Organic LETTERS

Letter

Cite This: Org. Lett. 2018, 20, 6769−6773

pubs.acs.org/OrgLett

Highly (*Z*)-Diastereoselective Synthesis of Trifluoromethylated *exo*-Glycals via Photoredox and Copper Catalysis

Christophe J.-M. Frédéric,[†] Jérôme Cornil,[†] Mathilde Vandamme,[†] Lidia Dumitrescu,[†] Abdellatif Tikad,[‡] Raphaël Robiette,[§] and Stéphane P. Vincent*[,†]

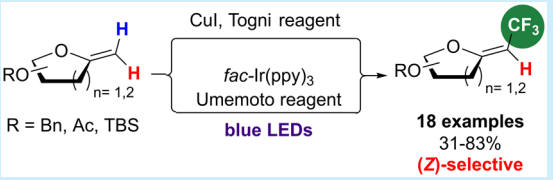
[†]Université de Namur, Laboratoire de Chimie Bio-Organic (CBO), rue de Bruxelles 61, 5000 Namur, Belgium

[‡]Laboratoire de Chimie Moléculaire et Substances Naturelles, Faculté des Sciences, Université Moulay Ismail, Zitoune, Meknès 1120, Morocco

[§]Université Catholique de Louvain, Institute of Condensed Matter and Nanosciences, Place Louis Pasteur 1, 1348 Louvain-la-Neuve, Belgium

Supporting Information

ABSTRACT: Highly (*Z*)-diastereoselective approaches for the synthesis of trifluoromethylated *exo*-glycals by copper and photoredox catalysis are described. These complementary reactions are applicable to a wide range of methylene *exo*-glycals generated from the corresponding pyranoses and furanoses and give trifluoromethylated compounds under mild conditions in moderate to good yields. DFT calculations have allowed a rationalization of the observed (*Z*)-stereoselectivity.



exo-Glycals, such as the molecule **1**-(*Z*),[1] have been recognized as important structural motifs for the inhibition of enzymes, which include glycosidases and glycosyltransferases.[2] In this context, our group has reported several methods for preparing phosphono-*exo*-glycals **2**-(*Z*,*E*) (Figure 1) which could inhibit UDP-glactopyranose mutase (UGM) and galactofuranosyltransferases 1 and 2 (Glf*T*s).[3−6] These enzymes are involved in the biosynthesis of the *Mycobacterium tuberculosis* cell wall, the causative agent of tuberculosis, and are validated targets for the development of antitubercular drugs.[7−10] The presence of several fluorine atoms in close proximity within the scaffold of the inhibitor (e.g., CF_3-CF_2, CF_3 etc.) could likely greatly enhance the affinity of the ligand for the host enzyme.[11−13] Several nucleophilic,[14−17] electrophilic,[18−21] and radical methods for $C-CF_3$ bond formation have been described,[22−24] including a variety of transition-metal-catalyzed[25−27] and photoredox[28,29] approaches that directly form a Csp_2-CF_3 bond. It is noteworthy that the photoredox trifluoromethylation of enol ether or esters to generate α-trifluoromethylated ketones was recently reported.[30−32] However, for the modification of carbohydrates, only one procedure of *endo*-glycal trifluoromethylation is currently available (Figure 1).[33] Moreover, beyond their interest as inhibitor scaffolds and key intermediates in many synthetic applications, we were interested in constructing *exo*-glycals such as **5** because the synthetic method has to work stereoselectively on highly functionalized molecules.

