Diastereoselective Synthesis of *C*-Vinyl Glycosides via Gold(I)-Catalyzed Tandem 1,3-Acyloxy Migration/Ferrier Rearrangement

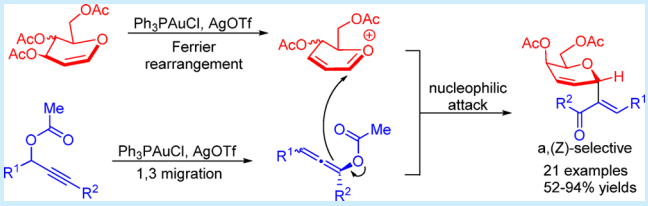
Nianyu Huang,[§,‡] Hongze Liao,[§,†] Hui Yao,[†] Tianpeng Xie,[‡] Shasha Zhang,[†] Kun Zou,[*,‡] and Xue-Wei Liu[*,†]

[†]Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371

[‡]Hubei Key Laboratory of Natural Products Research and Development, College of Biological and Pharmaceutical Sciences, China Three Gorges University, Yichang 443002, P. R. China

Supporting Information

ABSTRACT: A novel gold-catalyzed *C*-glycosylation has been developed to gain access to $\alpha,(Z)$-selective *C*-vinyl glycosides, starting from readily available glycals and propargylic carboxylate. This reaction involves a tandem intermolecular gold-catalyzed 1,3-acyloxy migration/Ferrier rearrangement with the involvement of allenic ester as the glycosyl acceptor. A wide range of substrate scope with good to excellent yields was achieved with complete diastereoselectivity.

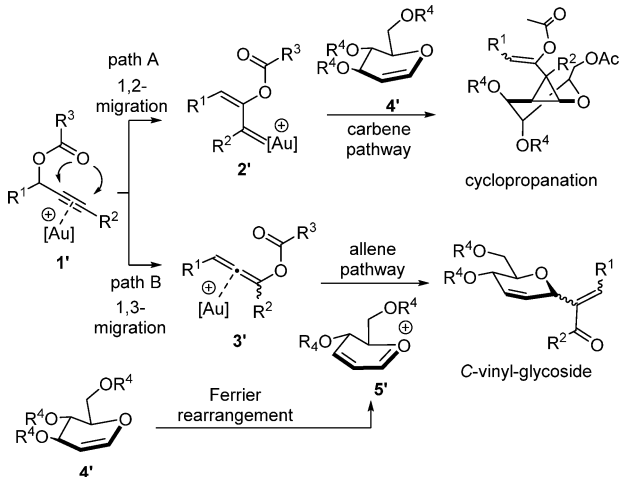


In recent years, glycosylation with gold catalysis has received considerable attention owing to the high alkynophilicity and carbophilic Lewis acidity of gold salts.[1] The glycosyl donors such as propargyl-*O*-glycosides,[2] glycosyl *ortho*-alkynylbenzoates,[3] thioglycosides,[4] and glycosyl trichloroacetimidates[5] were exploited to construct the glycosidic bonds. $AuCl_3$ was also reported to catalyze the Ferrier rearrangement of substituted glycals[6] or to work with phenylacetylene as the catalyst system.[5b,7] However, most cases focused on *O*- or *N*-glycosylation, and only a few examples about gold-catalyzed *C*-glycosylation were reported.

Propargylic carboxylate is a versatile molecular motif and is often used for studies on transition-metal catalyzed reactions.[8] It can undergo two distinct transformations in the presence of gold catalysts, namely, 1,2-acyloxy migration and 1,3-acyloxy migration, to form gold vinyl carbenoid species **2′** or carboxyallene **3′**, respectively.[9] The two intermediates could initiate other transformations, depending on the reaction conditions or properties of substrates.[10] For allenic intermediate, most studies covered the electrophilic character of the intermediate.[11] The studies about the nucleophilic character were limited to reactions through intramolecular fashion.[12] There were only two cases about the allenic intermediate that underwent an intermolecular addition to soft electrophiles such as NIS[13] or oxocarbenium ion,[14] respectively.

