Organic LETTERS

Letter

Cite This: Org. Lett. 2018, 20, 3447−3450

pubs.acs.org/OrgLett

Kinetic Resolution of 1,2-Diols via NHC-Catalyzed Site-Selective Esterification

Bin Liu,[†,∥] Jiekuan Yan,[†,∥] Ruoyan Huang,[†] Weihong Wang,[†] Zhichao Jin,[†,§] Giuseppe Zanoni,[§] Pengcheng Zheng,[†] Song Yang,*[,†] and Yonggui Robin Chi*[,†,‡]

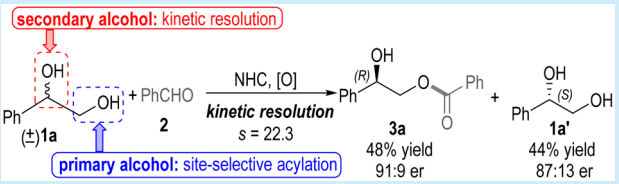
[†]Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Huaxi District, Guiyang 550025, China

[‡]Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

[§]Department of Chemistry, University of Pavia, Pavia 27100, Italy

Supporting Information

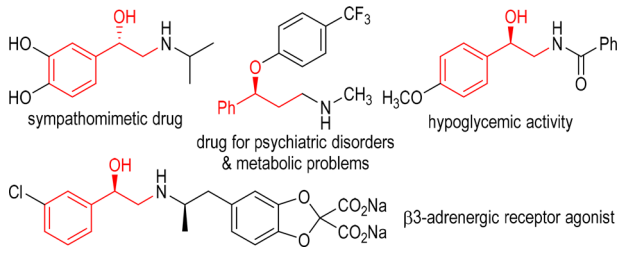
ABSTRACT: A kinetic resolution of 1,2-diols bearing both a secondary and a primary alcohol motif through an N-heterocyclic carbene-catalyzed oxidative acylation reaction has been developed. A site- and enantioselective esterification reaction is involved for this process. Both the monoacylated diols obtained and the remaining enantioenriched 1,2-diols are versatile building blocks for the preparation of functional molecules with proven biological activities.



Chiral 1-arylethane-1,2-diols are versatile building blocks for the preparation of various pharmaceuticals and natural products.[1] Their derivatives have found tremendous applications in both medicinal and biological research (Scheme 1). For example, amino alcohols derived from 1-arylethane-1,2-diols have been used as drugs for sympathomimetic diseases[2] as well as psychiatric disorders and metabolic problems.[3] They have also been used as hypoglycemic agents[4] and β3-adrenergic receptor agonists[5] in biological research. Therefore, the preparation of chiral 1-arylethane-1,2-diols has attracted much attention (Scheme 2a).[6−9] Nowadays, chiral 1-arylethane-1,2-diols can be obtained through asymmetric oxidation of styrenes,[6] hydrolysis of epoxides,[7] reduction of 1,2-dicarbonyl compounds,[8] and enantioenrichment of racemic 1,2-diols.[9] Notably, most of the reported methods have used transition metals or enzymes as the reaction catalysts. The use of small organic molecules as catalysts for enantioselective access to 1,2-diol compounds remains less developed.[10]

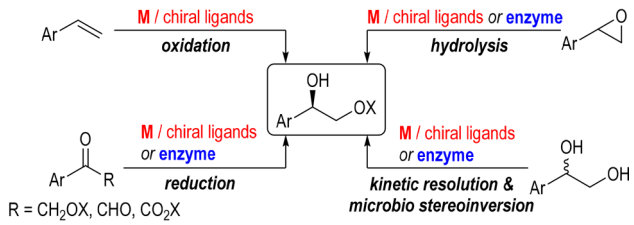
We are interested in developing novel activation modes and efficient synthetic methods for quick access to functional molecules using N-heterocyclic carbenes (NHCs or carbenes) as organic catalysts.[11]

Scheme 1. Chiral 1-Arylethane-1,2-diol Derivatives

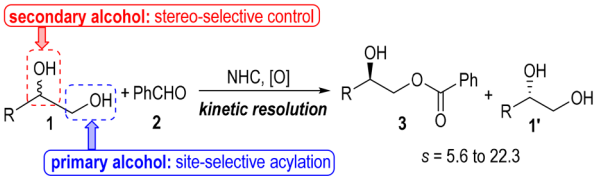


Scheme 2. Access to 1-Arylethane-1,2-diols

a) preparation of chiral 1-arylethane-1,2-diols:



***b) this work:* NHC-catalyzed kinetic resolution of 1,2-diols:**

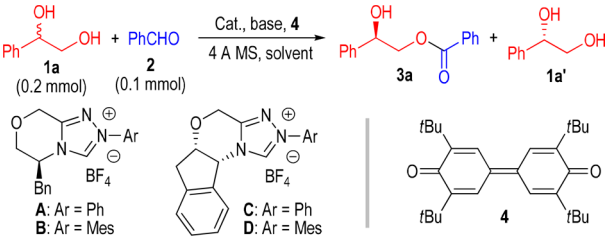


In Kinetic resolution is one of the practical methods for preparing enantioenriched organic compounds from racemic mixtures.[12] A number of kinetic resolution methods via NHC catalysis have been reported in recent years.[13,14] The first NHC-catalyzed kinetic resolution was reported by Suzuki and co-workers in 2004.[14a] In Suzuki's study, C_2-symmetric imidazolium-derived NHC catalysts were used in the

Received: March 31, 2018
Published: June 4, 2018

DOI: 10.1021/acs.orglett.8b01029
Org. Lett. 2018, 20, 3447−3450

Table 1. Optimization of the Reaction Conditions[a]



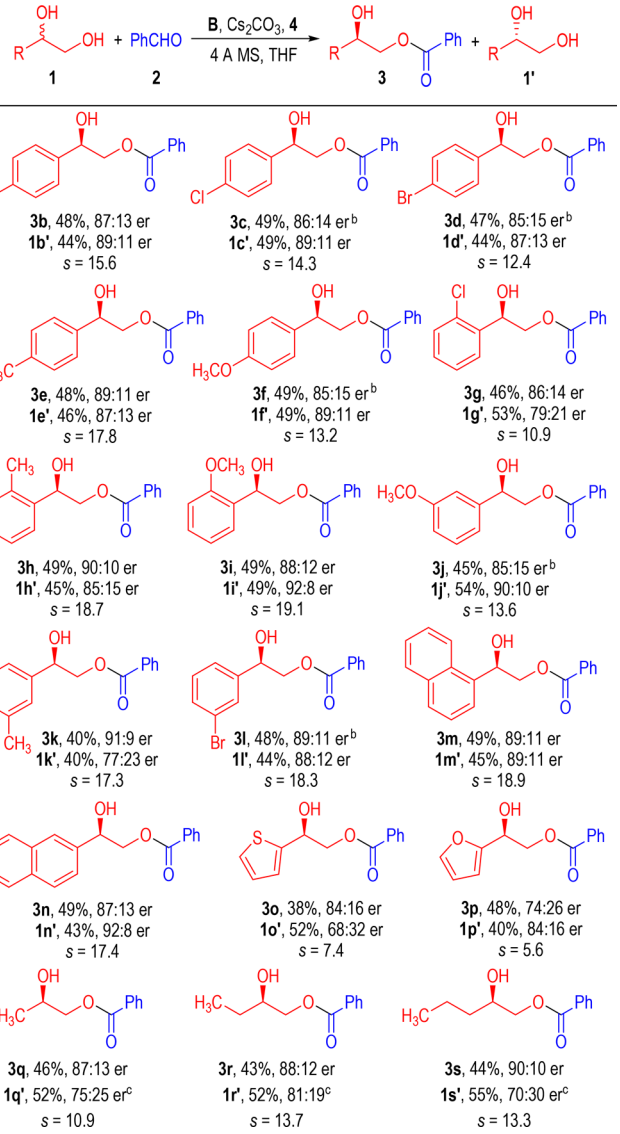
			yield (%)[b]; er[c]		
entry	cat.	solvent	**3a**	**1a'**	*s*
1	**A**	THF	44; 81:19	55; 79:21	7.5
2	**B**	THF	47; 89:11	52; 82:18	15.5
3	**C**	THF	41; 66:34	53; 66:34	2.6
4	**D**	THF	40; 68:32	58; 58:42	2.5
5[d]	**B**	THF	48; 86:14	50; 80:20	11.2
6[d]	**B**	toluene	37; 86:14	59; 65:35	8.2
7[d]	**B**	CH_2Cl_2	<5; –	–; –	–
8[d,e]	**B**	THF	30; 91:9	47; 87:13	22.3
9[d,e,f]	**B**	**THF**	**48; 91:9**	**44; 87:13**	**22.3**
10[d,f,g]	**B**	THF	37; 93:7	58; 73:27	20.9