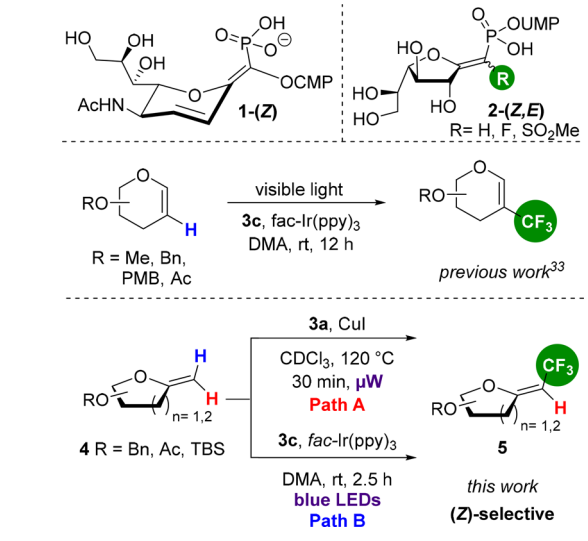


Figure 1. *exo*-Glycals designed as enzyme inhibitors.

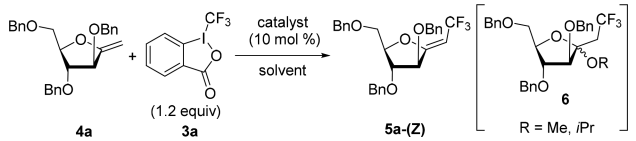
Herein, we describe the synthesis of trifluoromethylated *exo*-glycals via photoredox and copper catalysis, two complementary methods. The stereoselectivity and the scope of this transformation with regard to substrates and reaction conditions will be discussed and the stereoselectivity rationalized by DFT calculations.

We initiated this study by examining the copper-catalyzed trifluoromethylation of the 1-methylidene-2,3,5-tri-*O*-benzyl-D-arabinofuranoside **4a** with Togni reagent **3a** as the CF_3 source based on the methodologies developed by Gouverneur and Sodeoka (Table 1).[34,35] When the reaction was performed in

Received: September 10, 2018
Published: October 12, 2018

DOI: 10.1021/acs.orglett.8b02891
Org. Lett. 2018, 20, 6769−6773

Table 1. Optimization of the Copper-Catalyzed Trifluoromethylation of 4a[a]



entry	catalyst	solvent	time (h)	temp (°C)	yield[b] (%)
1	CuCl[c]	MeOH	1	70	5
2	CuCl[c]	*i*-PrOH	3	70	23
3	CuI	$CDCl_3$	24	60	46
4	CuI	$CDCl_3$	0.5	120[d]	73 (64)[e]
5	CuI	$CDCl_3$	1	120[d]	74
6	CuI	$CHCl_3$	0.5	120[d]	71

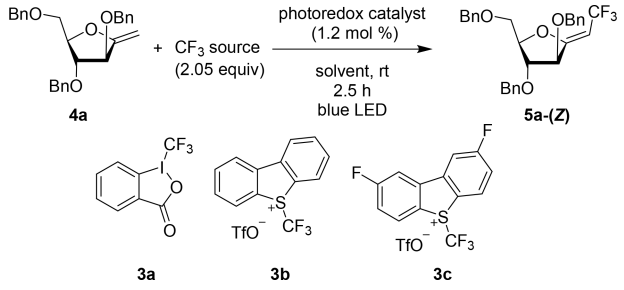
[a]Reaction conditions: **4a** (0.10 mmol), Togni reagent **3a** (1.2 equiv), copper catalyst (10 mol %), solvent (1 mL), argon atmosphere. [b]Yields determined by ^{19}F NMR using hexafluorobenzene as an internal standard. [c]20 mol %. [d]Under microwave irradiations. [e]Isolated yield.

MeOH or *i*-PrOH in the presence of 20 mol % of CuCl, the desired compound **5a-(Z)** was obtained in 5 and 23% yield, respectively (entries 1 and 2). This poor yield can be explained by the generation of adduct **6** resulting from the solvent addition on the anomeric carbon during the reaction. The formation of **6** could be avoided using the conditions developed by Szabó et al.[36] and copper iodide (10 mol %) in deuterated chloroform under microwave irradiation, giving access to trifluoromethylated *exo*-glycal **5a-(Z)** in 64% isolated yield with an excellent *Z*-selectivity (entry 4). Neither the use of nondeuterated chloroform nor the increase in reaction time affected the yield (entries 5 and 6).