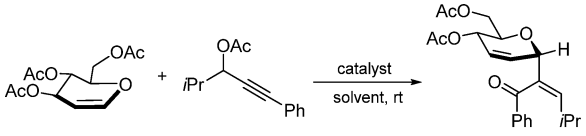
We were interested in developing highly efficient and stereoselective gold-catalyzed *C*-glycosylation. Inspired by the reports of gold-catalyzed reactions between glycals and propargylic carboxylates, we envisioned that there were two possible pathways for the reaction between glycal and propargylic carboxylate in the presence of gold catalysts (Scheme 1). In path A, after activation by the gold catalyst, the propargylic carboxylate underwent 1,2-acyloxy migration to generate the carbenoid intermediate **2′**, which subsequently took a cyclopropanation process to furnish the cyclopropane product.[15] In path B, the allylic carbocation intermediate **5′**[16] would be generated first from the glycal via a Ferrier-type rearrangement and subsequently underwent electrophilic attacked to allenic intermediate **3′**, which was transferred from the propargylic carboxylate via 1,3-acyloxy migration. Then after hydrolysis the *C*-vinyl-glycoside product was afforded. Our method holds great potential for the synthesis of various pyran-embedded natural products such as okadaic acid, forskolin, and aspergillide C.[17]

Scheme 1. Two Proposed Pathways for Reaction between Glycal and Propargylic Ester



To validate our hypothesis, a gold-catalyzed tandem reaction of propargylic carboxylate **2d** and tri-*O*-acetyl-D-glucal **1** was carried out in the presence of catalytic $AuCl_3$. To our delight, the vinyl-*C*-glycoside product **3d** proposed in path A was furnished in 44% yield with complete α-selectivity in the anomeric position and *Z*-selectivity in the olefin position (Table 1, entry 1). It was

Table 1. Optimization of Gold-Catalyzed Glycosylation[a]



1 **2d** **3d**

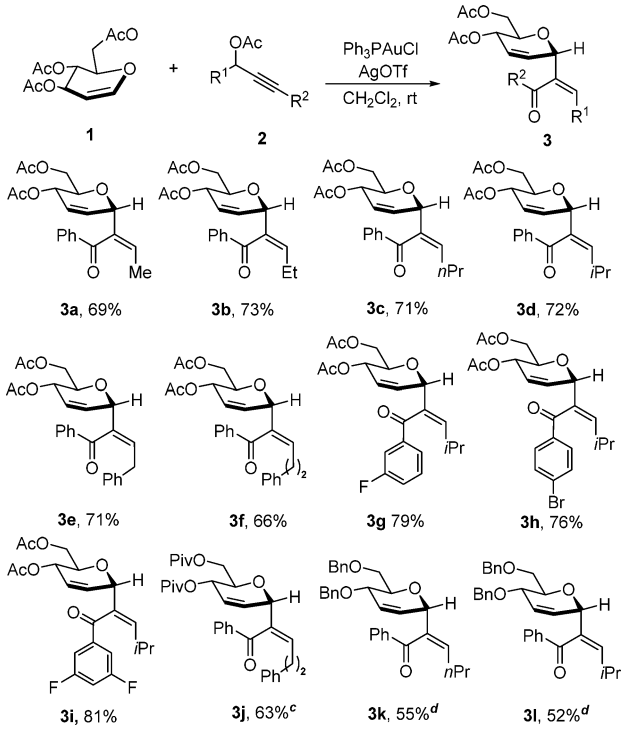
entry	catalyst	solvent	time (h)	yield (%)[d]
1	$AuCl_3$	CH_2Cl_2	4	44
2	AuCl	CH_2Cl_2	4	35
3	XPhosAuCl/AgOTf	CH_2Cl_2	4	24
4	((*t*Bu)$_2$(*o*-biphenyl)P) -AuCl/AgOTf	CH_2Cl_2	24	31
5	$Ph_3PAuNTf_2$	CH_2Cl_2	4	52
6	$Ph_3PAuCl/AgSbF_6$	CH_2Cl_2	4	57
7	$Ph_3PAuCl/AgClO_4$	CH_2Cl_2	4	64
8	$Ph_3PAuCl/AgOTf$	CH_2Cl_2	4	72
9	Ph_3PAuCl	CH_2Cl_2	24	n.r.
10	AgOTf	CH_2Cl_2	24	n.r.
11	$Ph_3PAuCl/AgOTf$	DCE	4	66
12	$Ph_3PAuCl/AgOTf$	Toluene	4	43
13	$Ph_3PAuCl/AgOTf$	CH_3NO_2	4	66
14	$Ph_3PAuCl/AgOTf$	CH_3CN	24	Trace
15[b]	$Ph_3PAuCl/AgOTf$	CH_2Cl_2	4	68
16[c]	$Ph_3PAuCl/AgOTf$	CH_2Cl_2	4	58