[a]General conditions (unless otherwise specified): **1a** (0.20 mmol), **2a** (0.10 mmol), NHC (0.02 mmol), K_2CO_3 (0.02 mmol), **4** (0.10 mmol), 4 Å MS (50 mg), solvent (2.0 mL), 25 °C, 3 h. [b]Isolated yields of **3a** based on **1a** after purification via SiO_2 column chromatography. [c]Enantiomeric ratios of **3a** determined via HPLC on a chiral stationary phase. [d]**B** (0.005 mmol) and K_2CO_3 (0.005 mmol) were used. [e]At −5 °C for 20 h. [f]Cs_2CO_3 (0.005 mmol) was used instead of K_2CO_3 (0.005 mmol). [g]At −10 °C for 20 h.

enantioselective transesterification reactions of secondary alcohols. Studer and co-workers reported NHC-catalyzed oxidative esterification reactions for the kinetic resolution of secondary alcohols using aldehydes as the acylation reagents. Recently, Zhao and co-workers successfully realized the kinetic resolution of tertiary alcohols[14e] and axially chiral alcohols[14f] through NHC-catalyzed asymmetric oxidative acylation reactions. However, to the best of our knowledge, the kinetic resolution of 1,2-diols bearing both a primary and a secondary alcohol motif has remained undeveloped. Challenges exist in the control of both the chemo- and enantioselectivity of the NHC-catalyzed asymmetric acylation of the two alcohol motifs presented in the same substrate. Herein we report the kinetic resolution of secondary alcohols through an NHC-catalyzed monoesterification of the adjacent primary alcohol motifs (Scheme 2b). Non-covalent interactions involving the secondary alcohol moiety likely influence both the chemo (regio)-selective acylation and kinetic resolution processes. Similar effects of an adjacent hydroxyl group have been observed in related studies.[14f,h,15]

Readily available 1-phenylethane-1,2-diol (**1a**) was chosen as the model substrate for optimization of the reaction conditions (Table 1). Substrate **1a** could be selectively monoacylated by benzaldehyde (**2**) on the primary alcohol site through an NHC-catalyzed oxidative esterification reaction. The use of 2 equiv of **1a** is necessary for efficient chiral resolution since the primary alcohol motifs in both enantiomers of **1a** can be acylated under these catalytic conditions. Various chiral NHC catalysts were first evaluated in the formation of the enantioenriched monoester product **3a** (entries 1 to 4). Triazolium-derived NHC catalysts were found to be efficient for this transformation, and the use of NHC catalyst **B**, first developed by

Scheme 3. Scope of Diols[a]

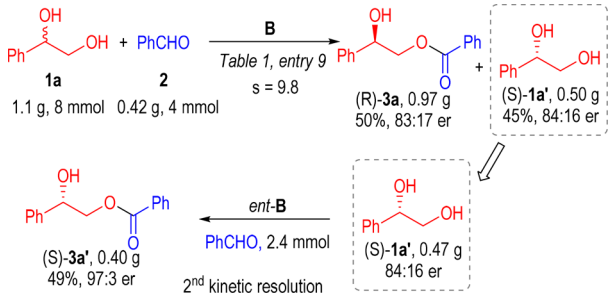


[a]The reaction conditions were those stated in Table 1, entry 9. Isolated yields after purification via SiO_2 column chromatography are shown. Er values were determined via HPLC on a chiral stationary phase. [b]The reaction was carried out at 25 °C for 2 h. [c]Er of the recovered (unreacted) diol (see the Supporting Information for details).

Scheidt and co-workers,[16] gave **3a** in nearly quantative yield with moderate enantioselectivity (entry 2). The catalyst loading could be decreased to 0.005 mmol without seriously deteriorating the reaction outcome (entry 5). A screen of reaction solvents did not provide further improvements in the product yield or er value (entries 6 and 7). The er value of **3a** could be improved to 91:9 when the reaction was carried out at a lower temperature, although the product yield was decreased (entry 8). The product **3a** could be obtained in excellent yield with good optical purity when Cs_2CO_3 was used as the base (entry 9). Further decreasing the reaction temperature led to a lower product yield, with a slightly improved er value (entry 10). It is worth noting that the *s* value calculated using Kagan's equation is independent of the conversion (as shown in Table S5 in the Supporting Information), supporting its relevance in evaluating the selectivity.

