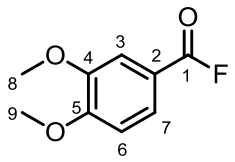
IV.38

All acid fluorides were synthesized using a literature procedure[234] with little modification.

To a stirred suspension of diethylaminodifluorosulfinium tetrafluoroborate (1.0 equiv) in dichloromethane (6.25 mL/mmol substrate) at room temperature was added the carboxylic acid (1.0 equiv) and triethylamine trihydrofluoride (1.0 equiv). The resulting mixture was stirred under nitrogen for 5 h at room temperature. The reaction was then quenched with a 5% $NaHCO_3$ aqueous solution, stirred for 15 minutes, until the effervescence ceased and the resulting mixture was extracted twice using DCM. The organic phases were combined, dried over Na_2SO_4, filtered and concentrated. The crude mixture was purified by flash chromatography.

HRMS spectra of acyl fluorides could not be obtained using standard ionization methods due to the lack of stability of these compounds in these conditions.

3,4-dimethoxybenzoyl fluoride (IV.38c)



$C_9H_9FO_3$
M = 184.16 g.mol^{-1}

Following procedure J starting with 5 mmol of 3,4-dimethoxybenzoic acid.

Flash chromatography: PE/Et_2O 95:5 to 9:1 to 8:2

Yield: 560 mg (61% yield) of a white solid.

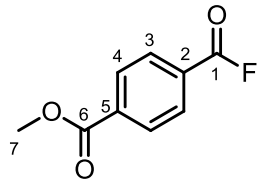
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) 7.71 (dd, *J* = 8.5, 2.0 Hz, 1H, H_7), 7.48 (d, *J* = 1.8 Hz, 1H, H_3), 6.94 (d, *J* = 8.0 Hz, 1H, H_6), 3.97 (s, 3H,

[234] F. Beaulieu, L.-P. Beauregard, G. Courchesne, M. Couturier, F. LaFlamme, A. L'Heureux, *Org. Lett.* **2009**, *11*, 5050-5053.

H_{8or9}), 3.94 (s, 3H, H_{8or9})

^{13}C NMR (δ, ppm) (125 MHz, $CDCl_3$)	157.5 (d, *J* = 340.0 Hz, C_1), 155.1 (C_{4or5}), 149.2 (C_{4or5}), 126.4 (d, *J* = 2.9 Hz, C_{3or7}), 117.0 (d, *J* = 62.1 Hz, C_2), 113.2 (d, *J* = 4.5 Hz, C_{3or7}), 110.8 (C_6), 56.3 (C_{8or9}), 56.3 (C_{8or9})
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	12.49
IR (cm^{-1}, neat)	2841 (m), 1782 (br s), 1596 (s), 1515 (s), 1464 (s), 1439 (m), 1418 (s), 1354 (m), 1275 (s), 1246 (s), 1209 (s), 1190 (m), 1167 (s), 1142 (s), 1132 (s), 1065 (s), 1038 (s), 1013 (s), 901 (s), 879 (s), 858 (s), 820 (s)

methyl 4-(fluorocarbonyl)benzoate (IV.38f)



$C_9H_7FO_3$
M = 182.15 g.mol^{-1}

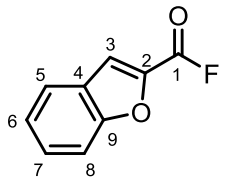
Following procedure J starting with 5 mmol of 4-(methoxycarbonyl)benzoic acid.

Flash chromatography: PE/Et_2O 9:1 to 1:1

Yield: 422 mg (46% yield) of a white solid.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	8.18 – 8.15 (m, 2H, H_{3or4}), 8.11 – 8.09 (m, 2H, H_{3or4}), 3.96 (s, 3H, H_7)
^{13}C NMR (δ, ppm) (125 MHz, $CDCl_3$)	165.7 (C_6), 156.6 (d, *J* = 345.7 Hz, C_1), 136.1 (C_5), 131.5 (d, *J* = 3.5 Hz, C_3), 130.2 (C_4), 128.7 (d, *J* = 61.7 Hz, C_2), 52.8 (C_7)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	16.90
IR (cm^{-1}, neat)	1811 (s), 1717 (s), 1612 (w), 1578 (w), 1502 (w), 1441 (s), 1410 (s), 1256 (s), 1238 (s), 1196 (m), 1109 (s), 1024 (s), 1011 (s), 959 (s), 874 (s), 831 (s)

benzofuran-2-carbonyl fluoride (IV.38g)



$C_9H_5FO_2$
M = 164.13 g.mol^{-1}

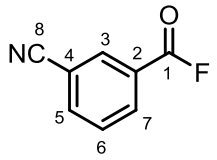
Following procedure J starting with 5 mmol of benzofuran-2-carboxylic acid.

Flash chromatography: PE/Et_2O 95:5

Yield: 597 mg (73% yield) of a white solid.

^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$)	7.76 – 7.74 (m, 2H, H_{5+8}), 7.62 (d, *J* = 8.5 Hz, 1H, H_{3or7}), 7.56 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H, H_{3or7}), 7.40 – 7.36 (m, 1H, H_6) (2D à faire)
^{13}C NMR (δ, ppm) (125 MHz, $CDCl_3$)	157.0 (C_9), 149.5 (d, *J* = 329.9 Hz, C_1), 139.9 (d, *J* = 89.5 Hz, C_2), 129.6 (C_{Ar}), 126.4 (C_4), 124.7 (C_{Ar}), 123.7 (C_{Ar}), 119.5 (C_{Ar}), 112.7 (C_{Ar})
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	14.21
IR (cm^{-1}, neat)	1801 (s), 1738 (s), 1699 (m), 1614 (m), 1556 (s), 1541 (m), 1477 (m), 1443 (m), 1350 (m), 1327 (m), 1294 (s), 1275 (s), 1209 (m), 1161 (s), 1136 (s), 1047 (s), 929 (s), 885 (s), 862 (s), 837 (s), 806 (m)

3-cyanobenzoyl fluoride (IV.38j)



C_8H_4FNO
M = 149.12 g.mol^{-1}

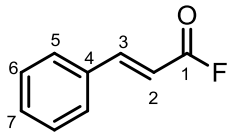
Following procedure J starting with 5 mmol of 3-cyano-benzoic acid.

Flash chromatography: PE/EtOAc 9 : 1

Yield: 494.1 mg (66% yield) of a white solid.

^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$)	8.33 – 8.32 (m, 1H, H_3), 8.29 – 8.27 (m, 1H, H_{5or7}), 8.00 (dt, *J* = 7.8, 1.4 Hz, 1H, H_{5or7}), 7.72 (t, *J* = 7.9 Hz, 1H, H_6)
^{13}C NMR (δ, ppm) (125 MHz, $CDCl_3$)	155.5 (d, *J* = 345.3 Hz, C_1), 135.3 (C_5), 135.3 (d, *J* = 3.6 Hz, C_7), 134.9 (d, *J* = 3.3 Hz, C_3), 130.4 (C_6), 126.5 (d, *J* = 64.2 Hz, C_2), 117.1 (C_8), 114.1 (C_4)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	16.26
IR (cm^{-1}, neat)	2235 (m), 1809 (s), 1605 (m), 1581 (w), 1481 (m), 1433 (m), 1294 (m), 1265 (s), 1184 (m), 1169 (m), 1057 (m), 1030 (s), 999 (m), 928 (m), 876 (m), 852 (m), 820 (m)

cinnamoyl fluoride (IV.38k)



C_9H_7FO

M = 150.15 g.mol^{-1}

Following procedure J starting with 5 mmol of cinnamic acid.

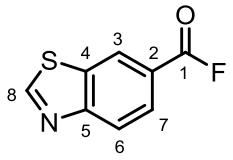
Flash chromatography: PE/EtOAc 9 : 1 to 8 : 2

Yield: 293.6 mg (24% yield) of a colourless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.85 (d, *J* = 16.0 Hz, 1H, H_3), 7.59 – 7.56 (m, 2H, H_{Ar}), 7.49 – 7.41 (m, 3H, H_{Ar}), 6.38 (dd, *J* = 16.0, 7.3 Hz, 1H, H_2)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	157.2 (d, *J* = 338.4 Hz, C_1), 151.6 (d, *J* = 6.1 Hz, C_3), 133.3 (C_4), 132.0 (C_7), 129.3 (C_{5or6}), 128.9 (C_{5or6}), 112.2 (d, *J* = 67.3 Hz, C_2)

^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	22.44
IR (cm^{-1}, neat)	1784 (s), 1693 (w), 1626 (s), 1601 (m), 1578 (m), 1539 (w), 1497 (m), 1450 (s), 1331 (m), 1304 (m), 1283 (m), 1267 (m), 1221 (s), 1190 (s), 1099 (s), 1028 (w), 980 (s), 939 (s), 856 (s), 831 (s)

benzo[d]thiazole-6-carbonyl fluoride (IV.38q)



C_8H_4FNOS
M = 181.19 g.mol^{-1}

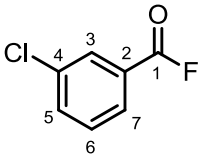
Following procedure J starting with 5 mmol of benzo[d]thiazole-6-carboxylic acid.

Flash chromatography: PE/EtOAc 9 : 1 to 8 : 2

Yield: 406.9 mg (45% yield) of a white solid.

^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$)	9.26 (s, 1H, H_8), 8.73 (d, *J* = 1.6 Hz, 1H, H_3), 8.26 (d, *J* = 8.6 Hz, 1H, H_6), 8.18 (dd, *J* = 8.6, 1.4 Hz, 1H, H_7)
^{13}C NMR (δ, ppm) (125 MHz, $CDCl_3$)	159.1 (C_8), 157.6 (C_5), 157.1 (d, *J* = 343.4 Hz, C_1), 134.5 (C_4), 128.8 (d, *J* = 3.9 Hz, C_{3or7}), 126.7 (d, *J* = 3.5 Hz, C_{3or7}), 124.4 (C_6), 122.2 (d, *J* = 61.9 Hz, C_2)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	15.62
IR (cm^{-1}, neat)	1794 (s), 1599 (m), 1464 (m), 1402 (s), 1332 (m), 1296 (m), 1269 (s), 1244 (s), 1200 (m), 1132 (w), 1055 (s), 1013 (s), 887 (s), 851 (s), 829 (s)

3-chlorobenzoyl fluoride (IV.38r)



C_7H_4ClFO
M = 158.56 g.mol^{-1}

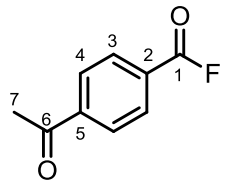
Following procedure J starting with 5 mmol of 3-chlorobenzoic acid.

Flash chromatography: PE to PE/Et_2O 99 : 1

Yield: 145.6 mg (18% yield) of a colourless oil.

^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$)	8.03 (t, *J* = 1.8 Hz, 1H, H_3), 7.95 (d, *J* = 7.8 Hz, 1H, H_7), 7.68 (ddd, *J* = 8.1, 2.1, 1.1 Hz, 1H, H_5), 7.49 (td, *J* = 7.9, 1.2 Hz, 1H, H_6)
^{13}C NMR (δ, ppm) (125 MHz, $CDCl_3$)	156.3 (d, *J* = 345.1 Hz, C_1), 135.5 (C_5), 135.5 (C_4), 131.4 (d, *J* = 3.7 Hz, C_3), 130.5 (C_6), 129.6 (d, *J* = 3.6 Hz, C_7), 126.8 (d, *J* = 62.5 Hz, C_2)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	15.98
IR (cm^{-1}, neat)	1813 (s), 1682 (w), 1576 (w), 1472 (w), 1427 (w), 1281 (w), 1242 (s), 1113 (w), 1047 (m), 1028 (m), 899 (w)

4-acetylbenzoyl fluoride (IV.38s)



$C_9H_7FO_2$
M = 166.15 g.mol^{-1}

Following procedure J starting with 5 mmol of 4-acetylbenzoic acid.