[a]Reaction conditions: tri-*O*-acetyl-D-glucal **1** (0.2 M in CH_2Cl_2), propargylic ester **2d** (0.2 M in CH_2Cl_2). [b]Reaction was carried out on scale of 1 M **1** and **2d**. [c]Catalyst (10 mol %). [d]Isolated yield.

noted that the cyclopropanation product was not observed in the reaction. To improve the yields and investigate the stereoselectivity, various gold catalysts and solvents were screened, and the results are summarized in Table 1. It was found that PPh_3AuOTf generated *in situ* from $PPh_3AuCl/AgOTf$ afforded the best result for this reaction (Table 1, entry 8). Other commercially available gold catalysts such as AuCl, XPhosAuCl/AgOTf, and ((*t*Bu)$_2$(*o*-biphenyl)P)AuCl/AgOTf could also catalyze this reaction but gave lower yields (Table 1, entry 2–4). It is worth noting that Ph_3PAuCl or AgOTf was inactive when employed individually (Table 1, entries 9 and 10). The counterion effect was also investigated, and the OTf-ion presented the best performance (Table 1, entries 5–8). Solvent screen was also conducted, and CH_2Cl_2 was found to be most suitable for this reaction (Table 1, entries 11–14). Reaction on larger scale (1 M) also proceeded smoothly and afforded **3d** in 68% yield (Table 1, entry 15). Notably, lower yield was observed when the catalyst loading was increased (Table 1, entry 16).

With the optimized condition in hand, the scope of this gold-catalyzed tandem intermolecular 1,3-acyloxy migration/Ferrier rearrangement was investigated with a variety of propargylic carboxylates **2** and tri-*O*-acetyl-D-glucal **1** (Scheme 2). In general, the desired products were obtained in good to excellent yields. The aliphatic substituents of R^1 such as methyl, ethyl, *n*-propyl, isopropyl, and benzyl substituents provided good yields (Scheme 2, entries **3a**–**3f**). For substrates with aromatic substituents R^2,

Scheme 2. Substrate Scope with D-Glucal[a,b]

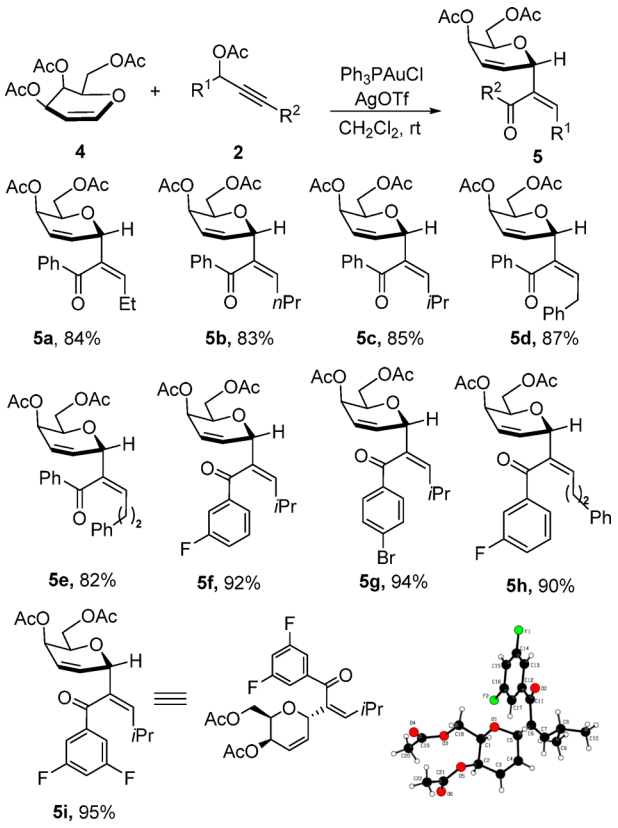


[a]Reaction conditions: tri-*O*-acetyl-D-glucal **1** (0.2 M in CH_2Cl_2), propargylic carboxylate **2** (0.2 M in CH_2Cl_2), 5 mol % gold catalyst, 5 mol % silver catalyst. [b]Isolated yield. [c]Tri-*O*-pivaloyl-D-glucal substrate. [d]Tri-*O*-benzyl-D-glucal substrate.