Encouraged by these results, we turned our attention to photoredox-catalyzed trifluoromethylation[28,29,33] in order to compare the two methodologies. 1-Methylidene-2,3,5-tri-*O*-benzyl-D-arabinofuranoside **4a** was used as the model substrate to investigate the reaction conditions. Under blue LED irradiation, the influence of several parameters was evaluated: mainly the trifluoromethylating reagent, the solvent, and the catalyst (Table 2). In the presence of Umemoto reagent **3b** in DMF with $[Ru(bpy)_3](PF_6)_2$ as photocatalyst, the product **5a-(Z)** was obtained in 31% yield in 2.5 h (entry 1). The study of the solvent effect showed that the yields were considerably better in highly polar solvents, such as DMSO and DMA (entries 1−8). Then different CF_3 sources, including Togni reagent **3a** and Umemoto reagent **3c**, were investigated. While only traces of **5a-(Z)** were observed when **3a** was employed (entry 10), the use of Umemoto reagent **3c** afforded **5a-(Z)** in 66% (entry 11). Using only 1.5 equiv of reagent **3c** considerably reduced the reactivity (entry 12). The comparison of classical photocalysts revealed that *fac*-$Ir(ppy)_3$ was the best choice to perform this trifluoromethylation (entry 14). Increasing the reaction time (entry 9) or adding a base as additive (entries 15 and 16) did not improve the reaction efficiency. Importantly, the photocatalyst and blue LED irradiation were both crucial for the success of this reaction (entries 17 and 18). Thus, the optimal conditions were as follows: *fac*-$Ir(ppy)_3$ (1.2 mol %), Umemoto reagent **3c** (2.05 equiv) in DMA under blue LED irradiation for 2.5 h at room temperature.

Having established the optimal reaction conditions for the trifluoromethylation via copper and photoredox catalyses

Table 2. Optimization of Trifluoromethylation Reaction via Photoredox Catalysis[a]



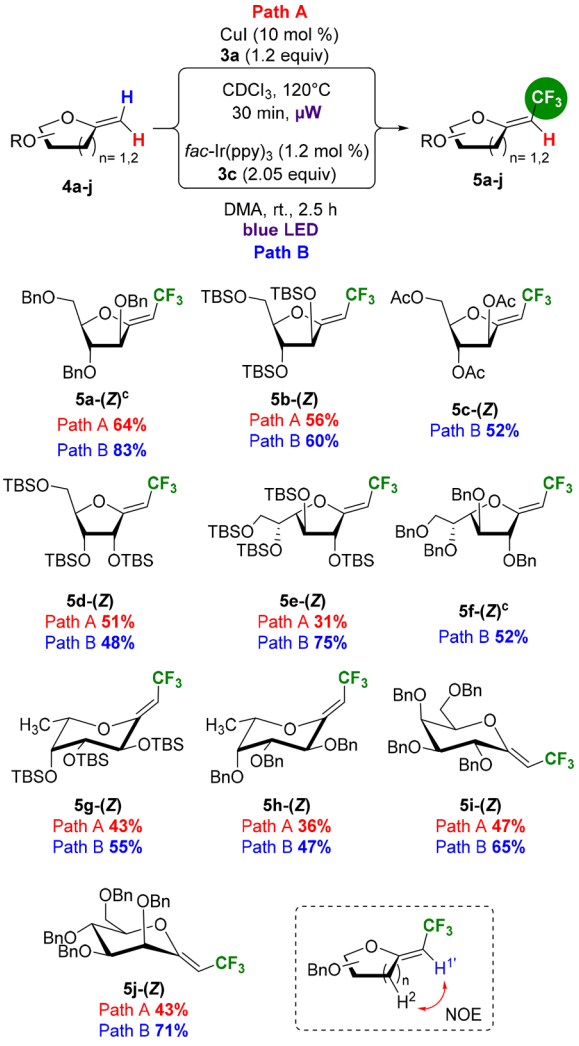
entry	CF_3 source	solvent	additive	catalyst	yield[b] (%)
1	**3b**	DMF		$[Ru(bpy)_3](PF_6)_2$	31
2	**3b**	DCM		$[Ru(bpy)_3](PF_6)_2$	0
3	**3b**	Toluene		$[Ru(bpy)_3](PF_6)_2$	0
4	**3b**	THF		$[Ru(bpy)_3](PF_6)_2$	0
5	**3b**	CH_3CN		$[Ru(bpy)_3](PF_6)_2$	0
6	**3b**	*t*-BuOH		$[Ru(bpy)_3](PF_6)_2$	7
7	**3b**	DMSO		$[Ru(bpy)_3](PF_6)_2$	46
8	**3b**	DMA		$[Ru(bpy)_3](PF_6)_2$	58 (56)[c]
9[d]	**3b**	DMA		$[Ru(bpy)_3](PF_6)_2$	58
10	**3a**	DMA		$[Ru(bpy)_3](PF_6)_2$	2
11	**3c**	DMA		$[Ru(bpy)_3](PF_6)_2$	66
12[e]	**3c**	DMA		$[Ru(bpy)_3](PF_6)_2$	46
13	**3b**	DMA		*fac*-$Ir(ppy)_3$	63
14	**3c**	DMA		*fac*-$Ir(ppy)_3$	86 (83)[c]
15	**3c**	DMA	K_2HPO_4	*fac*-$Ir(ppy)_3$	48
16	**3c**	DMA	DIPEA	*fac*-$Ir(ppy)_3$	23
17	**3c**	DMA			0
18[f]	**3c**	DMA		*fac*-$Ir(ppy)_3$	0