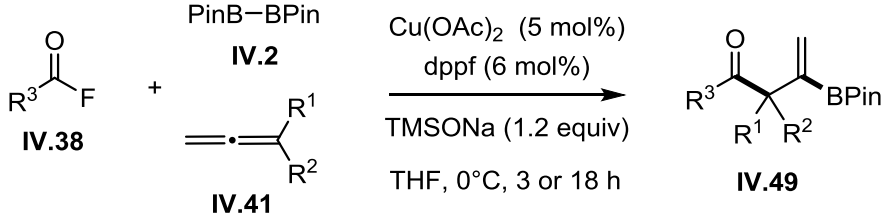
Flash chromatography: PE/Et_2O 9 : 1 to 1 : 1

Yield: 421.5 mg (51% yield) of a white solid.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	8.16 – 8.14 (m, 2H, H_3), 8.09 – 8.06 (m, 2H, H_4), 2.67 (s, 3H, H_7)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	197.1 (C_6), 156.6 (d, *J* = 345.8 Hz, C_1), 142.1 (C_5), 131.8 (d, *J* = 3.7 Hz, C_3), 128.8 (C_4), 128.7 (d, *J* = 61.8 Hz, C_2), 27.1 (C_7)
^{19}F NMR (δ, ppm) (282 MHz, $CDCl_3$)	17.04
IR (cm^{-1}, neat)	1803 (s), 1691 (s), 1575 (m), 1501 (m), 1429 (m), 1402 (s), 1364 (s), 1313 (s), 1261 (s), 1236 (s), 1184 (m), 1119 (m), 1078 (s), 1026 (s), 1003 (s), 960 (s), 858 (s)

Copper-catalyzed boroacylation of allenes

General procedure K for the copper-catalyzed boroacylation of allenes



A flame-dried Schlenk was loaded with anhydrous copper(II) acetate (0.05 equiv, 0.025 mmol, 4.5 mg) and 1,1'-bis(diphenylphosphino)ferrocene (0.06 equiv, 0.030 mmol, 16.6 mg). After 3 vacuum/argon cycles, THF (0.8 mL) was added until the solids were dissolved. To the obtained blue/green solution was added TMSONa (1 M in THF, 1.2 equiv, 0.6 mmol, 0.6 mL). The resulting yellow solution was cooled down to 0 °C in a water/ice bath. Bispinacolatodiboron **IV.2** (1.2 equiv, 0.6 mmol, 152.4 mg) in solution in THF (0.8 mL) was added and the mixture immediately turned

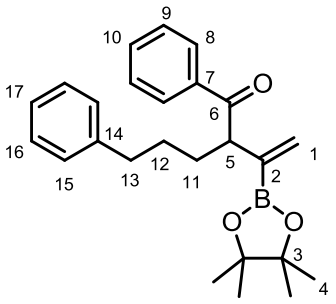
into a brown slurry. The allene **IV.41** (1.0 equiv, 0.5 mmol) and the acyl fluoride **IV.38** (1.5 equiv, 0.75 mmol) were simultaneously added in solution in THF (0.8 mL).

Procedure K_1: The mixture was stirred for 3 h at 0 °C.

Procedure K_2: The mixture was stirred for 18 h while warming up to room temperature.

The reaction mixture was filtered through silica (eluent: Et_2O + 1% NEt_3) and the solvents were removed under reduced pressure. Purification by flash chromatography on silica gel afforded the desired product **IV.49**.

1,5-diphenyl-2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)pentan-1-one (IV.49a)



$C_{25}H_{31}BO_3$
M = 390.32 g.mol^{-1}

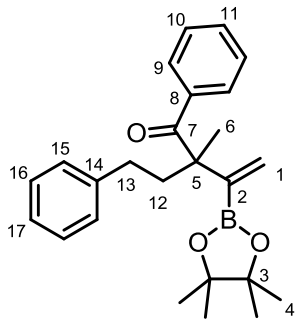
Following procedure K_1 starting with 0.5 mmol hexa-4,5-dien-1-ylbenzene (**IV.41a**), bis(pinacolato)diboron (**IV.2**) and benzoyl fluoride (**IV.38a**).

Flash chromatography: PE/Et_2O 95:5 + 1% Et_3N.

^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$) 7.98 – 7.95 (m, 2H, H_{Ar}), 7.52 – 7.47 (m, 1H, H_{Ar}), 7.42 – 7.37 (m, 2H, H_{Ar}), 7.27 – 7.23 (m, 2H, H_{Ar}), 7.18 – 7.15 (m, 3H, H_{Ar}), 5.92 (d, *J* = 2.4 Hz, 1H, H_1), 5.67 (d, *J* = 2.0 Hz, 1H, $H_{1'}$), 4.29 – 4.25 (m, 1H, H_5), 2.68 – 2.60 (m, 2H, H_{13}), 2.00 – 1.95 (m, 1H, H_{11}),

	1.73 – 1.63 (m, 3H, $H_{11'+12}$), 1.27 (s, 6H, H_4), 1.25 (s, 6H, $H_{4'}$)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	200.8 (C_6), 142.6 (C_{6or14}), 137.1 (C_{6or14}), 132.7 (C_{Ar}), 131.9 (C_1), 128.8 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 125.7 (C_{Ar}), 84.0 (C_3), 50.1 (C_5), 36.0 (C_{13}), 32.5 (C_{11or12}), 29.6 (C_{11or12}), 24.9 (C_4), 24.8 ($C_{4'}$) (C_2 could not be observed because of quadrupolar coupling effects due to boron)
IR (cm^{-1}, neat)	3057 (w), 2964 (m), 2920 (m), 2851 (w), 1718 (w), 1684 (s), 1597 (m), 1446 (m), 1356 (s), 1343 (s), 1250 (m), 1217 (m), 1134 (s), 1078 (m), 966 (m)
MS (HRMS ESI)	Calcd for $[M+H]^+$ $C_{25}H_{32}O_3B$: 391.2439 Found: 391.2441

2-methyl-2-phenethyl-1-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-one (IV.54b)



$C_{25}H_{31}BO_3$
M = 390.32 g.mol^{-1}

Following procedure K_1 starting with 0.5 mmol (3-methylpenta-3,4-dien-1-yl)benzene (**IV.41b**), bis(pinacolato)diboron (**IV.2**) and benzoyl fluoride (**IV.38a**).

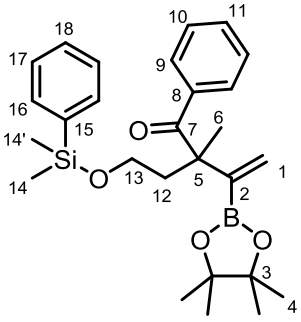
Flash chromatography: PE/Et_2O 95:5 + 1% Et_3N.

Yield: 155.1 mg (80% yield) of a slightly yellow oil.

^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$)	7.93 – 7.91(m, 2H, H_{Ar}), 7.44 – 7.41 (m, 1H, H_{11}), 7.35 – 7.32 (m, 2H, H_{Ar}), 7.25 – 7.22 (m, 2H, H_{15or16}),

	7.15 – 7.10 (m, 3H, H_{Ar}), 6.10 (d, *J* = 2.2 Hz, 1H, H_1), 5.90 (d, *J* = 2.2 Hz, 1H, $H_{1'}$), 2.57 – 2.51 (m, 1H, H_{12}), 2.39 – 2.33 (m, 1H, $H_{12'}$), 2.27 – 2.21 (m, 2H, H_{13}), 1.52 (s, 3H, H_6), 1.00 (s, 6H, H_4), 1.00 (s, 6H, $H_{4'}$)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	203.9 (C_7), 142.9 (C_{14}), 137.7 (C_8), 131.7 (C_{Ar}), 129.6 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.0 (C_{Ar}), 127.8 (C_1), 125.8 (C_{Ar}), 81.7 (C_3), 54.8 (C_5), 40.2 (C_{13}), 31.1 (C_{12}), 24.6 (C_4), 24.4 ($C_{4'}$), 24.0 (C_6) (C_2 could not be observed because of quadrupolar coupling effects due to boron)
IR (cm^{-1}, neat)	2978 (m), 2928 (m), 1680 (s), 1597 (m), 1578 (w), 1497 (w), 1447 (m), 1412 (s), 1371 (s), 1354 (s), 1315 (s), 1271 (m), 1242 (s), 1213 (m), 1167 (s), 1140 (s), 1103 (m), 1029 (m), 1003 (m), 967 (s), 945 (m)
MS (HRMS APCI)	Calcd for $[M+H]^+$ $C_{25}H_{32}O_3B$: 391.2439 Found: 391.2440

2-(2-((dimethyl(phenyl)silyl)oxy)ethyl)-2-methyl-1-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-one (IV.49c)



$C_{27}H_{37}BO_4Si$
M = 464.48 g.mol^{-1}

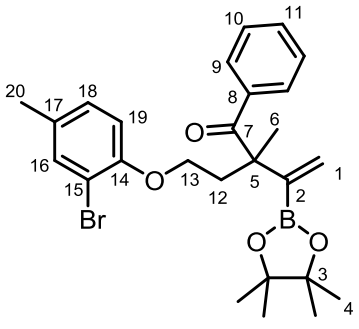
Following procedure K_1 starting with 0.5 mmol dimethyl((3-methylpenta-3,4-dien-1-yl)oxy)(phenyl)silane (**IV.41c**), bis(pinacolato)diboron (**IV.2**) and benzoyl fluoride (**IV.38a**).

Flash chromatography: PE/Et_2O 95:5 + 1% Et_3N.

Yield: 133.7 mg (58% yield) of a yellow oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.90 – 7.86 (m, 2H, H_{Ar}), 7.53 – 7.51 (m, 2H, H_{Ar}), 7.45 – 7.29 (m, 6H, H_{Ar}), 6.02 (d, *J* = 2.2 Hz, 1H, H_1), 5.84 (d, *J* = 2.2 Hz, $H_{1'}$), 3.64 (dt, *J* = 10.3, 7.2 Hz, 1H, H_{13}), 3.51 (dt, *J* = 10.3, 7.5 Hz, 1H, $H_{13'}$), 2.27 – 2.22 (m, 2H, H_{12}), 1.43 (s, 3H, H_6), 0.97 (s, 6H, H_4), 0.97 (s, 6H, $H_{4'}$), 0.31 (s, 6H, H_{14})
^{13}C NMR (δ, ppm) (125 MHz, $CDCl_3$)	203.2 (C_7), 138.1 (C_{8or15}), 137.3 (C_{8or15}), 133.6 (C_{Aror1}), 131.6 (C_{Aror1}), 129.6 (C_{Aror1}), 129.6 (C_{Aror1}), 127.9 (C_{Aror1}), 127.9 (C_{Aror1}), 127.5 (C_{Aror1}), 83.7 (C_3), 60.0 (C_{13}), 53.3 (C_5), 40.7 (C_{12}), 24.5 (C_4), 24.5 ($C_{4'}$), 24.4 (C_6) -1.7 (C_{14}), -1.7 ($C_{14'}$) (C_2 could not be observed because of quadrupolar coupling effects due to boron)
IR (cm^{-1}, neat)	2970 (br s), 2332 (w), 1680 (s), 1597 (m), 1578 (w), 1447 (m), 1427 (m), 1412 (m), 1371 (m), 1354 (s), 1315 (s), 1252 (s), 1215 (m), 1188 (w), 1142 (s), 1115 (s), 1084 (s), 1043 (m), 1003 (w), 966 (s), 949 (m), 849 (s), 827 (s)
MS (HRMS APCI)	Calcd for $[M+H]^+$ $C_{27}H_{38}O_4BSi$: Found: 465.2632 465.2628

2-(2-(2-bromo-4-methylphenoxy)ethyl)-2-methyl-1-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-one (IV.49d)



$C_{26}H_{32}BBrO_4$
M = 499.25 g.mol^{-1}

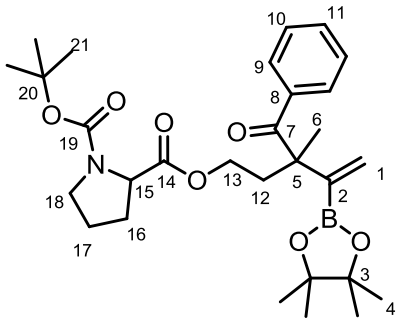
Following procedure K_1 starting with 0.5 mmol 2-bromo-4-methyl-1-((3-methylpenta-3,4-dien-1-yl)oxy)benzene (**IV.41d**), bis(pinacolato)diboron (**IV.2**) and benzoyl fluoride (**IV.38a**).

Flash chromatography: pentane/Et_2O 95:5 + 1% Et_3N.

Yield: 199.7 mg (79%) of a slightly yellow oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.96 – 7.92 (m, 2H, H_{Ar}), 7.43 – 7.35 (m, 1H, H_{11}), 7.35 – 7.26 (m, 3H, H_{Ar}), 6.99 (ddd, *J* = 8.3, 2.2, 0.8 Hz, 1H, H_{18}), 6.76 (d, *J* = 8.4 Hz, 1H, H_{19}), 6.12 (d, *J* = 2.1 Hz, 1H, H_1), 5.97 (d, *J* = 2.1 Hz, 1H, $H_{1'}$), 4.07 (ddd, *J* = 9.7, 8.1, 5.8 Hz, 1H, H_{13}), 3.92 (ddd, *J* = 9.7, 8.0, 6.9 Hz, 1H, $H_{13'}$), 2.54 – 2.38 (m, 2H, H_{12}), 2.24 (s, 3H, H_{20}), 1.60 (s, 3H, H_6), 0.97 (s, 6H, H_4), 0.95 (s, 6H, $H_{4'}$)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	203.2 (C_7), 153.3 (C_{14}), 136.9 (C_8), 133.7 (C_{16}), 131.9 (C_{11}), 131.2 (C_{17}), 129.8 (C_{18}), 128.8 (C_{9or10}), 128.4 (C_1), 128.1 (C_{9or10}), 113.2 (C_{19}), 111.8 (C_{15}), 83.8 (C_3), 66.3 (C_{13}), 53.5 (C_5), 37.5 (C_{12}), 24.6 (C_6), 24.5 (C_4), 24.4 ($C_{4'}$), 20.3 (C_{20}) (C_2 could not be observed because of quadrupolar coupling effects due to boron)
IR (cm^{-1}, neat)	2976 (m), 2935 (m), 1678 (s), 1605 (m), 1578 (w), 1495 (s), 1468 (m), 1447 (m), 1412 (m), 1371 (s), 1354 (s), 1316 (s), 1275 (s), 1252 (s), 1213 (m), 1182 (m), 1140 (s), 1103 (s), 1049 (s), 1003 (s), 966 (s), 866 (m), 851 (m), 800 (m)
MS (HRMS APCI)	Calcd for $[M+H]^+$ $C_{26}H_{33}O_4B^{79}Br$: 499.1651 Found: 499.1653

2-(3-benzoyl-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-4-en-1-yl) 1-tert-butyl pyrrolidine-1,2-dicarboxylate (IV.49e)



$C_{29}H_{42}BNO_7$
M = 527.46 g.mol^{-1}

Following procedure K_1 starting with 0.5 mmol 1-(*tert*-butyl) 2-(3-methylpenta-3,4-dien-1-yl) pyrrolidine-1,2-dicarboxylate (**IV.41e**), bis(pinacolato)diboron (**IV.2**) and benzoyl fluoride (**IV.38a**).