the aryl substituents with an electron withdrawing group increased the yields compared to the phenyl substrate. Interestingly, when the acetyl group was changed to pivaloyl or benzyl group, the reaction also worked but with lower yields (Scheme 2, entries **3j**–**3l**). To our surprise, when the 3,4,6-tri-*O*-acetyl-D-galactal **4** was tested for this reaction, the desired vinyl-*C*-glycoside product **5** was obtained as expected, and the yields were much higher than the product from glucal (72%–85%), which could be ascribed to less steric hindrance between the substituted group on C4 of glycal and the propargylic carboxylate during the glycosidation process. It should be noted that all the substrates were detected as complete α,(*Z*)-diastereoselective isomers, and the stereochemistry of this vinyl-*C*-glycoside product was further confirmed by X-ray analysis of compound **5i** (Scheme 3).[18]

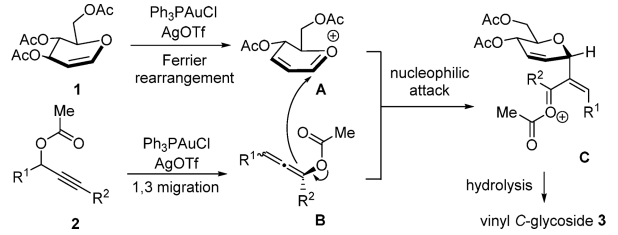
Based on the experimental results, the following mechanistic pathways were proposed. The gold catalyst should serve two purposes in this reaction. First, it served as a Lewis acid to promote the formation of allylic oxocarbenium ion **A** from tri-*O*-acetyl-D-glucal **1** via a Ferrier rearrangement. Second, it promoted the transformation of the propargylic carboxylate **1a** into the nucleophilic allenic intermediate **B** through a gold-catalyzed 1,3-acyloxy migration, which subsequently took nucleophilic attack to intermediate **A**. Finally, hydrolysis of oxocarbenium ion **C** delivered the product **3** (Scheme 4). To confirm this mechanism, an isotopic labeling experiment was conducted. The tri-*O*-acetyl-D-glucal **1** and propargylic carboxylate **2d**-^{18}**O** with an ^{18}O-enriched carbonyl oxygen atom were subjected to the optimized conditions, and the ^{18}O label was still present in the product **3d**-^{18}**O** (Scheme 6). This result fully

Scheme 3. Substrate Scope with D-Galactal[a,b]



[a]Reaction conditions: tri-*O*-acetyl-D-galactal **4** (0.2 M in CH_2Cl_2), propargylic carboxylate **2** (0.2 M in CH_2Cl_2), 5 mol % gold catalyst, 5 mol % silver catalyst. [b]Isolated yield.