[a]Reaction conditions: **4a** (0.10 mmol), CF_3 source (2.05 equiv), photocatalyst 1.2 mol %), solvent (1 mL), argon atmosphere, Kessil H150-blue LED light source of 34W, 2.5 h. [b]Yields determined by ^{19}F NMR using hexafluorobenzene as an internal standard. [c]Isolated yield. [d]16 h. [e]1.5 equiv of CF_3 source. [f]In the dark.

(paths A and B, Scheme 1), the scope of this transformation was examined with various methylene *exo*-glycals **4**. The starting enol ethers **4a−j** could be easily obtained in 60−75% yield by methylenation of the corresponding lactone using the Petasis reagent.[37,38] The results, gathered in Scheme 1, show that in all cases satisfactory yields were obtained by the two technologies. The two reactions were found to be general as satisfactory and comparable results were obtained with various protective groups on the sugar ring (Ac, TBS, or Bn) and different ring sizes (furanoses and pyranoses). However, in most cases photoredox catalysis was found to be more efficient, likely because of the milder reaction conditions required, as compared to the Cu-catalyzed trifluoromethylations. Indeed, the latter reaction was carried out in chloroform at 120 °C under microwave irradiation, inducing probably a partial degradation of the enol ethers **4**. However, the effect of the

DOI: 10.1021/acs.orglett.8b02891
Org. Lett. 2018, 20, 6769−6773

Scheme 1. Substrate Scope of the Trifluoromethylation of Several *exo*-Glycals[a,b]

