JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

A Chiral Electrophilic Selenium Catalyst for Highly Enantioselective Oxidative Cyclization

Yu Kawamata, Takuya Hashimoto, and Keiji Maruoka*

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

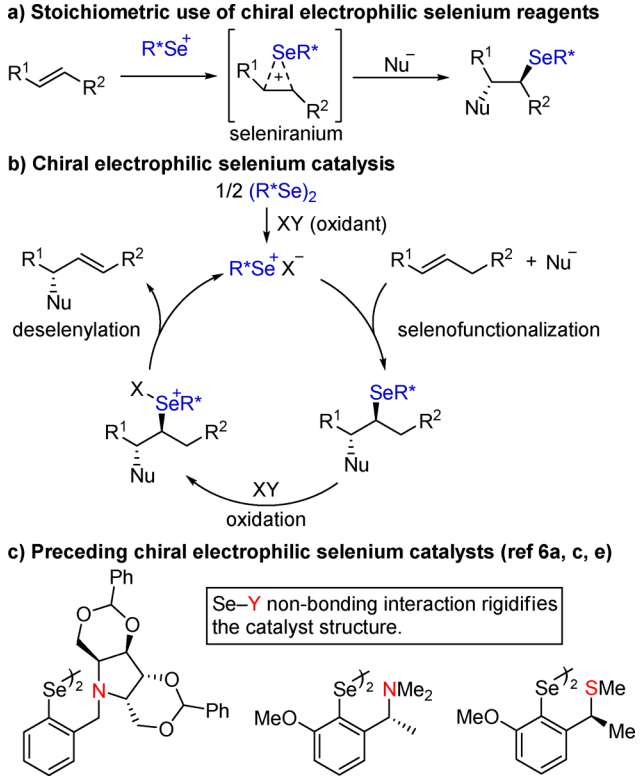
Supporting Information

ABSTRACT: Chiral electrophilic selenium catalysts have been applied to catalytic asymmetric transformations of alkenes over the past two decades. However, highly enantioselective reactions with a broad substrate scope have not yet been developed. We report the first successful example of this reaction employing a catalyst based on a rigid indanol scaffold, which can be easily synthesized from a commercially available indanone. The reaction efficiently converts β,γ-unsaturated carboxylic acids into various enantioenriched γ-butenolides under mild conditions.

Asymmetric catalysis constitutes a robust synthetic tool which ensures high enantioselectivities in many transformations.[1] Since the middle of the twentieth century, a vast array of elements have been exploited as catalytic centers, surrounded by judiciously constructed chiral environment. However, there are still some elements which elude these efforts and remain underutilized despite their promising catalytic activities. A chiral selenium catalyst is one such example. Chiral nucleophilic selenium catalysts are rare, and only a few have been successfully developed so far;[2,3] yet in the case of chiral electrophilic selenium catalysis, there has been no general catalyst which achieves high enantioselectivities over a range of substrates.

Conventionally, chiral electrophilic selenium reagents have been utilized in stoichiometric amounts for asymmetric selenofunctionalization of unactivated alkenes, which installs a selenium functionality and a nucleophile in an *anti*-specific manner via a three-membered seleniranium intermediate (Scheme 1a).[4] A variety of chiral selenium reagents have been developed to date, which demonstrated high stereoselectivity mostly when the reactions were carried out at cryogenic temperature. The selenium moiety introduced can be later transformed into other functionalities under oxidative or reductive conditions, suitable for natural product and pharmaceutical syntheses.[5] Catalytic use of chiral electrophilic selenium species can be achieved by regenerating the catalyst via *in situ* oxidative deselenylation, allowing asymmetric introduction of a nucleophile and successive transformation of the selenium functionality to be realized in a single reaction (Scheme 1b).[6] The implementation of this sequence of transformations was first documented by Tomoda et al. in the 1990s in the form of asymmetric conversion of β-methylstyrene into an enantioenriched allylic ether.[6a] Since this represents a powerful strategy for accessing various optically active allylic compounds from unactivated alkenes,

Scheme 1. Strategies for Asymmetric Selenofunctionalization



several chiral electrophilic selenium catalysts have been examined over the past decades (Scheme 1c).[6b−f] However, since the catalysis had to be conducted at ambient temperature to overcome the turnover-limiting oxidative deselenylation, application of previous chiral electrophilic selenium reagents demonstrated poor enantioselectivity or very limited scope. A common feature of these catalysts is the noncovalent interaction of the heteroatom at the chiral acyclic side chain with the selenium for asymmetric induction.[7] We suspected that the chiral environment created by such an interaction might lose rigidity at ambient temperature. Accordingly, an innovative, robust catalyst design which enables high enantioselectivities even at ambient temperature is indispensable. Until now, highly enantioselective selenofunctionalization could only be achieved by recently emerged organocatalytic