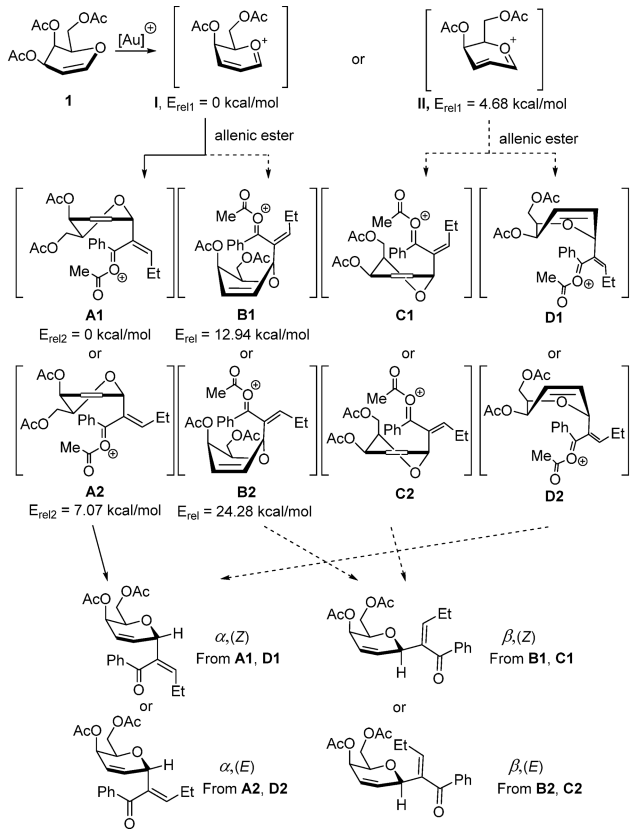
Scheme 4. Proposed Mechanism



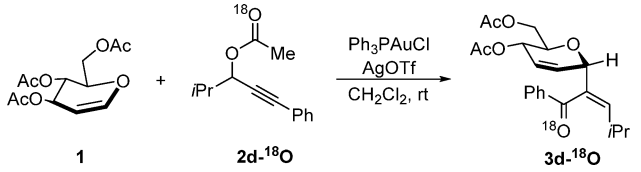
supported the proposed mechanism about the allene intermediate generated through the 1,3-acyloxy migration.

The stereochemistry of the anomeric position was mainly controlled by the conformation of oxocarbenium and the pathways of nucleophilic attack. Due to the lower energy transition state, the oxocarbenium intermediate favored conformation **I** more than **II**. The allene intermediate could attack from the bottom face to afford the α-anomer via half-chair conformation **A** or from the top face to afford the β-anomer via boat conformation **B**. Transition structures in this glycosylation were studied using the DFT method at the 6-311G(d,p) level, and the calculated results show that barrier energies for α-selectivity were much lower than β-selectivity, which is in agreement with the experimental result, which showed that only α-anomer was isolated. The complete (Z)-selectivity of the olefin could be ascribed to repulsion between the oxocarbenium and the allene intermediate during the nucleophilic attack process. It was geometrically favorable that the allene intermediate took the nucleophilic attack to the oxocarbenium intermediate from the π face of the enol ether motif, which is *anti* to the substituent R^1 (Scheme 5). This was also fully supported by the DFT computation.[19]

Scheme 5. Proposed Transition State Accounting for α,(Z)-Selectivity



Scheme 6. Isotope Labeling Experiments



In conclusion, an unprecedented homogeneous gold(I)-catalyzed *C*-glycosylation has been developed, and the mechanistic investigation suggests that this *C*-glycosylation proceeds through a tandem intermolecular 1,3-acyloxy migration/Ferrier rearrangement. This reaction can be utilized to access diastereomerically pure α,(Z)-selective *C*-vinyl glycosides, which are very important structural motifs in pharmaceutical and natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03062.

Experimental procedures, characterization data, crystallographic data, and calculation details (PDF)

Accession Codes

CCDC 1573304 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 Authors

*E-mail: kzou@ctgu.edu.cn.
*E-mail: xuewei@ntu.edu.sg.

ORCID

Xue-Wei Liu: 0000-0002-8327-6664

Author Contributions

§N.H. and H.L. contributed equally to this work.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the Ministry of Education (MOE 2013-T3-1-002), National Research Foundation (NRF2016NRF-NSFC002-005), Nanyang Technological University, Singapore (RG14/16), China Scholarship Council (No. 201508420062), and Youth Talent Development Foundation of China Three Gorges University for their financial support. Dr. Yongxin Li and Dr. Ganguly Rakesh in the division of chemistry and biological chemistry, Nanyang Technological University are also acknowledged for X-ray analysis.

REFERENCES

(1) (a) Li, X.; Zhu, J. *Eur. J. Org. Chem.* **2016**, *2016*, 4724−4767. (b) Li, X.; Zhu, J. *J. Carbohydr. Chem.* **2012**, *31*, 284−324.