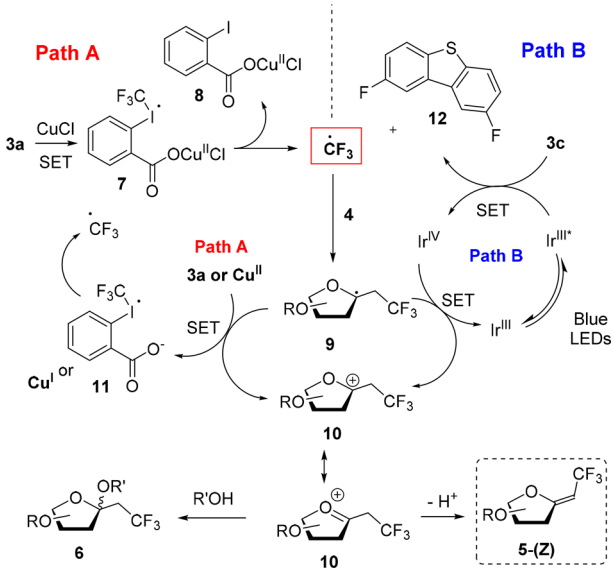


[a]Reaction conditions: **4a** (1 equiv), CF_3 source (2.05 equiv), photocatalyst 1.2 mol %), solvent (1 mL), under argon atmosphere, Kessil H150-blue LED light source of 34W, 2.5 h. [b]Isolated yield. [c]Bis-trifluoromethylation observed.

ligands of the Copper catalyst have not been investigated, which could lead to milder conditions being found. Very interestingly, the two reactions were found to be highly diastereoselective since, for all screened carbohydrates (**4a**−**j**), the sole isolated diastereomer always displays a *Z* configuration. Structural proof of all products (**5a**−**j**) has been accomplished by 1D homonuclear NOE analyses that systematically showed a NOE effect between the H-2 proton of the carbohydrate ring and the *exo*-methylene proton H-1′ (Scheme 1).

On the basis of these results and related studies,[33,34] a plausible mechanism is proposed in Scheme 2. For path A (copper catalysis), it is reasonable to invoke that Togni reagent **3a** is activated by CuCl via single-electron transfer generating **7**. The CF_3 radical is then released and can react with **4** to give **9**, which is oxidized by a Cu^{II} species or **3a** to generate **10**. Deprotonation of **10** leads to **5**-(**Z**), whereas in the presence of a nucleophile (for instance, ROH, see Table 1), the addition on the carbocationic species is observed. For path B (photoredox catalysis), the blue LED irradiation transforms

Scheme 2. Hypothetical Mechanism of the Trifluoromethylation via Copper (Path A) and Photoredox Catalysis (Path B)



fac-$Ir^{III}(ppy)_3$ into its excited state, *fac*-$Ir^{III}(ppy)_3$*, which reacts with the Umemoto reagent **3c** to afford the CF_3 radical. Subsequent addition of this species on **4** forms the compound **9**, which is oxidized by *fac*-$Ir^{IV}(ppy)_3$ to produce oxocarbenium **10**. In 2014, Qing et al. reported a stereoselective trifluoromethylation of styrenes using the ability of excited photocatalysts to take part in single-electron transfers as well as in triplet−triplet energy transfers (TTETs).[39] Such TTETs might also contribute to the stereoselectivity observed in our study.

As previously mentioned, both methods afford the desired compounds **5** with a high *Z*-stereoselectivity. In order to obtain a clear understanding of the origin of this high stereoselectivity, we set up a computational study. Calculations were carried out at the B3LYP-D3/6-311+G**//B3LYP-D3/6-31+G* level of theory, including a continuum description of THF as the solvent (see the SI for computational details). We have first explored the relative energy of *E* and *Z* isomers of the model *exo*-glycals **5k** and **5l** (Figure 2). The obtained results indicate that the *Z* *exo*-glycal **5k** is more stable than its *E* isomer by 1.1 kcal/mol.

Interestingly, the alkoxy group plays a determinant role in this thermodynamic selectivity as shown by the results on *exo*-glycal **5l**, missing the alkoxy group, for which the *E* isomer is now the most stable one (by 1.5 kcal/mol).

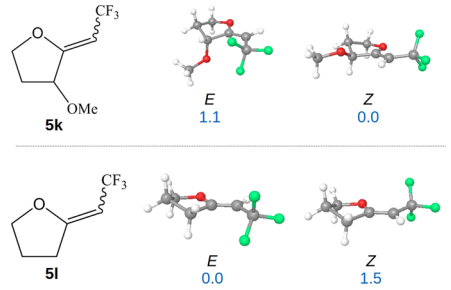


Figure 2. Computed relative energy (kcal/mol) of model *exo*-glycals.