Received: February 12, 2016
Published: April 11, 2016

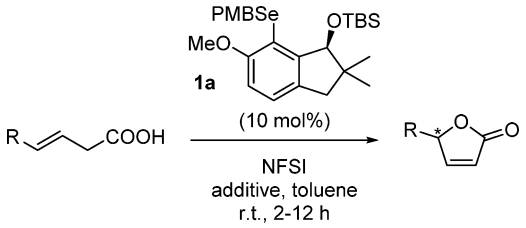
DOI: 10.1021/jacs.6b01462
J. Am. Chem. Soc. 2016, 138, 5206−5209

methods, which activate a stoichiometric amount of achiral electrophilic selenium by acid or base.[8−10]

Herein, we describe the first highly enantioselective oxidative cyclization of β,γ-unsaturated carboxylic acids using an electrophilic selenium catalyst, which affords various enantioenriched γ-butenolides with up to 97% ee.[6f] The key to this success is the design of a rigid catalyst based on an indanol scaffold which can be practically synthesized by establishing robust optical resolution and selenylation routes.

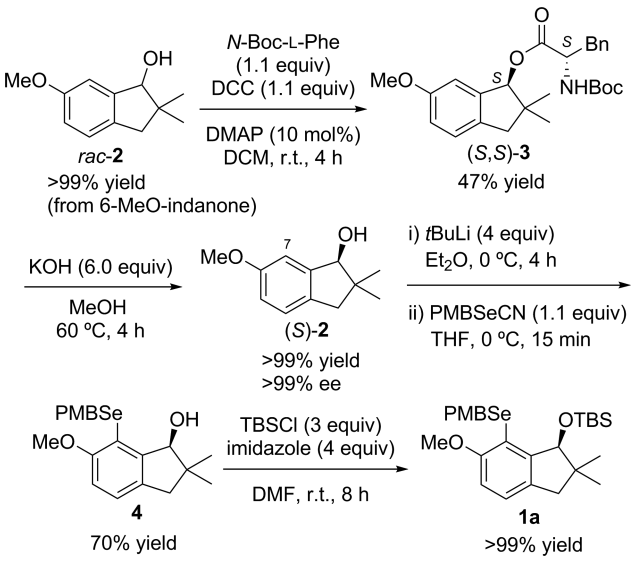
We began this research by designing a new chiral electrophilic selenium catalyst in the intramolecular oxidative cyclization of β,γ-unsaturated carboxylic acid. In the new catalyst design, we opted for an indanol scaffold,[11,12] which previously enabled us to effectively control the enantioselectivity of thiyl radical catalyzed cyclization.[13] Extensive screening of a variety of catalyst designs led us to find a suitable catalyst **1a**, which showed excellent enantioselectivity at ambient temperature in the target reaction (Scheme 2).

Scheme 2. Highly Enantioselective Oxidative Cyclization

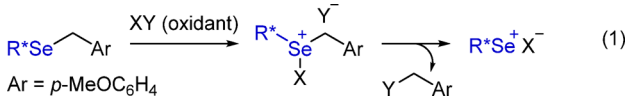


The catalyst **1a** can be easily synthesized from commercially available 6-methoxyindanone through a sequence of high-yielding reactions (Scheme 3). The key enantiopure indanol

Scheme 3. Catalyst Synthesis



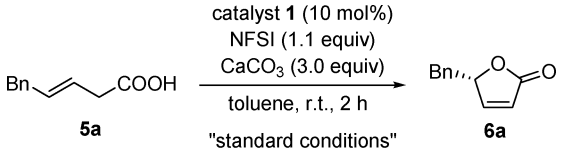
(*S*)-**2** was obtained by the optical resolution of rac-**2** by using phenylalanine derivative **3**. Two diastereomers (*S*,*S*)- and (*S*,*R*)-**3** were separated by recrystallization and column chromatography. Then ortho-lithiation and the reaction with elemental selenium were conducted to install diselenide at the 7-position. However, this typical protocol gave the corresponding diselenide as an inseparable mixture of products.[14] To overcome this hurdle, we devised the installation of the requisite selenium functionality as a *p*-methoxybenzyl selenide (**4**), which can also generate an electrophilic selenium catalyst directly under oxidative reaction conditions as shown in eq 1.