Flash chromatography: PE/Et_2O 8:2 + 1% Et_3N.

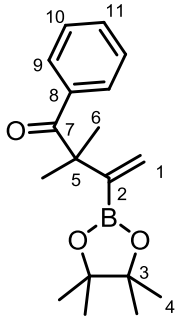
Yield: 113.3 mg (43% yield) of a yellow oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)
7.90 – 7.87 (m, 2H, H_{Ar}), 7.45 – 7.30 (m, 3H, H_{Ar}), 6.12 – 6.09 (m, 1H, H_1), 5.91 – 5.90 (m, 1H, $H_{1'}$), 4.23 – 4.01 (m, 3H, H_{13+15}), 3.53 – 3.33 (m, 2H, H_{18}), 2.30 – 2.06 (m, 3H, H_{Aliph}), 1.94 – 1.81 (m, 3H, H_{Aliph}), 1.52 (s, 3H, major, H_6), 1.50 (s, 3H, minor, H_6), 1.44 – 1.39 (m, 9H, H_{21}), 0.97 (s, 12H, minor, H_4), 0.96 (s, 12H, major, H_4)

^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)
202.9 (C_7), 173.2 (major, C_{14}), 172.9 (minor, C_{14}), 154.5 (minor, C_{19}), 154.0 (major, C_{19}), 137.0 (major, C_8), 137.0 (minor, C_8), 131.9 (major, C_{11}), 131.8 (minor, C_{11}), 129.7 (C_{9or10}), 128.5 – 128.4 (m, C_1), 128.0 (C_{9or10}), 83.9 (major, C_3), 83.8 (minor, C_3), 79.9 (major, C_{20}), 79.8 (minor, C_{20}), 62.4 (major, C_{13}), 62.3 (minor, C_{13}), 59.3 (major, C_{15}), 59.0 (minor, C_{15}), 53.4 (minor, C_5), 53.3 (major, C_5), 46.7 (minor, C_{18}), 46.4 (major, C_{18}), 36.9 (minor, C_{12}), 36.8 (major, C_{12}), 30.9 (C_{16or17}), 29.9 (C_{16or17}), 28.6 (minor, C_{21}), 28.5 (major, C_{21}), 24.6 – 24.3 (m, C_4), 23.9 – 23.8 (m, C_6)
(C_2 could not be observed because of quadrupolar coupling effects due to boron)

IR (cm^{-1}, neat)	2989 (br s), 1745 (s), 1682 (s), 1597 (m), 1578 (w), 1539 (w), 1447 (m), 1393 (s), 1354 (s), 1317 (s), 1260 (br s), 1165 (br s), 1088 (s), 1093 (m), 996 (s), 918 (m), 878 (m), 851 (s)	
MS (HRMS ESI)	Calcd for $[M+H]^+$ $C_{29}H_{43}O_7NB$: 528.3129	Found: 528.3128

2,2-dimethyl-1-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-one (IV.49f)



$C_{18}H_{25}BO_3$
M = 300.20 g.mol^{-1}

Following procedure K_1 starting with 0.5 mmol 3-methyl-1,2-butadiene (**IV.41f**), bis(pinacolato)diboron (**IV.2**) and benzoyl fluoride (**IV.38a**).

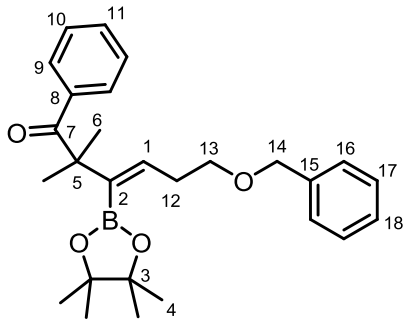
Flash chromatography: pentane/Et_2O 95:5 + 1% Et_3N.

Yield: 107.5 mg (72% yield) of a yellow oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.91 – 7.88 (m, 2H, H_{9or10}), 7.43 – 7.38 (m, 1H, H_{11}), 7.34 – 7.29 (m, 2H, H_{9or10}), 5.98 (d, *J* = 2.3 Hz, 1H, H1), 5.89 (d, *J* = 2.1 Hz, 1H, H1'), 1.45 (s, 6H, H6), 0.97 (s, 12H, H_4)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	204.6 (C_7), 137.2 (C_8), 131.6 (C_{11}), 129.7 (C_{9or10}), 127.9 (C_{9or10}), 126.3 (C_1), 83.7 (C_3), 51.4 (C_5), 26.8 (C_6), 24.5 (C_4) (C_2 could not be observed because of quadrupolar coupling effects due to boron)

IR (cm^{-1}, neat)	2976 (br s), 1682 (s), 1597 (m), 1578 (m), 1466 (m), 1447 (m), 1410 (s), 1371 (s), 1352 (s), 1313 (s), 1256 (s), 1213 (s), 1167 (s), 1140 (s), 1103 (s), 1013 (m), 1003 (m), 968 (s), 937 (s), 876 (s), 849 (s)
MS (HRMS APCI)	Calcd for $[M+H]^+$ $C_{18}H_{26}O_3B$: 301.1970 Found: 301.1969

(E)-6-(benzyloxy)-2,2-dimethyl-1-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-3-en-1-one (IV.49h)



$C_{27}H_{35}BO_4$
M = 434.38 $g.mol^{-1}$

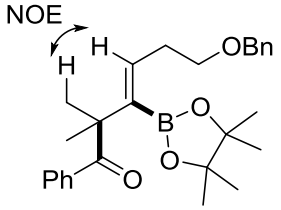
Following procedure K_1 starting with 0.5 mmol (((5-Methylhexa-3,4-dien-1-yl)oxy)methyl)benzene (**IV.41h**), bis(pinacolato)diboron (**IV.2**) and benzoyl fluoride (**IV.38a**).

Flash chromatography: pentane/Et_2O 95 : 5 + 1% Et_3N.

Yield: 55.8 mg (26% yield) of a colourless oil.

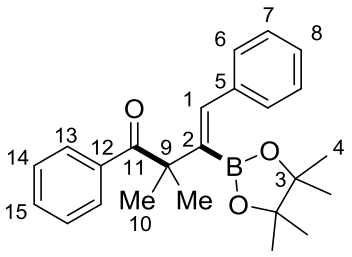
The stereochemistry was determined by H-H NOESY correlation.

For the only observed isomer, the NOESY spectrum showed a correlation between the vinylic proton H_1 and the *gem*-dimethyl protons H_6. This product was assigned to the *(E)*-isomer.



^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.92 – 7.89 (m, 2H, H_{Ar}), 7.41 – 7.25 (m, 8H, H_{Ar}), 6.24 (t, *J* = 7.4 Hz, 1H, H_1), 4.52 (s, 2H, H_{14}), 3.54 (t, *J* = 6.7 Hz, 2H, H_{13}), 2.71 (q, *J* = 6.8 Hz, 2H, H_{12}), 1.42 (s, 6H, H_6), 1.07 (s, 12H, H_4)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	205.0 (C_7), 138.9 (C_q), 138.8 (C_1), 137.1 (C_q), 131.4 (C_{Ar}), 129.9 (C_{Ar}), 128.5 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 127.6 (C_{Ar}), 83.4 (C_3), 72.8 (C_{14}), 70.2 (C_{13}), 52.0 (C_5), 31.9 (C_{12}), 27.5 (C_6), 24.8 (C_4) (C_2 could not be observed because of quadrupolar coupling effects due to boron)
IR (cm^{-1}, neat)	2978 (s), 2928 (m), 2893 (m), 1722 (w), 1678 (s), 1624 (m), 1597 (m), 1466 (m), 1447 (m), 1416 (m), 1371 (m), 1360 (m), 1304 (s), 1250 (s), 1213 (s), 1169 (s), 1140 (s), 1099 (s), 1018 (s), 970 (s), 910 (m)
MS (HRMS APCI)	Calcd for $[M+H]^+$ $C_{27}H_{36}O_4B$: 435.2703 Found: 435.2702

(E)-2,2-Dimethyl-1,4-diphenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-one (IV.49i)



$C_{24}H_{29}BO_3$
M = 376.30 g.mol^{-1}

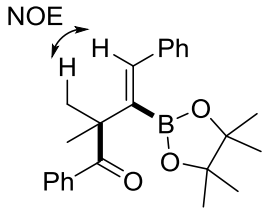
Following procedure K_1 starting with 0.5 mmol (3-methylbuta-1,2-dien-1-yl)benzene (**IV.41i**) , bis(pinacolato)diboron **IV.2** and benzoyl fluoride (**IV.38a**).

Flash chromatography: pentane/Et_2O 97.5 : 2.5 + 1% Et_3N.

Yield: 30.0 mg (16% yield) of a colourless oil.

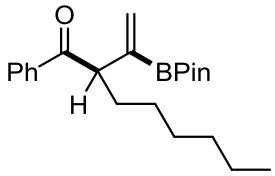
The stereochemistry was determined by H-H NOESY correlation.

For the only observed isomer, the NOESY spectrum showed a correlation between the vinylic proton and the *gem*-dimethyl protons. This product was assigned to the *(E)*-isomer.



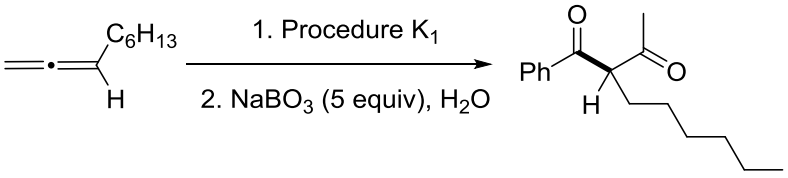
^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$)	8.00 – 7.98 (m, 2H, H_{Ar}), 7.46 – 7.42 (m, 1H, H_{Ar}), 7.39 – 7.36 (m, 2H, H_{Ar}), 7.32 – 7.30 (m, 2H, H_{Ar}), 7.28 – 7.25 (m, 2H, H_{Ar}), 7.23 – 7.20 (m, 1H, H_{Ar}), 6.88 (s, 1H, H_1), 1.50 (s, 6H, H_{10}), 1.18 (s, 12H, H_4)
^{13}C NMR (δ, ppm) (125 MHz, $CDCl_3$)	204.6 (C_{11}), 139.0 (C_{5or12}), 138.4 (C_1), 136.6 (C_{5or12}), 131.7 (C_{Ar}), 130.1 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 128.0 (C_{Ar}), 127.5 (C_{Ar}), 84.1 (C_3), 52.4 (C_9), 27.5 (C_{10}), 25.1 (C_4) (quaternary carbon next to boron could not be observed because of quadrupolar coupling effects)
IR (cm^{-1}, neat)	3026 (w), 2976 (m), 2939 (m), 2930 (m), 1724 (m), 1674 (s), 1609 (w), 1597 (w), 1576 (w), 1495 (w), 1464 (m), 1447 (m), 1389 (s), 1373 (s), 1348 (m), 1310 (s), 1252 (s), 1211 (m), 1167 (m), 1140 (s), 1111 (m), 1076 (w), 1011 (w), 974 (m), 920 (w), 883 (w), 854 (m), 829 (w)
MS (HRMS APCI)	Calcd for $[M+H]^+$ $C_{24}H_{30}O_3B$: 377.2883 Found: 377.2883

1-Phenyl-2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)octan-1-one (IV.49k)

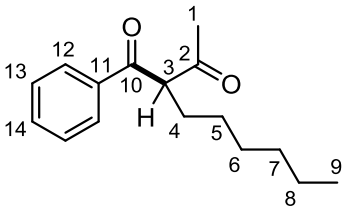


$C_{22}H_{33}BO_3$
M = 356,31 g.mol^{-1}

Because of the low stability of this compound in the presence of silica gel or alumina, a modified procedure was used: the obtained product was directly oxidized into the corresponding ketone, which was isolated and characterized.



