OL | Organic Letters

pubs.acs.org/OrgLett Letter

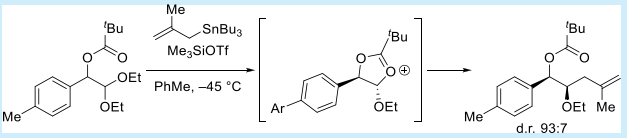
Using Neighboring-Group Participation for Acyclic Stereocontrol in Diastereoselective Substitution Reactions of Acetals

Amanda Ramdular and K. A. Woerpel*

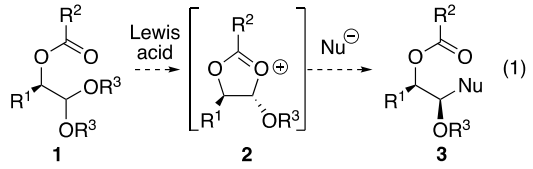
Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01166 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Neighboring-group participation of an ester enabled stereocontrol in substitution reactions of acyclic acetals. The ester group formed a *trans*-fused dioxolenium ion intermediate, which underwent a substitution reaction at the acetal carbon atom to afford the product with high diastereoselectivity. Neighboring-group participation was confirmed by isolating dioxolane products resulting from nucleophilic addition at C-2 of a 1,3-dioxolenium ion intermediate. Using a pivaloate ester as the participating group in combination with strong nucleophiles produced substitution products with diastereoselectivities of ≥90:10.



Neighboring-group participation is a widely used approach to control stereochemistry in substitution reactions of carbohydrate compounds.[1−3] Most commonly, acyloxy groups, namely, the acetate, benzoate, and pivaloate esters,[1,4,5] are used to favor the 1,2-*trans* products with high selectivity.[1,4,6] Neighboring-group participation has not emerged as a useful approach for controlling stereochemistry in reactions involving acyclic acetals, however.[7−18] The use of neighboring-group participation to control stereochemistry in acyclic systems, as illustrated in eq 1, would be significant because it would

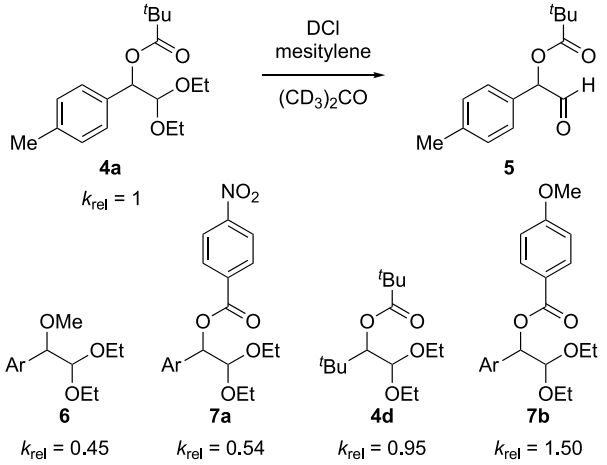


provide access to the products expected from nucleophilic additions to α-alkoxy aldehydes that would be governed by the Felkin−Anh or related[19−21] stereochemical models. Such transformations, however, often give products with modest diastereoselectivity.[8,16,22−24]

In this paper, we demonstrate that neighboring-group participation of an ester group adjacent to an acetal can provide high diastereoselectivity in substitution reactions. These reactions likely proceed through five-membered ring intermediates, such as **2**, which then undergo nucleophilic ring opening to provide the 1,2-*syn* products **3** (eq 1).

The rates of hydrolysis of acyclic acetals indicated that an acyloxy group near an acetal can influence the rate of ionization by neighboring-group participation, as observed for cyclic acetals.[25] The rates of hydrolysis of acetals **4a**, **4d**, **7a**, and **7b** bearing α-acyloxy groups were accelerated compared to the ionization of an acetal with an α-methoxy group, **6** (Scheme 1). This acceleration likely reflects stabilization of the developing positive charge by neighboring-group participation,

Scheme 1. Rates of Hydrolysis of Acetals with Different Neighboring Groups



considering that the magnitude of the acceleration is similar to that observed for carbohydrates.[5,26] As the donating ability of the acyl group increased,[5] the rate of ionization increased, which is consistent with participation of the carbonyl group (eq 1). The similar rates of hydrolysis of acetals bearing alkyl and aryl groups (i.e., **4a** and **4d**) indicate that the generation of the cationic intermediates in these reactions is dominated by the donation of electrons from the acyloxy group.[1,27] This observation contrasts with those of studies of β-phenyl-