DOI: 10.1021/acs.orglett.8b01029
Org. Lett. 2018, 20, 3447−3450

Scheme 4. Gram-Scale Kinetic Resolution of 1a[a]



[a]The reaction conditions were those stated in Table 1, entry 9. Isolated yields after purification via SiO_2 column chromatography are shown. Er values were determined via HPLC on a chiral stationary phase.

The optimized reaction conditions (as shown in Table 1, entry 9) were then applied to a range of substituted 1,2-diols to examine the scope of this kinetic resolution approach (Scheme 3). Both electron-donating and electron-withdrawing groups could be installed on the benzene ring of diol **1a**. Most of the products were isolated in good to excellent yields with good optical purities (**3b**–**j**), although in several cases an increase in the reaction temperature was needed in order to obtain an acceptable product yield (**3c**, **3d**, **3f**, **3j**, and **3l**). The benzene group on substrate **1a** could also be replaced with naphthyl groups without deterioration of the product yield or er value (**3m** and **3n**). Various heteroarylethane-1,2-diols could also be applied in this kinetic resolution process, but the corresponding monoester products were obtained either in lower yield (**3o**) or with a lower er value (**3p**). It is worth noting that the aromatic group on 1,2-diol substrate **1** could even be replaced with various aliphatic groups, as the corresponding linear monoesters were obtained in good to excellent yields with moderate er values under our current reaction conditions (**3q**–**s**).

We also carried out this kinetic resolution process on a gram scale using 1.1 g of **1a** and 0.42 g of **2** as the starting materials under the optimized conditions (Scheme 4). The scaled-up reaction gave 0.97 g of enantioenriched monoester (*R*)-**3a** (50%, 83:17 er) and 0.50 g of the (*S*)-enantiomer **1a′** (45%, 84:16 er). A second kinetic resolution of (*S*)-**1a′** with *ent*-**B** as the catalyst under otherwise identical reaction conditions gave 0.40 g of the monoester product (*S*)-**3a′** with an excellent er value (49%, 97:3 er).

In summary, we have developed a carbene-catalyzed kinetic resolution approach for the preparation of chiral 1,2-diols and their monoester derivatives. Both enantiomers of the chiral products could be isolated with good to excellent optical purities after a sequential kinetic resolution process. The chiral products accessed by this process are versatile synthetic building blocks for the preparation of various biologically active chiral compounds.[17] Further investigations into the NHC-catalyzed kinetic resolution process, dynamic kinetic resolution reactions via the combination of NHC with other catalysts, and application of kinetic resolutions for quick and straightforward access to bioactive functional molecules are under study in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01029.

Experimental procedures and spectral data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: robinchi@ntu.edu.sg.
*E-mail: jhzx.msm@gmail.com.

ORCID

Zhichao Jin: 0000-0003-3003-6437
Song Yang: 0000-0003-1301-3030
Yonggui Robin Chi: 0000-0003-0573-257X

Author Contributions

‖B.L. and J.Y. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge financial support from the National Natural Science Foundation of China (21772029 and 21472028); the National Key Technologies R&D Program (2014BAD23B01); the "Thousand Talent Plan"; The 10 Talent Plan (Shicengci) of Guizhou Province; the Guizhou Province Returned Oversea Student Science and Technology Activity Program, Guizhou University; the Singapore National Research Foundation (NRF-NRFI2016-06), the Ministry of Education of Singapore (MOE2013-T2-2-003, MOE2016-T2-1-032, and RG108/16); an A*STAR Individual Research Grant (A1783c0008); a Nanyang Research Award Grant; Nanyang Technological University; a Regione Lombardia-Cariplo Foundation Grant (Sottomisura B/2016); and the University of Pavia.

■ REFERENCES

(1) (a) Nelson, W. L.; Wennerstrom, J. E.; Sankar, S. R. *J. Org. Chem.* **1977**, *42*, 1006. (b) Bianchi, D.; Bosetti, A.; Cesti, P.; Golini, P. *Tetrahedron Lett.* **1992**, *33*, 3231. (c) Pandey, R. K.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2002**, *43*, 4425. (d) Weissman, S. A.; Rossen, K.; Reider, P. J. *Org. Lett.* **2001**, *3*, 2513. (e) Suzuki, Y.; Kaneno, D.; Miura, M.; Tomoda, S. *Tetrahedron Lett.* **2008**, *49*, 4223. (f) Huang, K.; Ortiz-Marciales, M.; Correa, W.; Pomales, E.; López, X. Y. *J. Org. Chem.* **2009**, *74*, 4195.