2-Hexyl-1-phenylbutane-1,3-dione (IV.57k)



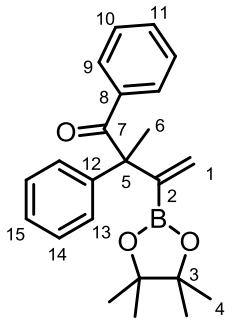
$C_{16}H_{22}O_2$
M = 246.35 g.mol^{-1}

A flame-dried Schlenk was loaded with anhydrous copper(II) acetate (0.05 equiv, 0.025 mmol, 4.5 mg) and 1,1'-bis(diphenylphosphino)ferrocene (0.06 equiv, 0.030 mmol, 16.6 mg). After 3 vacuum/argon cycles, THF (0.8 mL) was added until the solids were dissolved. To the obtained blue/green solution was added TMSONa (1 M in THF, 1.2 equiv, 0.6 mmol, 0.6 mL). The resulting yellow solution was cooled down to 0 °C in a water/ice bath. Bispinacolatodiboron (1.2 equiv, 0.6 mmol, 152.4 mg) in solution in THF (0.8 mL) was added and the mixture immediately turned into a brown slurry. Nona-1,2-diene (1.0 equiv, 0.5 mmol, 62.1 mg) and

benzoyl fluoride (1.5 equiv, 0.75 mmol, 81 µL) were simultaneously added in solution in THF (0.8 mL). After 3 h stirring at 0 °C, water (2.4 mL) and $NaBO_3$ (5 equiv, 2.5 mmol, 249.5 mg) were added and the mixture was vigorously stirred at room temperature for 3 h. Et_2O and $NH_4Cl_{(sat)}$ were added and the layers were separated. After extraction with Et_2O, the organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (PE/Et_2O 95 : 5) afforded the pure product as a slightly yellow oil (88.5 mg, 0.362 mmol, 72% yield).

^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$)	7.99 – 7.97 (m, 2H, H_{Ar}), 7.59 – 7.56 (m, 1H, (H_{14}), 7.49 – 7.45 (m, 2H, H_{Ar}), 4.42 (t, *J* = 7.1 Hz, 1H, H_3), 2.13 (s, 3H, H_1), 2.05 – 1.97 (m, 1H, H_4), 1.97 – 1.90 (m, 1H, $H_{4'}$), 1.30 – 1.22 (m, 8H, H_{Aliph}), 0.86 – 0.83 (m, 3H, H_9)
^{13}C NMR (δ, ppm) (125 MHz, $CDCl_3$)	204.6 (C_2), 196.6 (C_{10}), 136.7 (C_{11}), 133.8 (C_{14}), 129.0 (C_{12or13}), 128.8 (C_{12or13}), 63.7 (C_3), 31.6 (C_{Aliph}), 29.3 (C_{Aliph}), 29.2 (C_{Aliph}), 27.9 (C_{Aliph}), 27.8 (C_1), 22.6 (C_{Aliph}), 14.1 (C_9)
IR (cm^{-1}, neat)	2959 (s), 2928 (s), 2856 (m), 1720 (s), 1674 (s), 1597 (m), 1580 (m), 1448 (s), 1356 (s), 1283 (m), 1265 (m), 1211 (s), 1180 (s), 1161 (m), 1117 (w), 1076 (w), 1001 (m), 970 (m), 914 (m)
MS (HRMS ESI)	Calcd for $[M+H]^+$ $C_{16}H_{23}O_2$: 247.1693 Found: 247.1691

2-methyl-1,2-diphenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-one (IV.49l)



$C_{23}H_{27}BO_3$
M = 362.28 g.mol^{-1}

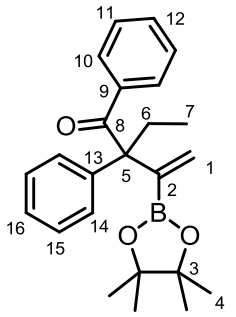
Following procedure K_1 starting with 0.5 mmol buta-2,3-dien-2-ylbenzene (**IV.41l**), bis(pinacolato)diboron (**IV.2**) and benzoyl fluoride (**IV.38a**).

Flash chromatography: PE/Et_2O 95:5 + 1% Et_3N.

Yield: 120.1 mg (66% yield) of a white solid.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.45 – 7.20 (m, 10H, H_{Ar}), 5.73 (d, *J* = 2.4 Hz, 1H, H_1), 4.79 (d, *J* = 2.5 Hz, 1H, $H_{1'}$), 1.87 (s, 3H, H_6), 1.32 (s, 6H, H_4), 1.31 (s, 6H, $H_{4'}$)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	204.2 (C_7), 141.6 (C_q), 137.2 (C_q), 131.6 (C_{Ar}), 129.5 (C_{Ar}), 128.7 (C_{Ar}), 128.3 (C_{Ar}), 128.0 (C_{Ar}), 127.2 (C_{Ar}), 127.0 (C_1), 83.4 (C_3), 61.3 (C_5), 25.2 (C_4), 24.6 ($C_{4'}$), 24.2 (C_6) (C_2 could not be observed because of quadrupolar coupling effects due to boron)
IR (cm^{-1}, neat)	2982 (w), 1672 (s), 1614 (w), 1597 (w), 1578 (w), 1458 (w), 1447 (m), 1410 (m), 1371 (s), 1350 (s), 1304 (s), 1248 (s), 1215 (m), 1143 (s), 1113 (w), 1099 (w), 1068 (w), 1028 (w), 1001 (w), 968 (s)
MS (HRMS APCI)	Calcd for $[M+H]^+$ $C_{23}H_{28}O_3B$: 363.2126 Found: 363.2123

2-ethyl-1,2-diphenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-one (IV.49m)



$C_{24}H_{29}BO_3$
M = 376.30 g.mol^{-1}

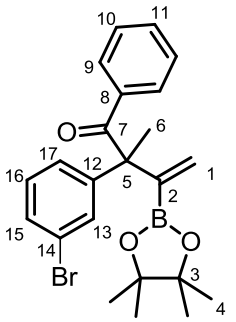
Following procedure K_1 starting with 0.5 mmol penta-1,2-dien-3-ylbenzene (**IV.41m**), bis(pinacolato)diboron (**IV.2**) and benzoyl fluoride (**IV.38a**).

Flash chromatography: pentane/Et_2O 95:5 + 1% Et_3N.

Yield: 114.9 mg (61%) of a slightly yellow oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.43 – 7.17 (m, 10H, H_{Ar}), 5.83 (d, *J* = 2.3 Hz, 1H, H_1), 5.05 (d, *J* = 2.2 Hz, 1H, $H_{1'}$), 2.43 (dq, *J* = 14.5, 7.3 Hz, 1H, H_6), 2.29 (dq, *J* = 14.9, 7.5 Hz, 1H, $H_{6'}$), 1.30 (s, 6H, H_4), 1.30 (s, 6H, $H_{4'}$), 0.87 (t, *J* = 7.4 Hz, 3H, H_7)
^{13}C NMR (δ, ppm) (125 MHz, $CDCl_3$)	203.8 (C_8), 141.7 (C_q), 137.4 (C_q), 131.6 (C_{Ar}), 129.5 (C_{Aror1}), 128.7 (C_{Aror1}), 128.6 (C_{Aror1}), 128.0 (C_{Aror1}), 127.6 (C_{Aror1}), 127.0 (C_{Aror1}), 83.2 (C_3), 65.5 (C_5), 28.2 (C_6), 25.0 (C_4), 24.8 ($C_{4'}$), 10.5 (C_7) (C_2 could not be observed because of quadrupolar coupling effects due to boron)
IR (cm^{-1}, CCl_4)	2976 (br s), 1668 (s), 1614 (m), 1597 (s), 1578 (m), 1447 (s), 1408 (m), 1371 (s), 1352 (s), 1296 (s), 1273 (s), 1234 (s), 1215 (s), 1180 (s), 1138 (s), 1111 (s), 1082 (m), 1081 (m), 1034 (w), 1009 (s), 968 (s), 881 (m), 860 (s), 841 (s)
MS (HRMS ESI)	Calcd for $[M+H]^+$ $C_{24}H_{30}O_3B$: 377.2283 — Found: 377.2282

2-(3-bromophenyl)-2-methyl-1-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-one (IV.49n)



$C_{23}H_{26}BBrO_3$
M = 441.17 g.mol^{-1}

Following procedure K_1 starting with 0.5 mmol 1-bromo-3-(buta-2,3-dien-2-yl)benzene (**IV.41n**), bis(pinacolato)diboron (**IV.2**) and benzoyl fluoride (**IV.38a**).

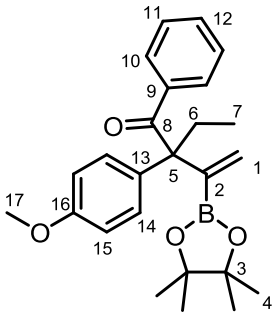
Flash chromatography: PE/Et_2O 95:5 + 1% Et_3N.

Yield: 112.4 mg (51% yield) of a white solid.

^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$)	7.54 – 7.53 (m, 1H, H_{Ar}), 7.46 – 7.37 (m, 4H, H_{Ar}), 7.27 – 7.19 (m, 4H, H_{Ar}), 5.76 (d, *J* = 2.2 Hz, 1H, H_1), 4.81 (d, *J* = 2.2 Hz, 1H, $H_{1'}$), 1.85 (s, 3H, H_6), 1.30 (s, 6H, H_4), 1.29 (s, 6H, $H_{4'}$)
^{13}C NMR (δ, ppm) (125 MHz, $CDCl_3$)	203.4 (C_7), 144.2 (C_q), 136.8 (C_q), 131.8 (C_{Ar}), 131.1 (C_{Ar}), 130.4 (C_{Ar}), 130.2 (C_{Ar}), 129.4 (C_{9or10}), 128.2 (C_{9or10}), 127.3 (C_1), 127.1 (C_{Ar}), 123.0 (C_{14}), 83.5 (C_3), 61.1 (C_5), 25.2 (C_4), 25.0 ($C_{4'}$), 24.2 (C_6) (C_2 could not be observed because of quadrupolar coupling effects due to boron)
IR (cm^{-1}, neat)	1674 (s), 1614 (w), 1593 (m), 1564 (m), 1474 (m), 1447 (m), 1410 (m), 1371 (m), 1348 (s), 1306 (s), 1271 (m), 1244 (s), 1215 (m), 1163 (m), 1142 (s), 1107 (s), 1059 (s), 997 (m), 912 (s), 912 (m), 868 (m), 847 (s)
MS	Calcd for $[M+H]^+$ $C_{23}H_{27}O_3B^{79}Br$: Found: 441.1231

(HRMS APCI) 441.1232

2-ethyl-1-(4-methoxyphenyl)-2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-one (IV.49o)



$C_{25}H_{31}BO_4$
M = 406.32 g.mol^{-1}

Following procedure K_1 starting with 0.5 mmol 1-methoxy-4-(penta-1,2-dien-3-yl)benzene (**IV.41o**), bis(pinacolato)diboron (**IV.2**) and benzoyl fluoride (**IV.38a**).

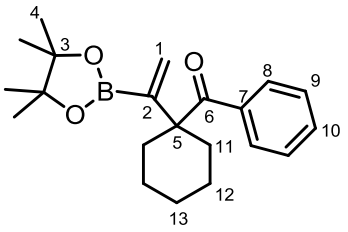
Flash chromatography: PE/Et_2O 95:5 + 1% Et_3N.

Yield: 120.2 mg (60%) of a yellow oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.42 – 7.20 (m, 7H, H_{Ar}), 6.89 – 6.84 (m, 2H, H_{Ar}), 5.83 (d, *J* = 2.3 Hz, 1H, H_1), 5.08 (d, *J* = 2.3 Hz, 1H, $H_{1'}$), 3.80 (s, 3H, H_{17}), 2.45 – 2.20 (m, 2H, H_6), 1.32 (s, 6H, H_4), 1.31 (s, 6H, $H_{4'}$), 0.86 (t, *J* = 7.4 Hz, 3H, H_7)
^{13}C NMR (δ, ppm) (125 MHz, $CDCl_3$)	204.1 (C_8), 158.5 (C_{16}), 137.7 (C_q), 133.4 (C_q), 131.4 (C_q), 129.9 (C_{Aror1}), 129.5 (C_{Aror1}), 128.0 (C_{Aror1}), 127.5 (C_{Aror1}), 114.0 (C_{Aror1}), 83.2 (C_3), 64.9, 55.3, 28.1, 25.0 (C_4), 24.8 ($C_{4'}$), 10.5 (C_7) (C_2 could not be observed because of quadrupolar coupling effects due to boron)
IR (cm^{-1}, neat)	2982 (m), 2939 (w), 2839 (w), 1666 (m), 1609 (m), 1578 (m), 1510 (s), 1464 (m), 1447 (m), 1410 (m), 1371 (m), 1354 (m), 1296 (m), 1252 (s), 1111 (m),

	1034 (m), 1011 (m), 968 (m), 945 (m), 881 (m), 864 (m), 825 (m)
MS (HRMS ESI)	Calcd for $[M+H]^+$ $C_{25}H_{32}O_4B$: 407.2389 Found: 407.2389

phenyl(1-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)cyclohexyl)methanone (IV.49p)



$C_{21}H_{29}BO_3$
$M = 340.26\ g.mol^{-1}$

Following procedure K_1 starting with 0.5 mmol 1-methoxy-4-(penta-1,2-dien-3-yl)benzene (**IV.41p**), bis(pinacolato)diboron (**IV.2**) and benzoyl fluoride (**IV.38a**).

Flash chromatography: PE/Et_2O 95:5 + 1% Et_3N.