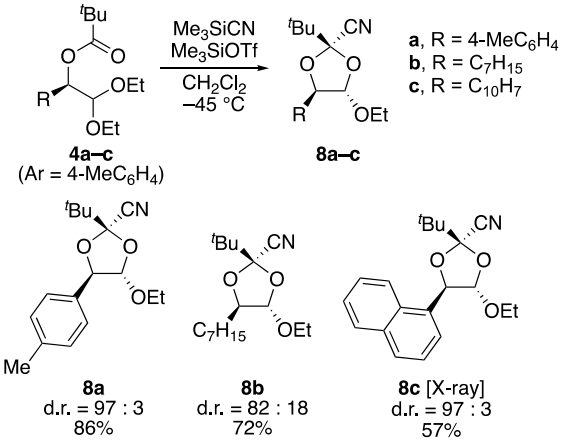
Received: April 1, 2020

https://dx.doi.org/10.1021/acs.orglett.0c01166
Org. Lett. XXXX, XXX, XXX−XXX

substituted acetals, where the phenyl group inductively destabilized the cationic intermediate, leading to a >20-fold slower ionization compared to an acetal without a phenyl group.[28]

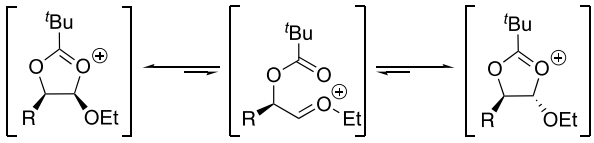
More direct evidence supporting the participation of the acyloxy group was obtained upon treatment of pivaloate esters **4a–c** with Me_3SiCN in the presence of a Lewis acid (Scheme 2).[29] The formation of dioxolane products **8a–c** represents an

Scheme 2. Reactions of Pivaloate Esters to Give Dioxolane Products



unusual case of nucleophilic addition at the participating pivaloyl group, which is generally sterically disfavored.[1,4,5,30,31] Dioxolane-substituted products **8a** and **8c** were obtained as 97:3 mixtures of diastereomers (Scheme 2).[25] The relative stereochemical configurations of these compounds were assigned by NOE measurements, and the structure of **8c** was confirmed by X-ray crystallography. These experiments reveal that the dioxolane favors a 1,2-*trans* relationship between the ethoxy and aryl groups (i.e., **11** in Scheme 3), likely because

Scheme 3. Equilibrium of Oxocarbenium and Dioxolenium Ions

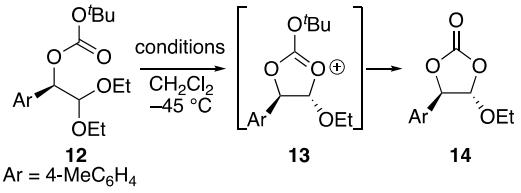


these groups would be eclipsed in the essentially planar five-membered ring intermediate in the *cis* isomer (**9**).[32] The stereochemical configuration at the nitrile-bearing carbon atom results from preferential nucleophilic attack on the major dioxolenium ion **11** from the more accessible face. Substitution reactions of acetal **4b** with Me_3SiCN, however, showed a decrease in diastereoselectivity of the dioxolane product (Scheme 2). The amount of the *trans* diastereomer of dioxolenium ion **11** (Scheme 3) with the smaller substituent decreases likely because the unfavorable eclipsing interactions are not as prominent between the alkyl and ethoxy groups.

The high diastereoselectivities observed for the formation of dioxolanes **8a** and **8c** (Scheme 2) suggest that formation of dioxolenium ion **11** (Scheme 3) is reversible. If this ionization step were not reversible, the Lewis acid would need to differentiate between the two diastereotopic ethoxy groups, which is unlikely.[33] This reversibility would require that the acyclic oxocarbenium ion **10** not be too high in energy compared to dioxolenium ions **9** and **11** (Scheme 3).[2,3,34,35]

Experiments with an acetal bearing a *tert*-butyl carbonate group provided additional evidence that a dioxolenium ion was an intermediate in these reactions.[36] Upon treatment of carbonate **12** with a Lewis acid or SiO_2 gel, cyclic carbonate **14** was formed (Table 1), likely upon release of the *tert*-butyl

Table 1. Formation of Cyclic Carbonate



acid	nucleophile	dr (*anti*:*syn*)	% yield
Me_3SiOTf	none	96:4	71
SiO_2	none	76:24	39
Me_3SiOTf	$H_2C{=}CHCH_2SnBu_3$	76:24	9[a]

[a]The low yield resulted from difficulty in purifying the product.