DOI: 10.1021/acs.orglett.8b02891
Org. Lett. 2018, 20, 6769−6773

The observed stereoselectivity may thus be the result of a thermodynamic equilibrium favoring the most stable *Z* isomer. However, the stereoselectivity of trifluoromethylated *exo*-glycal formation may also be determined along the reaction pathway (kinetic selectivity). Accordingly, we performed a conformational analysis of the oxonium intermediates **10k** and **10l**. Indeed, according to our postulated mechanism (see Scheme 2), the selectivity-determining step in the formation of **5** could be the last step, the deprotonation of the oxonium intermediates **10**. Such an elimination requires that the C3−H bond which is broken is parallel to the empty p orbital on C2 (Figure 3) for stereoelectronic reasons. The computed

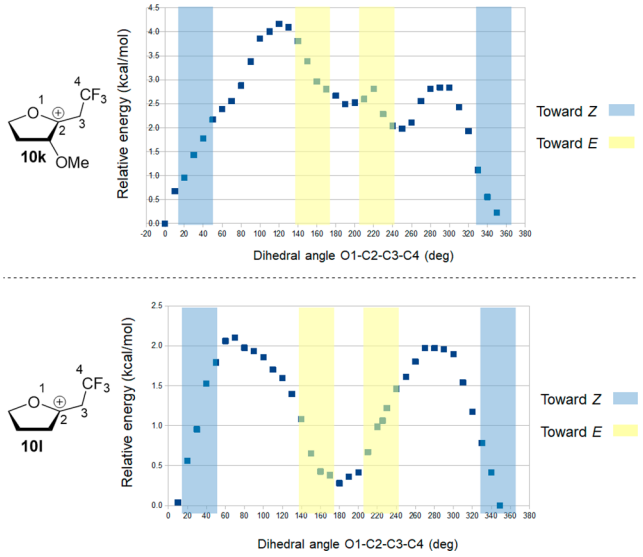


Figure 3. Conformational analysis of **10k,l**.

conformational profile of **10k** shows that the lower lying conformers present the trifluoromethyl group on the same side as the endocyclic oxygen atom (O1−C2−C3−C4 dihedral angle close to 0 deg), i.e., those which will lead to the *Z exo*-glycal after deprotonation and formation of the double bond. A high *Z* kinetic selectivity is thus predicted for **5k**. It is interesting to note that, here again, the alkoxy group plays an important role in determining selectivity since in absence of an alkoxy group at the 2-position **10l** no or a very low selectivity is predicted. Indeed, in the latter case, the conformers leading to *E* and *Z exo*-glycal are almost isoenergetic (<0.5 kcal/mol difference).

Thus, our calculations indicate that the *Z* isomer of **5** is the most favored product from both a thermodynamic and a kinetic point of view. A detailed electronic and structural analysis of *exo*-glycals **5k,l** and oxonium ions **10k,l** (see the SI for full results) reveals that this can be accounted for by the stabilization of the *Z* isomer/conformer by hydrogen-bonding interactions between the olefinic hydrogen atom and the oxygen atom of the ether substituent. Furthermore, the *E* isomer/conformer is destabilized by steric interactions between the CF_3 and the ether substituent, despite dipole−dipole interactions which favor the *E* isomer/conformer as compared to the *Z* one (Figure 4).[40]

In conclusion, we have developed two complementary strategies to synthesize trifluoromethylated *exo*-glycals. The scope and limitations of these reactions have been analyzed on various unsubstituted *exo*-glycals generated from the corresponding pyranoses and furanoses. The photoredox catalysis is in general more efficient due to the milder conditions used compared to the Cu-catalyzed reaction. Both methods afford the desired compounds in moderate yield but with high *Z*-stereoselectivity, which could be rationalized by computational studies. Further studies are still required to answer to the challenging question of generating, in a stereoselective manner and high yield, tetrasubstituted CF_3-containing enol ethers and other ethylenic compounds. Work is in progress in our laboratories to answer this important question.