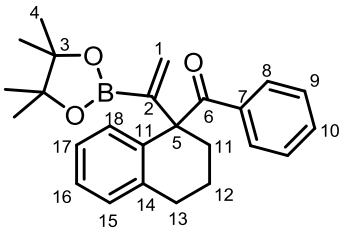
Yield: 120.2 mg (60%) of a yellow oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.80 – 7.77 (m, 2H, H_{8or9}), 7.43 – 7.37 (m, 1H, H_{10}), 7.35 – 7.28 (m, 2H, H_{8or9}), 5.96 (d, *J* = 2.0 Hz, 1H, H_1), 5.77 (d, *J* = 1.8 Hz, 1H, $H_{1'}$), 2.28 – 2.22 (m, 2H, H_{11}), 1.80 – 1.71 (m, 2H, $H_{11'}$), 1.57 – 1.24 (m, 6H, H_{12+13}), 1.18 (s, 12H, H_4)
^{13}C NMR (δ, ppm) (125 MHz, $CDCl_3$)	205.3 (C_6), 138.4 (C_7), 131.1 (C_{10}), 129.3 (C_{8or9}), 129.1 (C_1), 127.8 (C_{8or9}), 83.7 (C_3), 56.1 (C_5), 34.8 (C_{11}), 26.0 (C_{12or13}), 24.7 (C_4), 23.2 (C_{12or13}) (C_2 could not be observed because of quadrupolar coupling effects due to boron)
IR (cm^{-1}, neat)	2955 (br s), 1674 (s), 1597 (m), 1578 (m), 1447 (s), 1421 (s), 1371 (s), 1346 (s), 1310 (s), 1275 (s), 1225

(s), 1197 (s), 1134 (s), 1076 (m), 1051 (m), 1030 (m), 987 (s), 968 (s),951 (s), 876 (s), 851 (s)

MS (HRMS ESI)	Calcd for $[M+H]^+$ $C_{21}H_{30}O_3{}^{10}B$: 340.2319	Found: 340.2320

phenyl(1-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-1,2,3,4-tetrahydronaphthalen-1-yl)methanone (IV.49q)



$C_{25}H_{29}BO_3$
M = 388.31 g.mol^{-1}

Following procedure K_1 starting with 0.5 mmol 1-vinylidene-1,2,3,4-tetrahydronaphthalene (**IV.41q**), bis(pinacolato)diboron (**IV.2**) and benzoyl fluoride (**IV.38a**).

Flash chromatography: pentane/Et_2O 95:5 + 1% Et_3N.

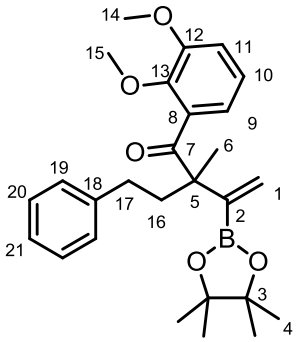
Yield: 34.1 mg (18%) of a yellow oil.

^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$)	7.41 – 7.38 (m, 2H, H_{Ar}), 7.37 – 7.34 (m, 2H, H_{Ar}), 7.24 – 7.20 (m, 3H, H_{Ar}), 7.17 (td, *J* = 7.4, 1.3 Hz, 1H, H_{Ar}), 7.02 – 6.99 (m, 1H, H_{Ar}), 6.83 (dd, *J* = 7.7, 1.2 Hz, 1H, H_{Ar}), 5.87 (d, *J* = 2.7 Hz, 1H, H_1), 4.67 (d, *J* = 2.8 Hz, 1H, $H_{1'}$), 2.91 – 2.88 (m, 2H, H_{13}), 2.41 – 2.37 (m, 1H, H_{11}), 2.23 (td, *J* = 13.3, 3.4 Hz, 1H, $H_{11'}$), 1.80 – 1.74 (m, 2H, H_{12}), 1.35 (s, 6H, H_4), 1.33 (s, 6H, $H_{4'}$)
^{13}C NMR (δ, ppm) (125 MHz, $CDCl_3$)	204.8 (C_6), 137.8 (C_q), 137.0 (C_q), 135.7 (C_q), 131.5 (C_{Ar}), 130.6 (C_{Ar}), 129.6 (C_{Ar}), 129.6 (C_{Ar}), 129.2 (C_1), 128.1 (C_{Ar}), 127.1 (C_{Ar}), 126.3 (C_{Ar}), 83.3 (C_3), 62.7 (C_5), 31.1 (C_{11}), 29.8 (C_{13}), 25.3 (C_4), 24.6 ($C_{4'}$), 18.4 (C_{12}) (C_2 could not be observed because of quadrupolar

coupling effects due to boron)

IR (cm^{-1}, neat)	2970 (br m), 2926 (br m), 2332 (w), 1666 (s), 1614 (m), 1597 (m), 1578 (m), 1489 (m), 1447 (m), 1408 (m), 1352 (s), 1300 (s), 1275 (s), 1240 (s), 1215 (m), 1165 (m), 1136 (s), 1018 (m), 966 (m), 945 (m), 914 (m), 901 (m), 847 (m), 829 (m)
MS (HRMS ESI)	Calcd for $[M+H]^+$ $C_{25}H_{30}O_3B$: Found: 388.2329 388.2319

1-(2,3-dimethoxyphenyl)-2-methyl-2-phenethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-one (IV.49t)



$C_{27}H_{35}BO_5$
$M = 450.37\ g.mol^{-1}$

Following procedure K_1 starting with 0.5 mmol (3-methylpenta-3,4-dien-1-yl)benzene (**IV.41b**), bis(pinacolato)diboron (**IV.2**) and 3,4-dimethoxybenzoyl fluoride (**IV.38c**).

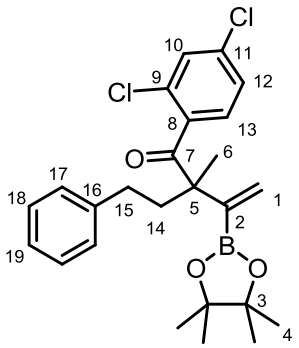
Flash chromatography: Pentane/Et_2O 95:5 + 1% Et_3N.

Yield: 122.7 mg (55% yield) of a white solid.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.66 – 7.60 (m, 2H, H_{Ar}), 7.24 – 7.12 (m, 5H, H_{19to21}), 6.78 (d, J = 8.5 Hz, 1H, H_{Ar}), 6.08 (d, J = 2.2 Hz, 1H, H_1), 5.86 (d, J = 2.2 Hz, 1H, $H_{1'}$), 3.90 (s, 3H, H_{14or15}), 3.89 (s, 3H, H_{14or15}), 2.61 – 2.52 (m, 1H, H_{16}), 2.37 – 2.19 (m, 3H, $H_{16'and17}$), 1.50 (s, 3H, H_6), 1.00 (s, 6H, H_4), 1.00 (s, 6H, $H_{4'}$)

^{13}C NMR (δ, ppm) (125 MHz, $CDCl_3$)	201.8 (C_7), 152.1 (C_q), 148.5 (C_q), 143.0 (C_q), 130.2 (C_q), 128.5 (C_{19or20}), 128.4 (C_{19or20}), 126.9 (C_1), 125.7 (C_{Ar}), 124.1 (C_{Ar}), 112.5 (C_{Ar}), 109.5 (C_{Ar}), 83.7 (C_3), 56.1 (C_{14or15}), 56.0 (C_{14or15}), 54.4 (C_5), 40.7 (C_{17}), 31.1 (C_{16}), 24.6 (C_4), 24.5 ($C_{4'}$), 24.4 (C_6) (C_2 could not be observed because of quadrupolar coupling effects due to boron)
IR (cm^{-1}, neat)	2976 (s), 1799 (w), 1668 (s), 1595 (s), 1583 (s), 1514 (s), 1456 (s), 1412 (s), 1371 (s), 1352 (s), 1315 (s), 1259 (s), 1225 (m), 1213 (m), 1165 (s), 1138 (s), 1024 (s), 968 (m), 947 (m), 866 (m), 847 (m), 816 (m)
MS (HRMS ESI)	Calcd for $[M+H]^+$ $C_{27}H_{36}O_5B$: 451.2651 Found: 451.2651

1-(2,4-dichlorophenyl)-2-methyl-2-phenethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-one (IV.49u)



$C_{25}H_{29}BCl_2O_3$
M = 459.21 g.mol^{-1}

Following procedure K_2 starting with 0.5 mmol (3-methylpenta-3,4-dien-1-yl)benzene (**IV.41b**), bis(pinacolato)diboron (**IV.2**) and 2,4-dichlorobenzoyl fluoride (**IV.38d**).

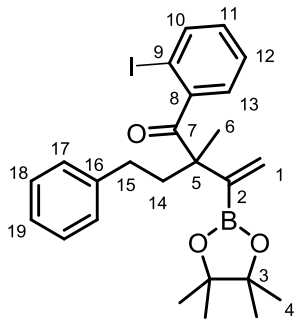
Flash chromatography: pentane/Et_2O 95:5 + 1% Et_3N.

Yield: 97.1 mg (42%) of a yellow oil.

^{1}H NMR (δ, ppm) 7.39 (d, *J* = 2.0 Hz, 1H, H_{Ar}), 7.31 – 7.14 (m, 7H, H_{Ar}),

(300 MHz, $CDCl_3$)	6.09 (d, *J* = 2.1 Hz, 1H, H_1), 5.78 (d, *J* = 2.1 Hz, 1H, $H_{1'}$), 2.51 – 2.39 (m, 3H, H_{14+15}), 2.08 – 1.99 (m, 1H, $H_{14'}$), 1.44 (s, 3H, H_6), 1.23 (s, 6H, H_4), 1.23 (s, 6H, $H_{4'}$)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	206.2 (C_7), 142.6 (C_{16}), 138.0 (C_q), 135.4 (C_q), 132.0 (C_q), 130.2 (C_{Ar}), 129.9 (C_1), 129.0 (C_{Ar}), 128.5 (C_{17or18}), 128.4 (C_{17or18}), 126.1 (C_{Ar}), 125.9 (C_{Ar}), 83.8 (C_3), 57.0 (C_5), 38.9 (C_{14}), 30.8 (C_{15}), 24.8 (C_4), 24.7 ($C_{4'}$), 21.1 (C_6) (C_2 could not be observed because of quadrupolar coupling effects due to boron)
IR (cm^{-1}, neat)	2980 (m), 1693 (s), 1583 (s), 1553 (m), 1497 (m), 1456 (s), 1418 (s), 1371 (s), 1350 (s), 1311 (s), 1265 (m), 1229 (m), 1215 (m), 1167 (m), 1136 (s), 1105 (s), 1059 (m), 962 (s), 851 (s), 824 (s)
MS (HRMS ESI)	Calcd for $[M+H]^+$ $C_{25}H_{30}O_3B^{35}Cl_2$: 459.1661 — Found: 459.1661

1-(2-iodophenyl)-2-methyl-2-phenethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-one (IV.49v)



$C_{25}H_{30}BIO_3$
M = 516.23 g.mol^{-1}

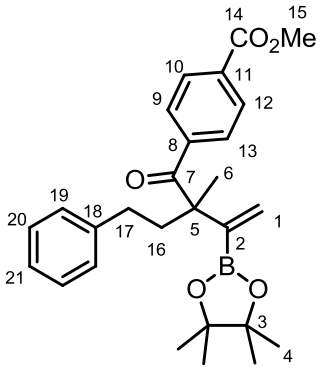
Following procedure K_2 starting with 0.5 mmol (3-methylpenta-3,4-dien-1-yl)benzene (**IV.41b**), bis(pinacolato)diboron (**IV.2**) and 2-iodobenzoyl fluoride (**IV.38e**).

Flash chromatography: pentane/Et_2O 95:5 + 1% Et_3N.

Yield: 128.0 mg (50% yield) of a colourless sticky oil.

^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$)	7.87 (dd, *J* = 7.9, 1.1 Hz, 1H, H_{Ar}), 7.33 (dd, *J* = 7.7, 1.7 Hz, 1H, H_{Ar}), 7.28 – 7.25 (m, 3H, H_{Ar}), 7.20 – 7.15 (m, 3H, H_{Ar}), 7.04 – 7.01 (m, 1H, H_{Ar}), 6.06 (d, *J* = 2.1 Hz, H_1), 5.79 (d, *J* = 2.1 Hz, $H_{1'}$), 2.55 – 2.45 (m, 3H, H_{14+15}), 2.16 – 2.07 (m, 1H, H_{14or15}), 1.47 (s, 3H, H_6), 1.24 (s, 6H, H_4), 1.23 (s, 6H, $H_{4'}$)
^{13}C NMR (δ, ppm) (125 MHz, $CDCl_3$)	208.1 (C_7), 144.9 (C_{8or16}), 142.9 (C_{8or16}), 140.5 (C_{Ar}), 130.5 (C_{Ar}), 129.4 (C_1), 128.6 (C_{17or18}), 128.4 (C_{17or18}), 127.7 (C_{Ar}), 127.0 (C_{Ar}), 125.8 (C_{Ar}), 93.1 (C_9), 83.8 (C_3), 56.6 (C_5), 39.6 (C_{15}), 31.1 (C_{14}), 24.9 (C_4), 24.8 ($C_{4'}$), 21.5 (C_6) (C_2 could not be observed because of quadrupolar coupling effects due to boron)
IR (cm^{-1}, neat)	2324 (w), 1690 (m), 1607 (w), 1558 (w), 1541 (w), 1497 (w), 1456 (m), 1418 (m), 1371 (m), 1352 (m), 1313 (m), 1275 (m), 1259 (m), 1140 (m), 1016 (w), 966 (w), 851 (w), 764 (s)
MS (HRMS ESI)	Calcd for $[M+H]^+$ $C_{25}H_{31}O_3B^{127}I$: 517.1407 Found: 517.1409

methyl-4-(2-methyl-2-phenethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enoyl)benzoate (IV.49w)



$C_{27}H_{33}BO_5$

M = 448.36 g.mol^{-1}

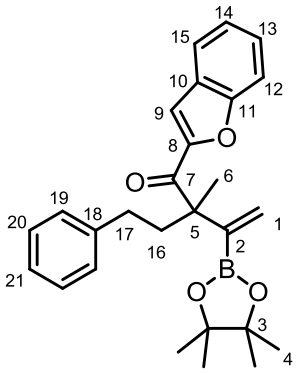
Following procedure K_2 starting with 0.5 mmol (3-methylpenta-3,4-dien-1-yl)benzene (**IV.41b**), bis(pinacolato)diboron (**IV.2**) and methyl 4-(fluorocarbonyl)benzoate (**IV.38f**).