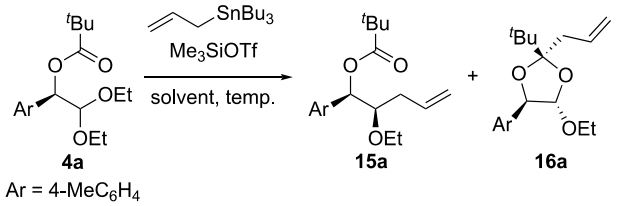
cation from dioxolenium ion **13**.[36] These products were prone to epimerization upon purification using SiO_2, so the diastereoselectivities are likely not representative of the kinetic products of cyclization.

With the demonstration that neighboring-group participation was possible with acyclic acetals, attention turned to the development of the ring opening of dioxolenium ions with carbon nucleophiles. The successful formation of acetal substitution products using allyltributylstannane as the nucleophile depended upon the reaction conditions. Substitutions of acetal **4a** bearing the pivaloyl protecting group using numerous Lewis acids were unsuccessful, likely because of the strongly electron-withdrawing nature of the acetoxy group.[5,26] The Lewis acids $BF_3{\cdot}OEt_2$, $SiCl_4$, $SnCl_4$, and Et_3SiOTf activated the acetal group, but only at temperatures above −40 °C. The use of Me_3SiOTf proved to be most successful, although $TiCl_4$ and $Bi(OTf)_3$ could also be used to form the desired products at low temperatures. The fact that the presence of the triflate ion was not necessary for high selectivity argues against a covalently bound triflate species as a reactive intermediate. These reactions provided both the desired product **15a** and the undesired dioxolane **16a**. With the more polar solvents MeCN and EtCN, significant quantities of undesired dioxolane product **16a** were formed (Table 2).[37,38] The major diastereomer of acyclic substitution product **15a** in the nitrile solvents was the same as for reactions with CH_2Cl_2 as the solvent, which indicates that there is no special influence of the nitrile solvent.[39−41] The nonpolar solvent toluene gave the highest proportion of desired acyclic product **15a** (Table 2). This observation is consistent with studies of product distributions as a function of solvent for carbohydrates with neighboring acyloxy groups.[37] Lower concentrations (0.1 M), which favor neighboring-group participation in reactions of carbohydrates,[42] gave the highest stereoselectivities. At temperatures below −45 °C, it is likely that ionization was too slow (Table 2).[43,44]

A control experiment indicated the importance of neighboring-group participation for obtaining the products with high diastereoselectivity. The substitution reaction of

https://dx.doi.org/10.1021/acs.orglett.0c01166
Org. Lett. XXXX, XXX, XXX−XXX

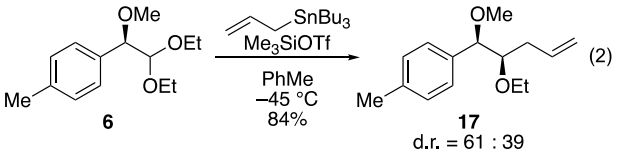
Table 2. Optimization of Reaction Conditions



solvent	polarity (E_T)	temp (°C)	15a:16a	dr (15a)	% yield (15a)
MeCN	46	−40	47:53	75:25	39
EtCN	43.7	−78	49:51	80:20	36
CH_2Cl_2	41	−45	70:30	90:10	53
CH_2Cl_2	41	−78	68:32	90:10	61
MePh	**33.9**	**−45**	**95:5**	**90:10**	**82**
MePh	33.9	−78	>99:1[a]	82:18	29

[a]Reaction proceeded to 30% completion.