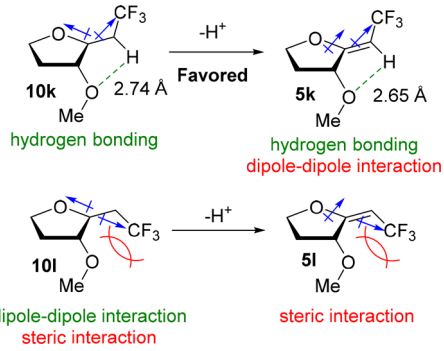


Figure 4. Rationale for observed *Z* selectivity with stabilizing (green) and destabilizing (red) interactions (dipoles were obtained at the B3LYP-D3/6-31+G* level of theory, and hydrogen bond interactions were analyzed using NCI plot[41] (see the Supporting Information for details)).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02891.

Experimental procedures and NMR spectra as well as computational details (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*Fax: (+32)81-72-45-17. E-mail: stephane.vincent@unamur.be

ORCID

Raphaël Robiette: 0000-0002-3449-565X

Stéphane P. Vincent: 0000-0001-6258-9058

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was funded by the F.R.S.-FNRS (Mandat de Chargé de recherche to A.T. and FRFC Nrant No. 2.4.625.08.F and F.R.I.A. fellowship to C.J.-M.F.). R.R. is a Maître de recherches of the F.R.S.-FNRS. Computational resources have been provided by the Université catholique de Louvain (CISM/UCL) and the Fédération Wallonie Bruxelles (CECI) funded by the F.R.S.-FNRS under Convention No. 2.5020.11.

■ REFERENCES

(1) Müller, B.; Schaub, C.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **1998**, *37*, 2893.

(2) Lin, C.-H.; Lin, H.-C.; Yang, W.-B. *Curr. Top. Med. Chem.* **2005**, *5*, 1431.

(3) Caravano, A.; Vincent, S. P. *Eur. J. Org. Chem.* **2009**, *2009*, 1771.