Flash chromatography: PE/Et_2O 9 :1 + 1% Et_3N.

Yield: 101.8 mg (45%) of a yellow solid.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	8.03 – 8.00 (m, 2H, H_{9or10}), 7.97 – 7.94 (m, 2H, H_{9or10}), 7.27 – 7.09 (m, 5H, H_{19to21}), 6.14 (d, *J* = 2.1 Hz, 1H, H_1), 5.92 (d, *J* = 2.0 Hz, $H_{1'}$), 3.93 (s, 3H, H_{15}), 2.58 – 2.48 (m, 1H, H_{16}), 2.40 – 2.31 (m, 1H, $H_{16'}$), 2.28 – 2.19 (m, 2H, H_{17}), 1.52 (s, 3H, H_6), 1.03 (s, 6H, H_4), 1.02 (s, 6H, $H_{4'}$)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	203.6 (C_7), 166.6 (C_{14}), 142.7 (C_q), 141.4 (C_q), 132.4 (C_q), 129.3 (C_{9or10}), 129.2 (C_{9or10}), 128.6 (C_1), 128.5 ($C1_{9or20}$), 128.5 (C_{19or20}), 125.8 (C_{21}), 83.9 (C_3), 55.0 (C_5), 52.5 (C_{15}), 40.1 (C_{17}), 31.0 (C_{16}), 24.6 (C_4), 24.5 ($C_{4'}$), 23.7 (C_6) (C_2 could not be observed because of quadrupolar coupling effects due to boron)
IR (cm^{-1}, neat)	3078 (w), 3030 (m), 2976 (s), 2935 (m), 1726 (s), 1682 (s), 1605 (m), 1568 (m), 1497 (m), 1454 (m), 1434 (s), 1414 (s), 1353 (s), 1315 (s), 1275 (s), 1238 (s), 1215 (s), 1190 (s), 1167 (s), 1138 (s), 1105 (s), 1030 (w), 1018 (m), 966 (s), 906 (w), 878 (m)
MS (HRMS ESI)	Calcd for $[M+H]^+$ $C_{27}H_{34}O_5B$: 449.2495 Found: 449.2495

1-(benzofuran-2-yl)-2-methyl-2-phenethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-one (IV.49x)



$C_{27}H_{31}BO_4$
M = 430.34 g.mol^{-1}

Following procedure K_2 starting with 0.5 mmol (3-methylpenta-3,4-dien-1-yl)benzene (**IV.41b**), bis(pinacolato)diboron (**IV.2**) and benzofuran-2-carboxylic acid (**IV.38g**).

Flash chromatography: PE/Et_2O 95:5 + 1% Et_3N.

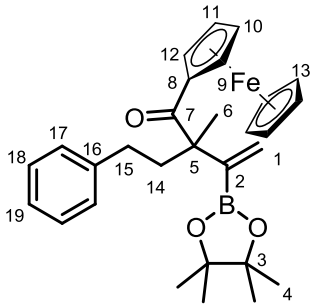
Yield: 83.4 mg (39% yield) of a white solid.

^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$)	7.66 – 7.63 (m, 1H, H_{Ar}), 7.58 – 7.55 (m, 1H, H_{Ar}), 7.46 – 7.40 (m, 2H, H_{Ar}), 7.30 – 7.23 (m, 3H, H_{Ar}), 7.18 – 7.13 (m, 3H, H_{Ar}), 6.19 (d, *J* = 2.2 Hz, 1H, H_1), 5.98 (d, *J* = 2.1 Hz, 1H, $H_{1'}$), 2.63 – 2.53 (m, 1H, H_{16}), 2.48 – 2.38 (m, 1H, $H_{16'}$), 2.30 – 2.24 (m, 2H, H_{17}), 1.55 (s, 3H, H_6), 1.02 (s, 6H, H_4), 1.01 (s, 6H, $H_{4'}$)
^{13}C NMR (δ, ppm) (125 MHz, $CDCl_3$)	194.0 (C_7), 154.9 (C_q), 151.8 (C_q), 142.8 (C_q), 128.5 (C_{19or20}), 128.4 (C_{19or20}), 128.3 (C_1), 127.8 (C_{Ar}), 127.1 (C_q), 125.8 (C_{Ar}), 123.7 (C_{Ar}), 123.2 (C_{Ar}), 114.0 (C_{Ar}), 112.4 (C_{Ar}), 83.8 (C_3), 54.2 (C_5), 39.4 (C_{17}), 31.0 (C_{16}), 24.5 (C_4), 24.5 ($C_{4'}$), 23.2 (C_6) (C_2 could not be observed because of quadrupolar coupling effects due to boron)
IR (cm^{-1}, neat)	3078 (w), 3057 (w), 3032 (w), 2976 (m), 2935 (w), 2928 (w), 1732 (w), 1676 (s), 1612 (m), 1545 (s), 1497 (m), 1447 (s), 1412 (s), 1371 (s), 1354 (s), 1315 (s), 1271 (s), 1213 (m), 1157 (s), 1136 (s), 1115 (s),

1030 (m), 991 (s), 966 (s), 949 (s), 918 (m), 876 (s)

MS (HRMS ESI)	Calcd for $[M+Na]^+$ $C_{27}H_{31}O_4BNa$: 453.2209	Found: 453.2209

2-Methyl-2-phenethyl-1-ferrocenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-one (IV.49z)



$C_{29}H_{35}BFeO_3$
M = 498.25 g.mol^{-1}

Following procedure K_2 starting with 0.5 mmol (3-methylpenta-3,4-dien-1-yl)benzene (**IV.41b**), bis(pinacolato)diboron (**IV.2**) and ferrocenoyl fluoride (**IV.38i**).

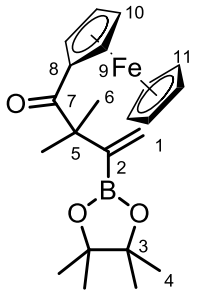
Flash chromatography: PE/Et_2O 95:5 + 1% Et_3N.

Yield: 153.6 mg (62% yield) of an orange-red solid.

^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$)	7.26 – 7.23 (m, 2H, H_{Ar}), 7.16 – 7.13 (m, 3H, H_{Ar}), 6.01 (d, *J* = 2.4 Hz, 1H, H_1), 5.76 (d, *J* = 2.4 Hz, 1H, $H_{1'}$), 4.90 (dt, *J* = 2.6, 1.3 Hz, 1H, H_{9or12}), 4.72 (dt, *J* = 2.5, 1.2 Hz, 1H, H_{9or12}), 4.39 (dtd, *J* = 7.0, 2.5, 1.4 Hz, 2H, H_{10+11}), 4.19 (s, 5H, H_{13}), 2.45 – 2.40 (m, 2H, H_{15}), 2.26 – 2.20 (m, 1H, H_{14}), 2.17 – 2.11 (m, 1H, $H_{14'}$), 1.62 (s, 3H, H_6), 1.13 (s, 6H, H_4), 1.11 (s, 6H, $H_{4'}$)
^{13}C NMR (δ, ppm) (125 MHz, $CDCl_3$)	209.0 (C_7), 143.2 (C_{16}), 128.5 (C_{17or18}), 128.4 (C_{17or18}), 126.2 (C_1), 125.6 (C_{19}), 83.4 (C_3), 78.2 (C_8), 71.6 (C_{9or12}), 71.2 (C_{Fc}), 71.1 (C_{Fc}), 70.9 (C_{Fc}), 70.0 (C_{13}), 55.7 (C_5), 39.3 (C_{14}), 31.0 (C_{15}), 24.8 (C_4), 24.7 ($C_{4'}$), 24.0 (C_6) (C_2 could not be observed because of quadrupolar

	coupling effects due to boron)
IR (cm^{-1}, neat)	1663 (br s), 1607 (w), 1497 (w), 1454 (m), 1439 (m), 1412 (m), 1371 (s), 1354 (s), 1313 (s), 1298 (m), 1259 (s), 1215 (m), 1165 (m), 1140 (s), 1107 (s), 1053 (s), 1028 (m), 1003 (m), 968 (s), 947 (m), 891 (m), 870 (m), 847 (s), 824 (s)
MS (HRMS ESI)	Calcd for $[M+H]^+$ $C_{29}H_{36}O_3BFe$: Found: 499.2105 499.2103

2,2-Dimethyl-1-ferrocenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-one (IV.49aa)



$C_{22}H_{29}BFeO_3$
M = 408.13 g.mol^{-1}

Following procedure K_2 starting with 1.5 mmol 3-methyl-1,2-butadiene (**IV.41f**), bis(pinacolato)diboron (**IV.2**) and ferrocenoyl fluoride (**IV.38i**).

Flash chromatography: (PE/Et_2O 9:1 to 85:15) + 1% Et_3N.

Yield: 481.2 mg (79% yield) of an orange-red solid.

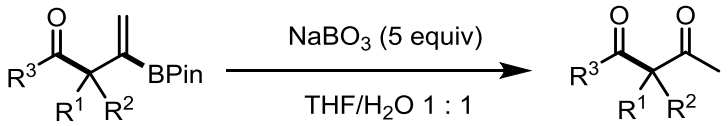
^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$)	5.87 (d, *J* = 2.4 Hz, 1H, H_1), 5.77 (d, *J* = 2.4 Hz, 1H, $H_{1'}$), 4.77 – 4.76 (m, 2H, H_{9or10}), 4.36 – 4.35 (m, 2H, H_{9or10}), 4.16 (s, 5H, H_{11}), 1.46 (s, 6H, H_6), 1.04 (s, 12H, H_4)
^{13}C NMR (δ, ppm) (125 MHz, $CDCl_3$)	209.2 (C_7), 125.1 (C_1), 83.4 (C_3), 78.1 (C_8), 71.4 (C_{9or10}), 70.9 (C_{9or10}), 69.9 (C_{11}), 51.8 (C_5), 26.5 (C_6), 24.7 (C_4) (C_2 could not be observed because of quadrupolar

coupling effects due to boron)

IR (cm^{-1}, neat)	2972 (s), 1734 (w), 1668 (s), 1466 (m), 1439 (s), 1412 (s), 1371 (s), 1352 (s), 1313 (s), 1267 (s), 1211 (m), 1142 (s), 1107 (s), 1055 (s), 1003 (m), 968 (s), 943 (m), 891 (m), 862 (m), 843 (s), 822 (s)
MS (HRMS ESI)	Calcd for $[M+H]^+$ $C_{22}H_{30}O_3BFe$: 409.1632 Found: 409.1633

Post-functionalization of allenes

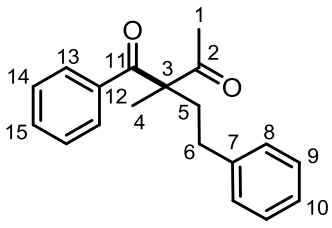
Oxidation of the vinylboron moiety: procedure L:



IV.49 **IV.57**

To a solution of **IV.49** (1 equiv, 0.2 mmol) in THF/H_2O 1 : 1 was added $NaBO_3$ (5 equiv, 1.0 mmol, 99.8 mg) and the mixture was vigorously stirred at room temperature for 2 h. Et_2O and $NH_4Cl_{(sat)}$ were added and the layers were separated. After extraction with Et_2O, the organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (PE/Et_2O) afforded the pure product.

2-Methyl-2-phenethyl-1-phenylbutane-1,3-dione (IV.57b)



$C_{19}H_{20}O_2$
M = 280.36 g.mol^{-1}

Following procedure L starting with 0.2 mmol 2-methyl-2-phenethyl-1-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-one (**IV.49b**).