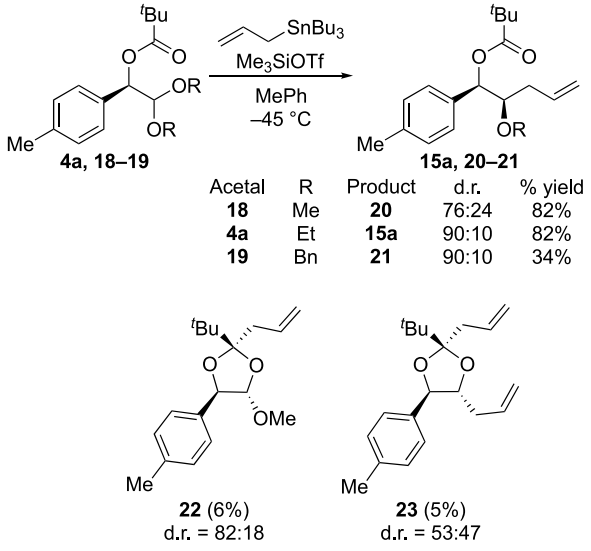
acetal **6** (eq 2) afforded the substitution product with no selectivity. This result confirms that reactions through an open



transition state resembling the Felkin−Anh transition state will not be stereoselective.

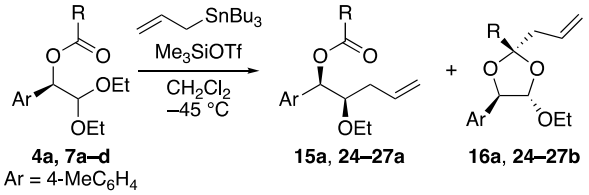
Substitution reactions of pivaloyl-substituted acetals **4a**, **18**, and **19** with different alkoxy groups (Scheme 4) under the optimized conditions provided additional support that these reactions involve equilibration of dioxolenium ions **9** and **11** and acyclic oxocarbenium ion **10** (Scheme 3). Substitution reactions of methyl acetal **18** gave small quantities of two dioxolane products, **22** and **23**. Benzyl acetal **19** reacted with the highest diastereoselectivity, but the yields were lower because this acetal was particularly prone to decomposition. The observation that increasing the size of the alkoxy groups of the acetal increased the diastereoselectivity of the products is consistent with the expected steric differences between dioxolenium ions **9** and **11**. The fact that ethyl acetal **4a** reacted with a diastereoselectivity [90:10 (Scheme 4)] lower than that observed for the reaction with Me_3SiCN [97:3 (Scheme 2)] confirms that an equilibrium is established with dioxolenium ions **9** and **11** and acyclic oxocarbenium ion **10** (Scheme 3). Formation of both isomers of the product requires that both *cis*- and *trans*-substituted dioxolenium ions **9** and **11** are present (Scheme 3) and that the product ratio reflects different rates of reaction of these intermediates with nucleophiles.

Scheme 4. Influence of the Size of the Alkoxy Group on Selectivity



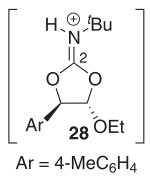
The ability of a carbonyl group to participate exerted a strong influence on the outcomes of these substitution reactions.[5,26] For the ester participating groups, increasing the donating ability of the participating group, as defined by the kinetic studies (Scheme 1), resulted in an increased level of formation of the undesired dioxolane regioisomer [acetal **7b** (Table 3)]. It is likely that the dioxolenium ion is more stabilized by the strong participating group, so the nucleophile cannot readily open it to form the acyclic product. By contrast, reactions of carbamate **7d** did not give products derived from attack at C-2 of dioxolenium ion **28**, likely because it is too stabilized.[26]

Table 3. Influence of Neighboring Groups on Selectivity



acetal	R	major product	ester:dioxolane	dr (ester)	% yield (ester)
7a	$4\text{-}O_2NC_6H_4$	**24a**	>99:1	78:22	43
4a	tBu	**15a**	70:30	90:10	53
7c	C_6H_5	**25a**	79:21	85:15	54
7b	$4\text{-}MeOC_6H_4$	**26b**	<1:99	–	72[a]
7d	NHtBu	**27a**	>99:1	78:22	88

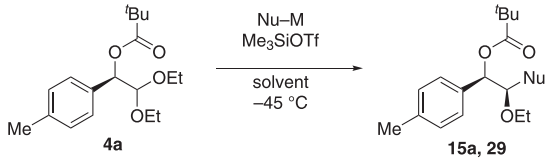
[a]Yield of dioxolane product **26b**.