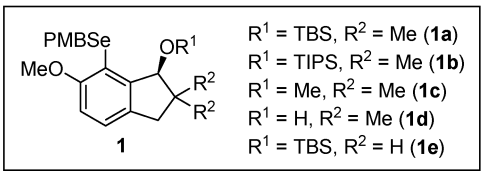


(1)

The data in Table 1 summarize the effect of various parameters on this reaction. With the optimal catalyst **1a**, the

Table 1. Selenium-Catalyzed Oxidative Cyclization of β,γ-Unsaturated Carboxylic Acid: Effect of Reaction Parameters[a]





entry	change from the standard conditions	% yield[b]	% ee[d]
1	none	99[c]	95
2	$PhI(OCOCF_3)_2$ instead of NFSI	13	91
3	$Na_2S_2O_8$ instead of NFSI	0	–
4	**1b** instead of **1a**	92	85
5	**1c** instead of **1a**	74	62
6	**1d** instead of **1a**	72	14
7	**1e** instead of **1a**	71	82
8	0 °C	9	93
9	no $CaCO_3$	83	88
10	1.0 mmol scale	>99	95

[a]Reactions performed with **5a** (0.1 mmol), oxidant (0.11 mmol), catalyst **1** (0.01 mmol) in solvent (0.7 mL) at room temperature. [b]NMR yield. [c]Yield of isolated product. [d]Determined by chiral HPLC.

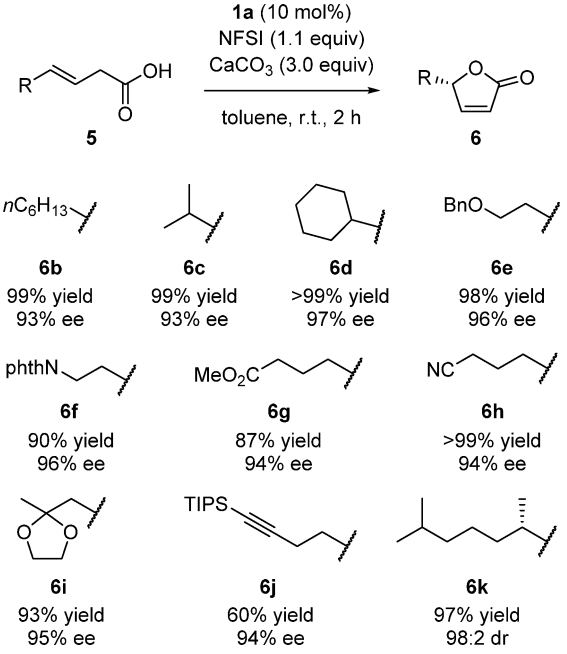
oxidative cyclization of β,γ-unsaturated carboxylic acid **5a** smoothly completed within 2 h to give the desired γ-butenolide **6a** in quantitative yield with high enantioselectivity (entry 1). The absolute configuration of the product was determined by comparison of the optical rotation value reported in the literature. NFSI[15] was selected as an oxidant since iodine(III)[6f,16] and persulfate[6a−d] gave low yields due to insufficient oxidizing ability or poor solubility (entries 2 and 3). The structure of the catalyst had a great impact on the enantioselectivity. When the catalyst TBS group was replaced with a bulkier TIPS group (**1b**), a slight decrease of enantioselectivity was observed (entry 4), whereas the catalyst **1c** with a small methyl group substantially diminished the enantioselectivity (entry 5). Interestingly, the catalyst **1d** bearing a free hydroxy group still catalyzed the reaction smoothly, albeit with low enantioselectivity (entry 6). In addition, the *gem*-dimethyl group was found to be essential for achieving high enantioselectivity (entry 7). The reaction temperature is also important since the reaction was significantly slowed down at 0 °C (entry 8). The productivity and selectivity of the reaction were slightly eroded in the

DOI: 10.1021/jacs.6b01462
J. Am. Chem. Soc. 2016, 138, 5206−5209

absence of $CaCO_3$ (entry 9). It should also be mentioned that the methoxy group at the ortho-position of the selenium is attached for a synthetic purpose (see Scheme 3). We have confirmed that the catalyst having the methoxy group at the para-position worked with similar reactivity and selectivity (data not shown). Finally, the reaction was carried out on a 1.0 mmol scale to verify the robustness of this procedure (entry 10).

After establishing the optimal reaction conditions, the oxidative cyclization of aliphatic β,γ-unsaturated carboxylic acids **5** was explored (Table 2). Generally, the reaction reached

Table 2. Substrate Scope for Aliphatic Substrates[a]