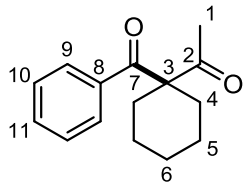
Flash chromatography: PE/Et_2O 9 : 1 to 8 : 2

Yield: 44.0 mg (78% yield) of a slightly yellow oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.83 – 7.79 (m, 2H, H_{Ar}), 7.58 – 7.52 (m, 1H, H_{Ar}), 7.46 – 7.41 (m, 2H, H_{Ar}), 7.27 – 7.21 (m, 2H, H_{Ar}), 7.19 – 7.14 (m, 1H, H_{Ar}), 7.09 – 7.06 (m, 2H, H_{Ar}), 2.48 – 2.20 (m, 4H, H_{5+6}), 2.13 (s, 3H, H_1), 1.56 (s, 3H, H_1)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	208.1 (C_{2or11}), 199.3 (C_{2or11}), 141.6 (C_{7or13}), 136.0 (C_{7or13}), 133.2 (C_{10or15}), 129.0 (C_{Ar}), 128.9 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 126.2 (C_{10or15}), 65.0 (C_3), 37.6 (C_{5or6}), 30.3 (C_{5or6}), 27.3 (C_1), 20.1 (C_4)
IR (cm^{-1}, neat)	2918 (m), 2849 (w), 1712 (s), 1670 (s), 1597 (m), 1580 (m), 1497 (m), 1447 (s), 1375 (m), 1356 (m), 1274 (s), 1246 (s), 1205 (m), 1180 (m), 1157 (m), 1097 (m), 1078 (w), 1001 (m), 986 (m), 955 (s)

MS (HRMS APCI)	Calcd for $[M+H]^+$ $C_{19}H_{21}O_2$: 281.15266	Found: 281.1535

1-(1-Benzoylcyclohexyl)ethan-1-one (IV.57p)



$C_{15}H_{18}O_2$
$M = 230.31\ g.mol^{-1}$

Following procedure L starting with 0.2 mmol phenyl(1-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)cyclohexyl)methanone (**IV.49p**).

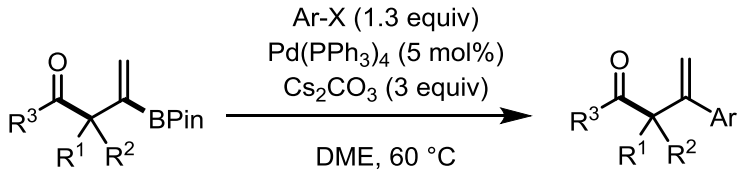
Flash chromatography: Pentane/Et_2O 96 : 4

Yield: 40.6 mg (88% yield) of a slightly yellow oil.

^{1}H NMR (δ, ppm) (500 MHz, $CDCl_3$)	7.72 – 7.70 (m, 2H, H_{Ar}), 7.51 – 7.48 (m, 1H, H_{Ar}), 7.40 – 7.37 (m, 2H, H_{Ar}), 2.25 – 2.20 (m, 2H, H_{Aliph}), 2.11 (s, 3H, H_1), 1.95 – 1.89 (m, 2H, H_{Aliph}), 1.60 – 1.54 (m, 2H, H_{Aliph}), 1.50 – 1.30 (m, 4H, H_{Aliph})
^{13}C NMR (δ, ppm) (125 MHz, $CDCl_3$)	208.4 (C_1), 200.6 (C_7), 137.0 (C_8), 132.7 (C_{11}), 128.6 (C_9), 128.6 (C_{10}), 66.6 (C_3), 31.9 (C_{Aliph}), 26.8 (C_1), 25.6 (C_{Aliph}), 22.5 (C_{Aliph})

Spectroscopic data are in agreement with those reported in the literature.[235]

Suzuki coupling: procedure M:



4 **6**

The Suzuki coupling was carried out according to a literature procedure.[236]

A flame-dried Schlenk was loaded with $Pd(PPh_3)_4$ (0.05 equiv, 0.01 mmol, 11.6 mg), aryl halide (1.3 equiv, 0.26 mmol) and Cs_2CO_3 (3 equiv, 0.6 mmol, 195.5 mg). After 3 vacuum/argon cycles, dried and degassed DME (2.0 mL) was added, followed by vinylboron **IV.54** (1 equiv, 0.2 mmol) in solution in DME (0.5 mL). The reaction mixture was stirred at 60 °C for the indicated time. After dilution with EtOAc, the reaction mixture was filtrated on silica (EtOAc) and concentrated

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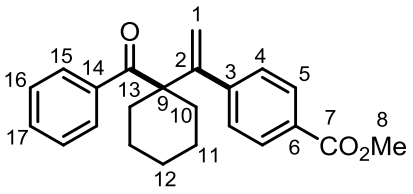
[235] W. Adam, T. Heidenfelder, C. Sahin, *Synthesis*, **1995**, *9*, 1163-1170.

[236] A. L. Moure, P. Mauleón, R. G. Arrayás, J. C. Carretero, *Org. Lett.* **2013**, *15*, 2054-2057.

under reduced pressure. Purification by flash chromatography afforded the desired coupling product.

Methyl 4-(1-(1-benzoylcyclohexyl)vinyl)benzoate (IV.58p)



$C_{23}H_{24}O_3$
M = 348,43 g.mol^{-1}

Following procedure M starting with 0.2 mmol phenyl(1-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)cyclohexyl)methanone **IV.49p** and methyl 4-bromobenzoate.

Flash chromatography: PE/Et_2O 95 : 5

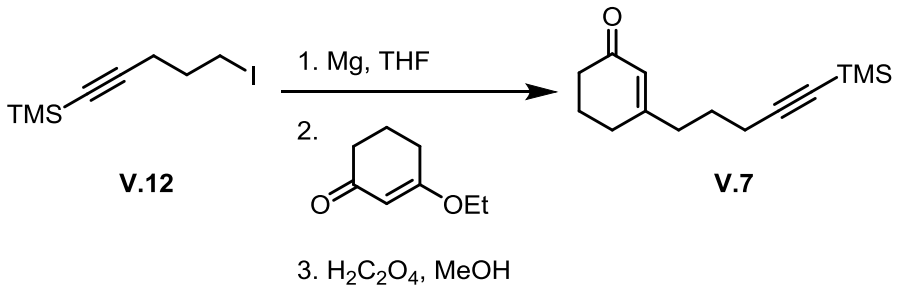
Yield: 50.7 mg (73% yield) of a colourless oil.

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.94 – 7.91 (m, 4H, H_{5+15}), 7.51 – 7.46 (m, 1H, H_{17}), 7.41 – 7.36 (m, 2H, H_{16}), 7.24 – 7.20 (m, 2H, H_6), 5.55 (s, 1H, H_1), 5.34 (s, 1H, $H_{1'}$), 3.89 (s, 3H, H_8), 2.30 – 2.26 (m, 2H, H_{Aliph}), 1.67 – 1.52 (m, 4H, H_{Aliph}), 1.43 – 1.18 (m, 4H, H_{Aliph})
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	204.3 (C_{12}), 167.0 (C_7), 153.1 (C_q), 146.4 (C_q), 139.0 (C_q), 131.7 (C_{17}), 129.3 (C_{Ar}), 129.1 (C_2), 128.9 (C_{Ar}), 128.7 (C_{Ar}), 128.4 (C_{Ar}), 118.1 (C_1), 57.2 (C_9), 52.2 (C_8), 34.9 (C_{Aliph}), 25.8 (C_{Aliph}), 22.8 (C_{Aliph})
IR (cm^{-1}, neat)	2918 (m), 2856 (m), 1720 (s), 1676 (s), 1607 (s), 1597 (m), 1578 (m), 1504 (w), 1452 (s), 1435 (s), 1400 (m), 1311 (m), 1275 (br s), 1227 (s), 1180 (s), 1155 (m), 1115 (s), 1053 (w), 1030 (w), 1018 (s), 986 (s), 970 (m), 912 (s), 883 (s), 862 (s), 833 (w), 814 (w)
MS (HRMS APCI)	Calcd for $[M+H]^+$ $C_{23}H_{25}O_3$: 349.1798 Found: 349.1798

V. Chapter IV: Towards the Development of Copper/Gold-Catalyzed 1,4-Reduction/Cyclization of Enones

(5-iodopent-1-yn-1-yl)trimethylsilane **V.12**,[237] (4-iodobut-1-yn-1-yl)benzene **V.15a**,[238] (4-bromobut-1-yn-1-yl)benzene **V.15b**,[239] (3-bromoprop-1-yn-1-yl)benzene **V.19,**[240] 2-(phenylethynyl)benzaldehyde **V.27**[241] were prepared according to literature procedures. Spectroscopic data obtained were in agreement with those previously reported.

3-(5-(trimethylsilyl)pent-4-yn-1-yl)cyclohex-2-en-1-one (V.7)



V.12 **V.7**

A three-neck round-bottom containing magnesium (2 equiv, 8.0 mmol, 194 mg) and equiped with a condenser was flame-dried and put under argon. THF (1.5 mL) and 1,2-dibromoethane (50 µL) were added and the mixture

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[237] F. Rodier, M. Rajzmann, J.-L. Parrain, G. Chouraqui, L. Commeiras, *Chem.–Eur. J.* **2013**, 19, 2467-2477.

[238] M. Fuchs, A. Fürstner, *Angew. Chem. Int. Ed.* **2015**, *54*, 3978-3982.

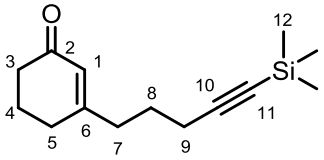
[239] F. Kleinbeck, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 9178-9179.

[240] M. E. Cinar, C. Vavilala, R. Jaquet, J. W. Bats, M. Schmittel, *Eur. J. Org. Chem.* **2014**, 5166-5177.

[241] D. Hack, C. C. J. Loh, J. M. Hartmann, G. Raabe, D. Enders, *Chem. - Eur. J.* **2014**, *20*, 3917-3921.

was heated at 60 °C for 5 minutes. A gas release was observed during this period. (5-iodopent-1-yn-1-yl)trimethylsilane **V.12** (1 equiv, 4.0 mmol, 1.065 g) and 1,2-dibromoethane (150 µL) dissolved in THF (2.5 mL) were added dropwise. The mixture was stirred 30 minutes at 60 °C. 3-ethoxycyclohex-2-en-1-one (1 equiv, 4.0 mmol, 561 mg, 0.58 mL) dissolved in THF (4 mL) was added dropwise and the mixture was stirred 1 h at 60 °C. After cooling down the reaction mixture to room temperature, $NH_4Cl_{(sat)}$ was added carefully (gas release). Extraction with Et_2O (x3), drying over $MgSO_4$ and concentration under reduced pressure afforded a crude alcohol.

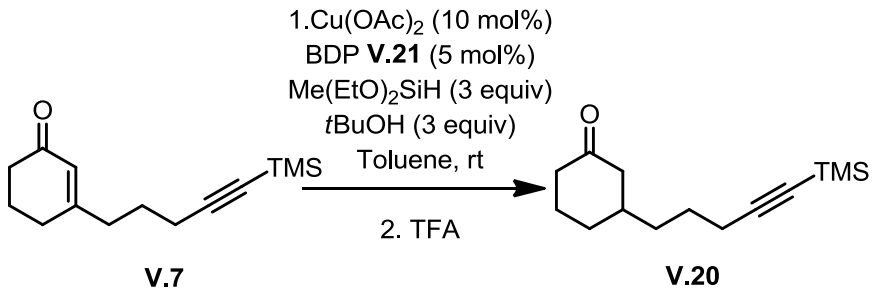
The crude alcohol was dissolved in MeOH (7 mL) and a saturated solution of oxalic acid (0.7 mL) was added. After 2 h stirring at room temperature, $NaHCO_{3(sat)}$ was added. The mixture was extracted with PE (x3), the organic layers were washed successively with $NaHCO_{3(sat)}$ and water, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (PE/EtOAc 9 : 1 to 85 : 15) afforded compound **V.7** as a yellow oil (477 mg, 2.03 mmol, 51% yield).



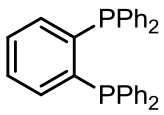
$C_{14}H_{22}OSi$
$M = 234.41\ g.mol^{-1}$

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	5.90 – 5.88 (m, 1H, H_1), 2.39 – 2.23 (m, 8H, $H_{3+5+7+9}$), 2.06 – 1.97 (m, 2H, H_4), 1.77 – 1.70 (m, 2H, H_8), 0.15 (s, 9H, H_{12})
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	199.9 (C_2), 165.5 (C_6), 126.2 (C_1), 106.3 (C_{10}), 85.7 (C_{11}), 37.5 (C_{3or7}), 37.0 (C_7), 29.8 (C_{3or7}), 26.0 (C_8), 22.8 (C_4), 19.6 (C_9), -0.27 (C_{12})
MS (HRMS APCI)	Calcd for $[M+H]^+$ $C_{14}H_{23}OSi$: 235.1513 Found: 235.1512

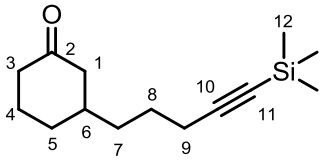
3-(5-(trimethylsilyl)pent-4-yn-1-yl)cyclohexanone (V.20)



BDP **V.21**



Copper(II) acetate (0.1 equiv, 0.05 mmol, 11.1 mg) and phosphine **V.21** (0.05 equiv, 0.025 mmol, 11.2 mg) were introduced into a flame-dried Schlenk flask. *t*BuOH (3 equiv, 1.5 mmol, 111.2 mg) dissolved in toluene (0.5 mL) was added and the resulting blue solution was stirred 20 min at room temperature. Methyldiethoxysilane (3 equiv, 1.5 mmol, 201.4 mg, 0.24 mL) was added and the solution became instantaneously yellow. Substrate **V.7** (1 equiv, 0.5 mmol, 117.2 mg) dissolved in toluene (0.3 mL) was added and the solution was stirred 4 h at room temperature. Trifluoroacetic acid (80 µL) was added, and the mixture was stirred for 15 min at room temperature. Water and ethyl acetate were added and the mixture was stirred for an extra hour at room temperature. The layers were separated and the aqueous layer was extracted with EtOAc (x3). The organic layers were washed successively with $NaHCO_{3(sat)}$ and with water, then dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (PE/EtOAc 95 : 5) afforded the pure product as a yellow oil (80.0 mg, 0.34 mmol, 68% yield).