The stabilizing influence of the acyloxy group is reflected in both the reactivity and stereoselectivity of these reactions. Attempted substitution reactions with nucleophiles that are weaker than allyltributylstannane,[43] such as allyltrimethylsilane and methallyltrimethylsilane, did not occur in PhMe. These reactions did proceed in CH_2Cl_2, however, producing the substitution products with little stereoselectivity (Table 4). These results can be understood by postulating an increased concentration of oxocarbenium ion **10** compared to that of dioxolenium ion **11** in the more polar solvent (Scheme 5). This change in concentration would result because oxocarbenium ions, which have a higher charge density, would be more favored in the polar medium. In the more polar solvent, oxocarbenium ion **10**, although formed in only small amounts,

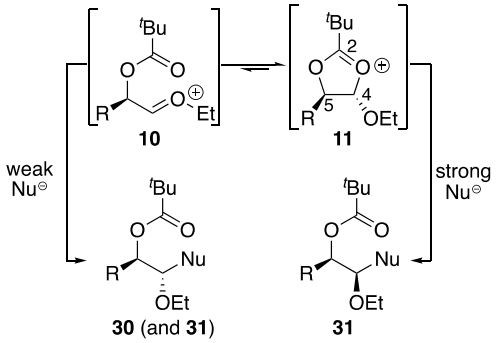
https://dx.doi.org/10.1021/acs.orglett.0c01166
Org. Lett. XXXX, XXX, XXX−XXX

Table 4. Influence of the Nucleophile and Solvent on Reactivity



Nu–M	*N* factor[43]	solvent	product	dr	% yield
$H_2C{=}C(Me)CH_2SnBu_3$	7.48	MePh	**29**	93:7	45
$H_2C{=}CHCH_2SnBu_3$	5.46	MePh	**15a**	90:10	82
$H_2C{=}C(Me)CH_2SiMe_3$	4.41	CH_2Cl_2	**29**	70:30	89
$H_2C{=}CHCH_2SiMe_3$	1.68	CH_2Cl_2	**15a**	54:46	87

Scheme 5. Nucleophiles React by Different Pathways

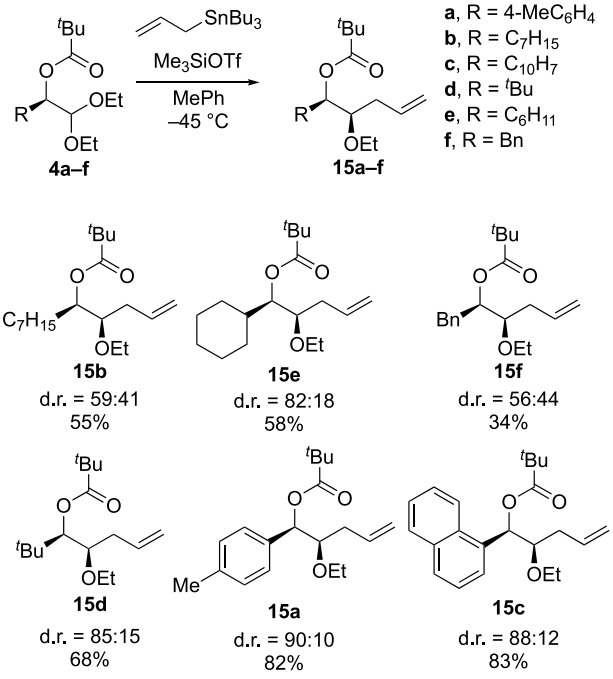


would be electrophilic enough to react with the allylic silane nucleophiles. Considering that these reactions would proceed through open carbocations, it is reasonable that they would react with diastereoselectivities comparable to that of the reaction of the methyl ether **6a** (eq 2).[35] By contrast, reactions with a stronger nucleophile, methallyltrimethylstannane,[43] occurred with higher diastereoselectivity (Table 4). The increased diastereoselectivity observed with an increase in the nucleophilicity of the nucleophile suggests that this reaction proceeds through the stabilized intermediate **11** (Scheme 5).[45]

The scope of the reaction demonstrates that the general features of the substitution reaction hold for other substrates. Substitution reactions of acetals **4a–f** showed that increasing the steric demand of the side chain in comparison to that of the alkoxy group increased the diastereoselectivity of the reaction (Scheme 6). This correlation of steric size and reactivity could reflect a lower preference for the *trans* diastereomer of the dioxolenium ion with smaller substituents. Useful levels of stereochemical control can be achieved provided that the substituent is branched. The similar diastereomeric ratios of **15a** and **15d**, which have side chains of similar size, suggest that steric effects of the side chain influence stereoselectivity more so than electronic effects, a finding that is supported by the kinetic data (Scheme 1). The reaction of optically pure α-pivaloyloxy acetal **4f** (Scheme 6), which was readily prepared by enzymatic kinetic resolution,[46] demonstrates that this reaction can be used to prepare enantiomerically enriched products.[12,15]

In summary, neighboring-group participation to control the diastereoselectivity of acetal substitution reactions can be extended from carbohydrates to encompass acyclic acetals.