DOI: 10.1021/acs.orglett.8b02891
Org. Lett. 2018, 20, 6769−6773

(4) Caravano, A.; Dohi, H.; Sinaÿ, P.; Vincent, S. P. *Chem. - Eur. J.* **2006**, *12*, 3114.
(5) Caravano, A.; Vincent, S. P.; Sinay, P. *Chem. Commun.* **2004**, 1216.
(6) Frédéric, C. J.; Tikad, A.; Fu, J.; Pan, W.; Zheng, R. B.; Koizumi, A.; Xue, X.; Lowary, T. L.; Vincent, S. P. *Chem. - Eur. J.* **2016**, *22*, 15913.
(7) Mikušová, K.; Yagi, T.; Stern, R.; McNeil, M. R.; Besra, G. S.; Crick, D. C.; Brennan, P. J. *J. Biol. Chem.* **2000**, *275*, 33890.
(8) Kremer, L.; Dover, L. G.; Morehouse, C.; Hitchin, P.; Everett, M.; Morris, H. R.; Dell, A.; Brennan, P. J.; McNeil, M. R.; Flaherty, C.; Duncan, K.; Besra, G. S. *J. Biol. Chem.* **2001**, *276*, 26430.
(9) Crick, D. C.; Mahapatra, S.; Brennan, P. J. *Glycobiology* **2001**, *11*, 107R.
(10) Peltier, P.; Belanova, M.; Dianiskova, P.; Zhou, R.; Zheng, R. B.; Pearcey, J. A.; Joe, M.; Brennan, P. J.; Nugier-Chauvin, C.; Ferrieres, V.; Lowary, T. L.; Daniellou, R.; Mikušová, K. *Chem. Biol.* **2010**, *17*, 1356.
(11) Biffinger, J. C.; Kim, H. W.; DiMagno, S. G. *ChemBioChem* **2004**, *5*, 622.
(12) N'Go, I.; Golten, S.; Ardá, A.; Cañada, J.; Jiménez-Barbero, J.; Linclau, B.; Vincent, S. P. *Chem. - Eur. J.* **2014**, *20*, 106.
(13) van Straaten, K. E.; Kuttiyatveetil, J. R. A.; Sevrain, C. M.; Villaume, S. A.; Jimenez-Barbero, J.; Linclau, B.; Vincent, S. P.; Sanders, D. A. R. *J. Am. Chem. Soc.* **2015**, *137*, 1230.
(14) Ruppert, I.; Schlich, K.; Volbach, W. *Tetrahedron Lett.* **1984**, *25*, 2195.
(15) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393.
(16) Prakash, G. K. S.; Mandal, M. *J. Fluorine Chem.* **2001**, *112*, 123.
(17) Shono, T.; Ishifune, M.; Okada, T.; Kashimura, S. *J. Org. Chem.* **1991**, *56*, 2.
(18) Shibata, N.; Matsnev, A.; Cahard, D. *Beilstein J. Org. Chem.* **2010**, *6*, 65.
(19) Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757.
(20) Eisenberger, P.; Gischig, S.; Togni, A. *Chem. - Eur. J.* **2006**, *12*, 2579.
(21) Eisenberger, P.; Kieltsch, I.; Armanino, N.; Togni, A. *Chem. Commun.* **2008**, 1575.
(22) Besset, T.; Cahard, D.; Pannecoucke, X. *J. Org. Chem.* **2014**, *79*, 413.
(23) Merino, E.; Nevado, C. *Chem. Soc. Rev.* **2014**, *43*, 6598.
(24) Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950.
(25) Parsons, A. T.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 9120.
(26) Koike, T.; Akita, M. *J. Fluorine Chem.* **2014**, *167*, 30.
(27) Barata-Vallejo, S.; Lantaño, B.; Postigo, A. *Chem. - Eur. J.* **2014**, *20*, 16806.
(28) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224.
(29) Carboni, A.; Dagousset, G.; Magnier, E.; Masson, G. *Org. Lett.* **2014**, *16*, 1240.
(30) Jiang, H.; Cheng, Y.; Zhang, Y.; Yu, S. *Eur. J. Org. Chem.* **2013**, *2013*, 5485.
(31) Cantillo, D.; de Frutos, O.; Rincón, J. A.; Mateos, C.; Kappe, C. O. *Org. Lett.* **2014**, *16*, 896.
(32) Thomoson, C. S.; Dolbier, W. R. *J. Fluorine Chem.* **2015**, *178*, 327.
(33) Wang, B.; Xiong, D.-C.; Ye, X.-S. *Org. Lett.* **2015**, *17*, 5698.
(34) Mizuta, S.; Galicia-López, O.; Engle, K. M.; Verhoog, S.; Wheelhouse, K.; Rassias, G.; Gouverneur, V. *Chem. - Eur. J.* **2012**, *18*, 8583.
(35) Shimizu, R.; Egami, H.; Hamashima, Y.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4577.
(36) Janson, P. G.; Ghoneim, I.; Ilchenko, N. O.; Szabó, K. J. *Org. Lett.* **2012**, *14*, 2882.
(37) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.
(38) Singh, J.; Ghosh, S.; Deb, M.; Elias, A. *J. Organomet. Chem.* **2016**, *818*, 85.
(39) Lin, Q.-Y.; Xu, X.-H.; Qing, F.-L. *J. Org. Chem.* **2014**, *79*, 10434.
(40) For other studies where dipole−dipole interactions are postulated to be important for determining reactivity in carbohydrate chemistry, see: (a) Hale, K. J.; Hough, L.; Manaviazar, S.; Calabrese, A. *Org. Lett.* **2014**, *16*, 4838. (b) Hale, K. J.; Hough, L.; Manaviazar, S.; Calabrese, A. *Org. Lett.* **2015**, *17*, 1738.
(41) Johnson, E. R.; Keinan, S.; Mori-Sánchez, P.; Contreras-García, J.; Cohen, A. J.; Yang, W. *J. Am. Chem. Soc.* **2010**, *132*, 6498.

DOI: 10.1021/acs.orglett.8b02891
Org. Lett. 2018, 20, 6769−6773