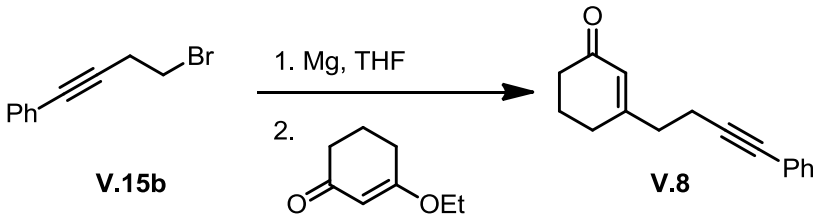
$C_{14}H_{24}OSi$
M = 236.43 g.mol^{-1}

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$) 2.45 – 2.29 (m, 5H, H_{1+3+9}), 2.08 – 1.24 (m, 10H, H_{Aliph}), 0.14 (s, 9H, H_{12})

^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$) 212.0 (C_2), 107.2 (C_{10}), 84.9 (C_{11}), 48.3 (C_{1or3}), 41.6 (C_{1or3}), 38.8 ($C_{4or5or6}$), 35.8 (C_7), 31.3 (C_{4or5}), 25.9 ($C_{4or5or6}$), 25.4 (C_8), 20.0 (C_9), 0.3 (C_{12})

MS (HRMS APCI) Calcd for $[M+H]^+$ $C_{14}H_{25}OSi$: 237.1669 Found: 237.1669

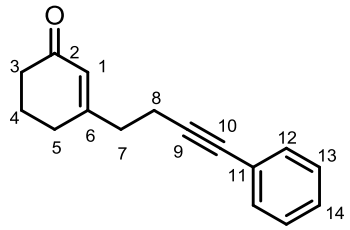
3-(4-phenylbut-3-yn-1-yl)cyclohex-2-enone (V.8)



A three-neck round-bottom containing magnesium (3.3 equiv, 12.3 mmol, 300 mg) and equiped with a condenser was flame-dried and put under argon. THF (1.0 mL) and 1,2-dibromoethane (40 µL) were added and the mixture was heated carefully with a heat gun until a gas release was observed. (4-bromobut-1-yn-1-yl)benzene **V.15b** (2.2 equiv, 8.2 mmol, 1.712 g) dissolved in THF (10 mL) was added dropwise and the mixture was stirred 30 minutes at room temperature. 3-ethoxycyclohex-2-en-1-one (1.0 equiv, 3.8 mmol, 531 mg, 0.55 mL) was added and the mixture was stirred overnight at room temperature. After cooling down the reaction mixture to 0 °C, HCl (1 mol.L^{-1} in water) was added carefully (gas release). The layers were separated, and

the aqueous layer was extracted with Et_2O (x3). The organic layers were dried over Na_2SO_4 and concentrated.

Purification by flash chromatography (PE/EtOAc 85 : 15 to 8 : 2) afforded compound **V.8** as a yellow oil (456 mg, 2.04 mmol, 54% yield).

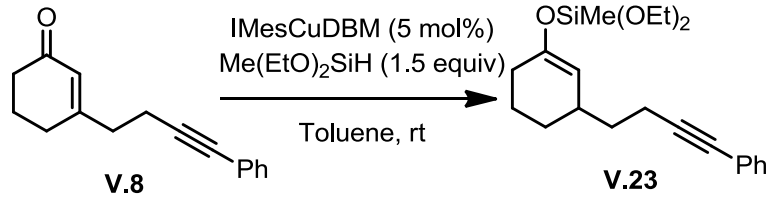


$C_{16}H_{16}O$
$M = 224.30\ g.mol^{-1}$

^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.38 – 7.35 (m, 2H, H_{Ar}), 7.30 – 7.26 (m, 3H, H_{Ar}), 5.98 (s, 1H, H_1), 2.67 – 2.62 (m, 2H, H_8), 2.55 – 2.50 (m, 2H, H_7), 2.41 – 2.35 (m, 4H, H_{3+5}), 2.07 – 1.98 (m, 2H, H_4)
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	199.9 (C_2), 164.0 (C_6), 131.7 (C_{12or13}), 128.4 (C_{12or13}), 128.0 (C_{14}), 126.5 (C_1), 123.5 (C_{11}), 88.2 (C_9), 82.0 (C_{10}), 37.5 (C_{3or5}), 36.9 (C_7), 29.8 (C_{3or5}), 22.8 (C_4), 17.7 (C_8)

Spectroscopic data are in agreement with those reported in the literature.[242]

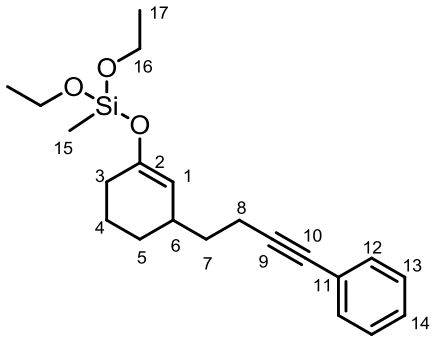
diethoxy(methyl)((3-(4-phenylbut-3-yn-1-yl)cyclohex-1-en-1-yl)oxy)silane (V.23)



V.8 **V.23**

[242] R. Shintani, S. Isobe, M. Takeda, T. Hayashi, *Angew. Chem. Int. Ed.* **2010**, *49*, 3795-3798.

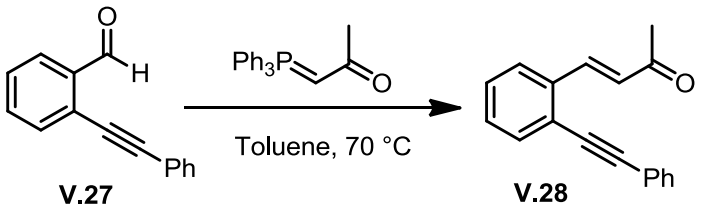
IMesCuDBM (0.05 equiv, 0.0125 mmol, 7.5 mg) was introduced into a flame-dried Schlenk flask and toluene (0.5 mL). Substrate **V.8** (1 equiv, 0.25 mmol, 56 mg) dissolved in toluene (0.5 mL) was added, followed by methyldiethoxysilane (1.5 equiv, 0.375 mmol, 50.3 mg, 60 µL). The mixture was stirred 24 h at room temperature and was filtered over silica (PE/EtOAc 1 : 1). The solvents were removed under reduced pressure, and purification by flash chromatography (PE/EtOAc 95 : 5) afforded the silyl enol ether **V.23** contaminated with some amounts of the dimer **V.24**. The isolated yield was estimated to 36%. 26% of the reduced product were also isolated.



$C_{21}H_{30}O_3Si$
M = 358,55 g.mol^{-1}

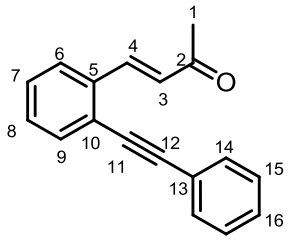
^{1}H NMR (δ, ppm) (300 MHz, $CDCl_3$)	7.41 – 7.38 (m, 2H, H_{Ar}), 7.30 – 7.27 (m, 3H, H_{Ar}), 5.00 – 4.99 (m, 1H, H_1), 3.86 (q, *J* = 7.0 Hz, 4H, H_{16}), 2.45 (t, J = 7.4 Hz, 2H, H_8), 2.42 – 2.30 (br s, 1H, H_6), 2.09 – 2.08 (m, 2H, H_{4or5}), 1.80 – 1.77 (m, 2H, H_{3+4or5}), 1.68 – 1.54 (m, 2H, $H_{3'+7}$), 1.25 (t, *J* = 7.0 Hz, 6H, H_{17}), 1.24 – 1.21 (m, 1H, H_{4or5})
^{13}C NMR (δ, ppm) (75 MHz, $CDCl_3$)	149.8 (C_2), 131.7 (C_{12or13}), 128.3 (C_{12or13}), 127.6 (C_{14}), 124.2 (C_{11}), 108.9 (C_1), 90.3 (C_9), 80.8 (C_{10}), 58.7 (C_{16}), 35.7 (C_7), 33.8 (C_6), 29.6 (C_{4or5}), 28.4 (C_{4or5}), 21.7 (C_3), 18.3 (C_{17}), 17.1 (C_8), -6.5 (C_{15})
MS (HRMS APCI)	Calcd for $[M+H]^+$ $C_{21}H_{31}O_3Si$: 359.2037 Found: 359.2035

(E)-4-(2-(phenylethynyl)phenyl)but-3-en-2-one (V.28)



This compound was prepared according to a literature procedure.[241] A suspension of aldehyde **V.27** (1 equiv, 12.0 mmol, 2.473 g) and 1-(triphenylphosphoranylidene)propan-2-one (1.1 equiv, 13.2 mmol, 4.202 g) in toluene (25 mL) was heated at 70 °C for 4 h 30. After evaporation of the solvent under reduced pressure, and a pentane/Et_2O mixture was added. The resulting suspension was filtered and the filtrate was concentrated under reduced pressure.

Purification by flash chromatography (PE/EtOAc 9 : 1 to 8 : 2) afforded compound **V.28** as a white solid (2.229 g, 9.17 mmol, 76% yield).



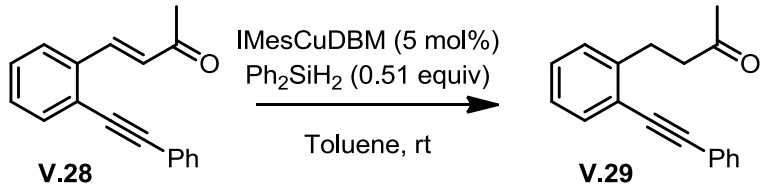
$C_{18}H_{14}O$
M = 246.30 g.mol^{-1}

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$): 8.15 (d, *J* = 16.5 Hz, 1H, H_4), 7.69 – 7.67 (m, *J* = 16.4 Hz, 1H, H_{Ar}), 7.61 – 7.56 (m, 3H, H_{Ar}), 7.40 – 7.36 (m, 5H, H_{Ar}), 6.79 (d, *J* = 16.4 Hz, H_3), 2.45 (s, 3H, H_1)

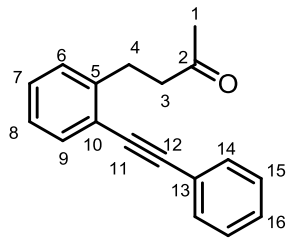
^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$): 198.8 (C_2), 141.7 (C_4), 135.9 (C_q), 133.0 (C_{Ar}), 131.7 (C_{14or15}), 130.1 (C_{Ar}), 128.9 (C_{Ar}), 128.9 (C_{Ar}), 128.8 (C_{Ar}), 128.7 (C_{14or15}), 126.3 (C_3), 124.4 (C_q), 122.9 (C_q), 95.8 (C_{11or12}), 87.0 (C_{11or12}), 27.2 (C_1)

Spectroscopic data are in agreement with those reported in the literature.[241]

4-(2-(phenylethynyl)phenyl)butan-2-one (V.29)



IMesCuDBM (0.05 equiv, 0.025 mmol, 15.0 mg) was introduced into a flame-dried Schlenk flask. Substrate **V.28** (1 equiv, 0.5 mmol, 123.2 mg) dissolved in toluene (1.0 mL) was added, followed by diphenylsilane (0.51 equiv, 0.255 mmol, 47.0 mg, 47 µL). The solution was stirred 1 h at room temperature, and TBAF (1 M in THF, 1 equiv, 0.5 mmol, 0.5 mL) and MeOH were added. The mixture was filtered over silica (Et_2O) and the solvents were removed under reduced pressure. Purification by flash chromatography (PE/EtOAc 95 : 5) afforded the pure product **V.29** (96 mg, 0.39 mmol, 78% yield).



$C_{18}H_{16}O$
$M = 248.32\ g.mol^{-1}$

^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$): 7.53 – 7.51 (m, 2H, H_{Ar}), 7.38 – 7.34 (m, 2H, H_{Ar}), 7.27 – 7.19 (m, 2H, H_{Ar}), 3.14 (t, J = 7.7 Hz, 2H, H_4), 2.86 (t, J = 7.7 Hz, 2H, H_3), 2.15 (s, 3H, H_1)

^{13}C NMR (δ, ppm) (101 MHz, $CDCl_3$): 208.2 (C_2), 143.1 (C_q), 132.4 (C_{Ar}), 131.6 (C_{14or15}), 129.2 (C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{14or15}), 128.5 (C_{Ar}), 126.4 (C_{Ar}), 123.4 (C_q), 122.6 (C_q), 93.6 (C_{11or12}), 87.8 (C_{11or12}), 44.4 (C_3), 30.2 (C_1), 29.1 (C_4)