Scheme 6. Influence of Side Chain on Selectivity



This reaction provides a highly stereoselective alternative route for preparing products expected from Felkin–Anh additions to carbonyl compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01166.

Experimental procedures, characterization of new compounds, stereochemical proofs, kinetic data, X-ray data, and ^1H and ^{13}C NMR spectra of new compounds (PDF)

Accession Codes

CCDC 1987988 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

K. A. Woerpel − *Department of Chemistry, New York University, New York, New York 10003, United States;* orcid.org/0000-0002-8515-0301; Email: kwoerpel@nyu.edu

Author

Amanda Ramdular − *Department of Chemistry, New York University, New York, New York 10003, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01166

Notes

The authors declare no competing financial interest.

https://dx.doi.org/10.1021/acs.orglett.0c01166
Org. Lett. XXXX, XXX, XXX−XXX

■ ACKNOWLEDGMENTS

This research was supported by the National Institutes of Health (NIH), National Institute of General Medical Sciences (1R01GM129286). The authors acknowledge New York University's Shared Instrumentation Facility and the support provided by National Science Foundation Grant CHE-01162222 and NIH Grant S10-OD016343. The authors thank Dr. Chin Lin (New York University) and Dr. Chunhua (Tony) Hu (New York University) for their help with NMR and X-ray data, respectively.