(2) Konzett, H. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1940**, *197*, 27.

(3) (a) Robertson, D. W.; Jones, N. D.; Swartzendruber, J. K.; Yang, K. S.; Wong, D. T. *J. Med. Chem.* **1988**, *31*, 185. (b) Robertson, D. W.; Krushinski, J. H.; Fuller, R. W.; Leander, J. D. *J. Med. Chem.* **1988**, *31*, 1412. (c) Corey, E. J.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5207.

(4) Shoeb, A.; Kapil, R. S.; Popli, S. P. *Phytochemistry* **1973**, *12*, 2071.

(5) (a) Cantello, B. C. C.; Smith, S. A. *Drugs Future* **1991**, *16*, 797. (b) Bloom, J. D.; Claus, T. H. *Drugs Future* **1994**, *19*, 23. (c) Cecchi, R.; Croci, T.; Boigegrain, R.; Boveri, S.; Baroni, M.; Boccardi, G.; Guimbard, J. P.; Guzzi, U. *Eur. J. Med. Chem.* **1994**, *29*, 259.

(6) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 13210. (c) Sugimoto, H.; Kitayama, K.; Mori, S.; Itoh, S. *J. Am. Chem. Soc.* **2012**, *134*, 19270. (d) Wu, S.; Chen, Y.; Xu, Y.; Li, A.; Xu, Q.; Glieder, A.; Li, Z. *ACS Catal.* **2014**, *4*,