(2) (a) Rao, B. V.; Manmode, S.; Hotha, S. *J. Org. Chem.* **2015**, *80*, 1499−1505. (b) Koppolu, S. R.; Niddana, R.; Balamurugan, R. *Org. Biomol. Chem.* **2015**, *13*, 5094−5097. (c) Thadke, S. A.; Mishra, B.; Hotha, S. *Org. Lett.* **2013**, *15*, 2466−2469. (d) Vidadala, S. R.; Gayatri, G.; Sastry, G. N.; Hotha, S. *Chem. Commun.* **2011**, *47*, 9906−9908. (e) Hotha, S.; Kashyap, S. *J. Am. Chem. Soc.* **2006**, *128*, 9620−9621.

(3) (a) Chen, X.; Wang, Q.; Yu, B. *Chem. Commun.* **2016**, *52*, 12183−12186. (b) Tang, Y.; Li, J.; Zhu, Y.; Li, Y.; Yu, B. *J. Am. Chem. Soc.* **2013**, *135*, 18396−18405. (c) Zhang, Q.; Sun, J.; Zhu, Y.; Zhang, F.; Yu, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 4933−4936. (d) Li, Y.; Yang, X.; Liu, Y.; Zhu, C.; Yang, Y.; Yu, B. *Chem. - Eur. J.* **2010**, *16*, 1871−1882.

(4) (a) Palanivel, A.; Chennaiah, A.; Dubbu, S.; Mallick, A.; Vankar, Y. D. *Carbohydr. Res.* **2017**, *437*, 43−49. (b) Vibhute, A. M.; Dhaka, A.; Athiyarath, V.; Sureshan, K. M. *Chem. Sci.* **2016**, *7*, 4259−4263. (c) Adhikari, S.; Baryal, K. N.; Zhu, D.; Li, X.; Zhu, J. *ACS Catal.* **2013**, *3*, 57−60.

(5) (a) Peng, P.; Schmidt, R. R. *J. Am. Chem. Soc.* **2015**, *137*, 12653−12659. (b) Roy, R.; Palanivel, A. K.; Mallick, A.; Vankar, Y. D. *Eur. J. Org. Chem.* **2015**, *2015*, 4000−4005.

(6) Balamurugan, R.; Koppolu, S. R. *Tetrahedron* **2009**, *65*, 8139−8142.

(7) (a) Mallick, A.; Mallikharjunarao, Y.; Rajasekaran, P.; Roy, R.; Vankar, Y. D. *Eur. J. Org. Chem.* **2016**, *2014*, 5564−5573. (b) Roy, R.; Rajasekaran, P.; Mallick, A.; Vankar, Y. D. *Eur. J. Org. Chem.* **2014**, *2014*, 5564−5573.

(8) (a) Ma, S. *Eur. J. Org. Chem.* **2004**, *2004*, 1175−1183. (b) Tsuji, J.; Mandai, T. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 585−618.

(9) Toste, F. D. In *Modern Gold Catalyzed Synthesis*; Hashmi, A. S. K., Toste, F. D., Eds.; Wiley-VCH: Weinheim, 2012; pp 75−134.

(10) (a) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028−9072. (b) Fensterbank, L.; Malacria, M. *Acc. Chem. Res.* **2014**, *47*, 953−965. (c) Kazem Shiroodi, R.; Gevorgyan, V. *Chem. Soc. Rev.* **2013**, *42*, 4991−5001. (d) Shu, X.-Z.; Shu, D.; Schienebeck, C. M.; Tang, W. *Chem. Soc. Rev.* **2012**, *41*, 7698−7711. (e) Dudnik, A. S.; Gevorgyan, N. C. *Aldrichimica Acta* **2010**, *43*, 37−46. (f) Wang, S.; Zhang, G.; Zhang, L. *Synlett* **2010**, *2010*, 692−706. (g) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351−3378. (h) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333−346. (i) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180−3211.