■ REFERENCES

(1) Williams, R. J.; McGill, N. W.; White, J. M.; Williams, S. J. *J. Carbohydr. Chem.* **2010**, *29*, 236.
(2) Bérces, A.; Enright, G.; Nukada, T.; Whitfield, D. M. *J. Am. Chem. Soc.* **2001**, *123*, 5460.
(3) Nukada, T.; Berces, A.; Zgierski, M. Z.; Whitfield, D. M. *J. Am. Chem. Soc.* **1998**, *120*, 13291.
(4) Hernán-Gómez, A.; Orr, S. A.; Uzelac, M.; Kennedy, A. R.; Barroso, S.; Jusseau, X.; Lemaire, S.; Farina, V.; Hevia, E. *Angew. Chem., Int. Ed.* **2018**, *57*, 10630.
(5) Farrell, M. P.; Doyle, L. M.; Murphy, P. V. *Tetrahedron Lett.* **2018**, *59*, 2726.
(6) Nigudkar, S. S.; Demchenko, A. V. *Chem. Sci.* **2015**, *6*, 2687.
(7) Kudo, K.; Hashimoto, Y.; Sukegawa, M.; Hasegawa, M.; Saigo, K. *J. Org. Chem.* **1993**, *58*, 579.
(8) Prévost, M.; Dostie, S.; Waltz, M.-E.; Guindon, Y. *J. Org. Chem.* **2014**, *79*, 10504.
(9) Saniger, E.; Campos, J. M.; Entrena, A.; Marchal, J. A.; Boulaiz, H.; Aránega, A.; Gallo, M. Á.; Espinosa, A. *Tetrahedron* **2003**, *59*, 8017.
(10) Fujioka, H.; Matsumoto, N.; Ohta, R.; Yamakawa, M.; Shimizu, N.; Kimura, T.; Murai, K. *Tetrahedron Lett.* **2015**, *56*, 2656.
(11) Mori, I.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 5966.
(12) Chapdelaine, D.; Cardinal-David, B.; Prévost, M.; Gagnon, M.; Thumin, I.; Guindon, Y. *J. Am. Chem. Soc.* **2009**, *131*, 17242.
(13) Graham, M. A.; Wadsworth, A. H.; Zahid, A.; Rayner, C. M. *Org. Biomol. Chem.* **2003**, *1*, 834.
(14) Guindon, Y.; Gagnon, M.; Thumin, I.; Chapdelaine, D.; Jung, G.; Guérin, B. *Org. Lett.* **2002**, *4*, 241.
(15) Gómez, J. A.; Trujillo, M. A.; Campos, J.; Gallo, M. A.; Espinosa, A. *Tetrahedron* **1998**, *54*, 13295.
(16) Kunz, T.; Janowitz, A.; Reißig, H.-U. *Chem. Ber.* **1989**, *122*, 2165.
(17) Molander, G. A.; Haar, J. P. *J. Am. Chem. Soc.* **1993**, *115*, 40.
(18) Hashimoto, Y.; Sato, Y.; Kudo, K.; Saigo, K. *Tetrahedron Lett.* **1993**, *34*, 7623.
(19) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.
(20) Evans, D. A.; Cee, V. J.; Siska, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 9433.
(21) Evans, D. A.; Siska, S. J.; Cee, V. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1761.
(22) Hosokawa, S. *Acc. Chem. Res.* **2018**, *51*, 1301.
(23) Rosenberg, R. E.; Kelly, W. J. *J. Phys. Org. Chem.* **2015**, *28*, 47.
(24) Borg, T.; Danielsson, J.; Mohiti, M.; Restorp, P.; Somfai, P. *Adv. Synth. Catal.* **2011**, *353*, 2022.
(25) Ethyl acetals were used because higher diastereomeric ratios and fewer side reactions were observed in substitution reactions of these compounds.
(26) Heuckendorff, M.; Pedersen, C. M.; Bols, M. *Org. Lett.* **2011**, *13*, 5956.
(27) Brown, H. C.; Ichikawa, K. *J. Am. Chem. Soc.* **1962**, *84*, 373.
(28) Kreevoy, M. M.; Taft, R. W. *J. Am. Chem. Soc.* **1955**, *77*, 5590.
(29) Chan, W. C.; Koide, K. *Org. Lett.* **2018**, *20*, 7798.
(30) Fraser-Reid, B.; Grimme, S.; Piacenza, M.; Mach, M.; Schlueter, U. *Chem. - Eur. J.* **2003**, *9*, 4687.
(31) Cainelli, G.; Giacomini, D.; Treré, A.; Galletti, P. *Tetrahedron: Asymmetry* **1995**, *6*, 1593.
(32) Paulsen, H.; Schüttpelz, E. *Chem. Ber.* **1979**, *112*, 3214.
(33) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1994**, *116*, 7915.
(34) Computational studies conducted using density functional methods (B3LYP/6-31G*) determined that the *trans* dioxolenium ion is energetically preferred over the *cis* conformer by 1.86 kcal/mol.
(35) Hansen, T.; Elferink, H.; van Hengst, J. M. A.; Houthuijs, K.; Remmerswaal, W. A.; Kromm, A.; Berden, G.; van der Vorm, S.; Rijs, A.; Overkleeft, H. S.; Filippov, D.; Rutjes, F. P. J. T.; van der Marel, G.; Martens, J.; Oomens, J.; Codée, J. D. C.; Boltje, T. Characterization of Glycosyl Dioxolenium Ions and Their Role in Glycosylation Reactions. *ChemRxiv* **2019**, DOI: 10.26434/chemrxiv.11310293.v1.
(36) Crich, D.; Hu, T.; Cai, F. *J. Org. Chem.* **2008**, *73*, 8942.
(37) Saliba, R. C.; Wooke, Z. J.; Nieves, G. A.; Chu, A.-H. A.; Bennett, C. S.; Pohl, N. L. B. *Org. Lett.* **2018**, *20*, 800.
(38) Reactions performed in tetrahydrofuran or diethyl ether afforded little conversion, likely because these solvents compete for the Lewis acid.
(39) Crich, D.; Patel, M. *Carbohydr. Res.* **2006**, *341*, 1467.
(40) Schmidt, R. R.; Michel, J. *Tetrahedron Lett.* **1984**, *25*, 821.
(41) Schmidt, R. R.; Reichrath, M.; Moering, U. *J. Carbohydr. Chem.* **1984**, *3*, 67.
(42) Chao, C.-S.; Lin, C.-Y.; Mulani, S.; Hung, W.-C.; Mong, K.-k. T. *Chem. - Eur. J.* **2011**, *17*, 12193.
(43) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938.
(44) Singleton, D. A.; Wang, Y.; Yang, H. W.; Romo, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1572.
(45) Garcia, A.; Sanzone, J. R.; Woerpel, K. A. *Angew. Chem., Int. Ed.* **2015**, *54*, 12087.
(46) Singh, O. V.; Han, H. *Org. Lett.* **2007**, *9*, 4801.

https://dx.doi.org/10.1021/acs.orglett.0c01166
Org. Lett. XXXX, XXX, XXX−XXX