DOI: 10.1021/acs.orglett.8b01029
Org. Lett. 2018, 20, 3447–3450

409. (e) Zang, C.; Liu, Y.; Xu, Z.-J.; Tse, C.-W.; Guan, X.; Wei, J.; Huang, J.-S.; Che, C.-M. *Angew. Chem., Int. Ed.* **2016**, *55*, 10253.
(7) (a) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307. (b) Berkessel, A.; Ertürk, E. *Adv. Synth. Catal.* **2006**, *348*, 2619.
(8) (a) Kamal, A.; Chouhan, G. *Tetrahedron Lett.* **2004**, *45*, 8801. (b) Matharu, D. S.; Morris, D. J.; Kawamoto, A. M.; Clarkson, G. J.; Wills, M. *Org. Lett.* **2005**, *7*, 5489. (c) Matharu, D. S.; Morris, D. J.; Clarkson, G. J.; Wills, M. *Chem. Commun.* **2006**, 3232. (d) Ohkuma, T.; Utsumi, N.; Watanabe, M.; Tsutsumi, K.; Arai, N.; Murata, K. *Org. Lett.* **2007**, *9*, 2565. (e) Kadyrov, R.; Koenigs, R. M.; Brinkmann, C.; Voigtlaender, D.; Rueping, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7556. (f) Touge, T.; Hakamata, T.; Nara, H.; Kobayashi, T.; Sayo, N.; Saito, T.; Kayaki, Y.; Ikariya, T. *J. Am. Chem. Soc.* **2011**, *133*, 14960. (g) Mahajabeen, P.; Chadha, A. *Tetrahedron: Asymmetry* **2011**, *22*, 2156. (h) Soni, R.; Jolley, K. E.; Clarkson, G. J.; Wills, M. *Org. Lett.* **2013**, *15*, 5110. (i) Wu, W.; Xie, Y.; Li, P.; Li, X.; Liu, Y.; Dong, X.-Q.; Zhang, X. *Org. Chem. Front.* **2017**, *4*, 555.
(9) (a) Virsu, P.; Liljeblad, A.; Kanerva, A.; Kanerva, L. T. *Tetrahedron: Asymmetry* **2001**, *12*, 2447. (b) Hasegawa, J.; Ogura, M.; Tsuda, S.; Maemoto, S.-i; Kutsuki, H.; Ohashi, T. *Agric. Biol. Chem.* **1990**, *54*, 1819.
(10) (a) Ishihara, K.; Kosugi, Y.; Akakura, M. *J. Am. Chem. Soc.* **2004**, *126*, 12212. (b) Geng, X.-L.; Wang, J.; Li, G.-X.; Chen, P.; Tian, S.-F.; Qu, J. *J. Org. Chem.* **2008**, *73*, 8558. (c) Shinisha, C. B.; Sunoj, R. B. *Org. Lett.* **2009**, *11*, 3242. (d) Cao, J.-L.; Qu, J. *J. Org. Chem.* **2010**, *75*, 3663.
(11) (a) Mo, J.; Chen, X.; Chi, Y. R. *J. Am. Chem. Soc.* **2012**, *134*, 8810. (b) Fu, Z.; Xu, J.; Zhu, T.; Leong, W. W. Y.; Chi, Y. R. *Nat. Chem.* **2013**, *5*, 835. (c) Zhang, J.; Xing, C.; Tiwari, B.; Chi, Y. R. *J. Am. Chem. Soc.* **2013**, *135*, 8113. (d) Zhu, T.; Mou, C.; Li, B.; Smetankova, M.; Song, B.-A.; Chi, Y. R. *J. Am. Chem. Soc.* **2015**, *137*, 5658. (e) Zhang, Y.; Du, Y.; Huang, Z.; Xu, J.; Wu, X.; Wang, Y.; Wang, M.; Yang, S.; Webster, R. D.; Chi, Y. R. *J. Am. Chem. Soc.* **2015**, *137*, 2416. (f) Huang, Z.; Huang, X.; Li, B.; Mou, C.; Yang, S.; Song, B.-A.; Chi, Y. R. *J. Am. Chem. Soc.* **2016**, *138*, 7524.
(12) For selected reviews of kinetic resolutions, see: (a) Müller, C. E.; Schreiner, P. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 6012. (b) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 1613. (c) Eames, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 885. (d) Dehli, J. R.; Gotor, V. *Chem. Soc. Rev.* **2002**, *31*, 365. (e) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430. (f) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492. (g) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169. (h) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119*, 2584. (i) Dong, S.; Liu, X.; Zhu, Y.; He, P.; Lin, L.; Feng, X. *J. Am. Chem. Soc.* **2013**, *135*, 10026. (j) Williamson, K. S.; Sawicki, J. W.; Yoon, T. P. *Chem. Sci.* **2014**, *5*, 3524. (k) Lin, X.; Ruan, S.; Yao, Q.; Yin, C.; Lin, L.; Feng, X.; Liu, X. *Org. Lett.* **2016**, *18*, 3602.
(13) For selected reviews of NHC catalysis, see: (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (b) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988. (c) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691. (d) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182. (e) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev.* **2011**, *40*, 5336. (f) Douglas, J.; Churchill, G.; Smith, A. D. *Synthesis* **2012**, *44*, 2295. (g) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 11686. (h) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*, 4906. (i) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485. (j) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307.
(14) For selected examples, see: (a) Suzuki, Y.; Yamauchi, K.; Muramatsu, K.; Sato, M. *Chem. Commun.* **2004**, 2770. (b) Kano, T.; Sasaki, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 1347. (c) De Sarkar, S.; Biswas, A.; Song, C. H.; Studer, A. *Synthesis* **2011**, *2011*, 1974. (d) Iwahana, S.; Iida, H.; Yashima, E. *Chem. - Eur. J.* **2011**, *17*, 8009. (e) Lu, S.; Poh, S. B.; Siau, W.-Y.; Zhao, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 1731. (f) Lu, S.; Poh, S. B.; Zhao, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 11041. (g) Binanzer, M.; Hsieh, S.-Y.; Bode, J. W. *J. Am. Chem. Soc.* **2011**, *133*, 19698. (h) Kuwano, S.; Harada, S.; Kang, B.; Oriez, R.; Yamaoka, Y.; Takasu, K.; Yamada, K. *J. Am. Chem. Soc.* **2013**, *135*, 11485.
(15) For computional studies of the effect of the adjacent hydroxyl groups, see: Maji, R.; Wheeler, S. E. *J. Am. Chem. Soc.* **2017**, *139*, 12441.
(16) Wadamoto, M.; Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 10098.
(17) Kumar, P.; Upadhyay, R. K.; Pandey, R. K. Tetrahedron. *Tetrahedron: Asymmetry* **2004**, *15*, 3955.

DOI: 10.1021/acs.orglett.8b01029
Org. Lett. 2018, 20, 3447−3450