(11) (a) Webster, S.; Sutherland, D. R.; Lee, A. L. *Chem. - Eur. J.* **2016**, *22*, 18593−18600. (b) Rettenmeier, E.; Hansmann, M. M.; Ahrens, A.; Rübenacker, K.; Saboo, T.; Massholder, J.; Meier, C.; Rudolph, M.; Rominger, F.; Hashmi, A. S. *Chem. - Eur. J.* **2015**, *21*, 14401−14409. (c) Hashmi, A. S.; Yang, W.; Yu, Y.; Hansmann, M. M.; Rudolph, M.; Rominger, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 1329−1332. (d) Teng, T.-M.; Liu, R.-S. *J. Am. Chem. Soc.* **2010**, *132*, 9298−9300. (e) Garayalde, D.; Gómez-Bengoa, E.; Huang, X.; Goeke, A.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 4720−4730. (f) de Brabander, J. K.; Liu, B.; Qian, M. *Org. Lett.* **2008**, *10*, 2533−2536. (g) Marion, N.; Díez-González, S.; de Frémont, P.; Noble, A. R.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3647−3650. (h) Buzas, A.; Gagosz, F. *J. Am. Chem. Soc.* **2006**, *128*, 12614−12615. (i) Buzas, A.; Istrate, F.; Gagosz, F. *Org. Lett.* **2006**, *8*, 1957−1959.

(12) (a) Liao, H.; Leng, W.-L.; Le Mai Hoang, K.; Yao, H.; He, J.; Voo, A. Y. H.; Liu, X.-W. *Chem. Sci.* **2017**, *8*, 6656−6661. (b) Manoni, E.; Daka, M.; Mastandrea, M. M.; Nisi, A. D.; Monari, M.; Bandini, M. *Adv. Synth. Catal.* **2016**, *358*, 1404−1409. (c) Cran, J. W.; Krafft, M. E. *Angew. Chem., Int. Ed.* **2012**, *51*, 9398−9402. (d) Rao, W.; Susanti, D.; Chan, P. W. *J. Am. Chem. Soc.* **2011**, *133*, 15248−15251. (e) Leboeuf, D.; Simonneau, A.; Aubert, C.; Malacria, M.; Gandon, V.; Fensterbank, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 6868−6871. (f) Luo, T.; Schreiber, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 5667−5674. (g) Luo, T.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8250−8253. (h) Zhao, J.; Hughes, C. O.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 7436−7437. (i) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804−16805.

(13) (a) Yu, M.; Zhang, G.; Zhang, L. *Org. Lett.* **2007**, *9*, 2147−2150. (b) Wang, D.; Ye, X.; Shi, X. *Org. Lett.* **2010**, *12*, 2088−2091.

(14) Yu, Y.; Yang, W.; Rominger, F.; Hashmi, A. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 7586−7589.

(15) (a) Miki, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2003**, *68*, 8505−8513. (b) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654−8655. (c) Johansson, M.; Gorin, D.; Staben, S.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002. (d) Marion, N.; Lemiere, G.; Moreau, X.; Cavallo, L.; Fensterbank, L.; Malacria, M.; Nolan, S. P. *Chem. - Eur. J.* **2009**, *15*, 3243. (e) Lemière, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2009**, *131*, 2993.

(16) (a) Gómez, A. M.; Lobo, F.; Uriel, C.; López, J. C. *Eur. J. Org. Chem.* **2013**, *2013*, 7221−7262. (b) Kumaran, E.; Santhi, M.; Balasubramanian, K. K.; Bhagavathy, S. *Carbohydr. Res.* **2011**, *346*, 1654−1661. (c) Nagaraj, P.; Ramesh, N. G. *Eur. J. Org. Chem.* **2008**, *2008*, 4607−4614.

(17) (a) Tachibana, K.; Scheuer, P. J.; Tsukitani, Y.; Kikuchi, H.; Van Engen, D.; Clardy, J.; Gopichand, Y.; Schmitz, F. J. *J. Am. Chem. Soc.* **1981**, *103*, 2469−2471. (b) Bhat, S. V.; Bajqwa, B. S.; Dornauer, H.; do Scusa, N. J.; Fehlhaber, H.-W. *Tetrahedron Lett.* **1977**, *19*, 1669−1672. (c) Kito, K.; Ookura, R.; Yoshida, S.; Namikoshi, M.; Ooi, T.; Kusumi, T. *Org. Lett.* **2008**, *10*, 225−228.

(18) See section E, Table 1 (**5i**, CCDC 1573304) in the Supporting Information for the crystal structure.

(19) See the Supporting Information for computation details.