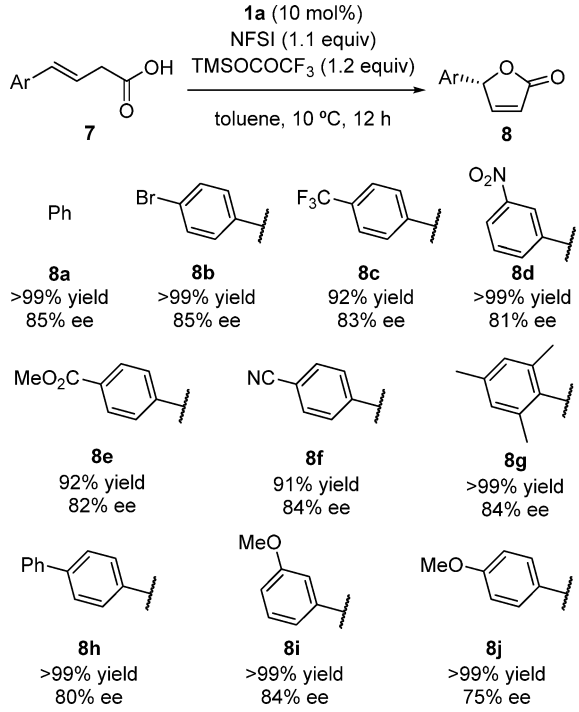


[a]Reactions performed with **5** (0.1 mmol), NFSI (0.11 mmol), $CaCO_3$ (0.3 mmol), catalyst **1a** (0.01 mmol) in toluene (0.7 mL) at room temperature. Yield of isolated product.

completion within 2 h to afford the product in high yield with excellent enantioselectivity at room temperature. γ-Butenolides with linear, branched, and cyclic aliphatic substitutions were obtained in excellent yields with uniformly high enantioselectivities (**6b**–**6d**). Oxygen- and nitrogen-containing functional groups were both tolerated in these reaction conditions (**6e** and **6f**). In addition, ester, nitrile, and ketal groups were also accommodated (**6g**–**6i**). A substrate bearing an alkyne moiety was also applicable to this reaction (**6j**).[17] Finally, an optically pure citronellal-derived substrate underwent a clean reaction with excellent diastereoselectivity, demonstrating that a stereogenic center adjacent to the transformed double bond did not affect the stereoselectivity (**6k**).[18]

Next, the oxidative cyclization of γ-aryl substrates **7** was explored. This was conducted under slightly modified reaction conditions (at 10 °C using $TMSOCOCF_3$ instead of $CaCO_3$) for improved enantioselectivity (see Supporting Information for details).[19] Under these conditions, a range of aromatic substrates gave the corresponding γ-butenolides in excellent yields with good enantioselectivities (Table 3). Generally, γ-butenolides with various electron-deficient groups were obtained with ee's above 80% (**8b**–**8f**). The product with an ortho-substituted aryl group was also obtained with high enantioselectivity (**8g**). A slightly lower ee value was observed

Table 3. Substrate Scope for Aromatic Substrates[a]

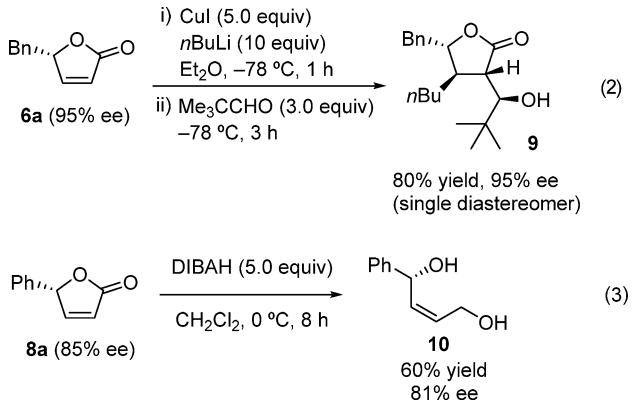


[a]Reactions performed with **7** (0.1 mmol), NFSI (0.11 mmol), $TMSOCOCF_3$ (0.12 mmol), catalyst **1a** (0.01 mmol) in toluene (0.7 mL) at 10 °C. Yield of isolated product.

in the case of the biphenyl product (**8h**). Although 3-methoxyphenyl product **8i** was obtained with comparable enantioselectivity, lower enantioselectivity was observed in the case of 4-methoxyphenyl product **8j**.

Finally, we explored synthetic applications of the products, while using transformations rarely applied to enantioenriched γ-butenolides. The first example is a tandem cuprate 1,4-addition/aldol reaction (Scheme 4, eq 2).[20] The reaction

Scheme 4. Synthetic Applications of the Products



proceeded to give the desired product **9** bearing four consecutive stereogenic centers, isolated as a single diastereomer in 80% yield without erosion of optical purity. The second example is DIBAL reduction of γ-phenyl butenolide **8a** (Scheme 4, eq 3). Although **8a** is prone to racemize under basic conditions, this reaction afforded a chiral (*Z*)-allyl alcohol **10** without a substantial decrease of optical purity.

DOI: 10.1021/jacs.6b01462
J. Am. Chem. Soc. 2016, 138, 5206–5209

In conclusion, we achieved the first highly enantioselective oxidative cyclization of β,γ-unsaturated carboxylic acids into various enantioenriched γ-butenolides catalyzed by a chiral electrophilic selenium catalyst. To achieve this goal, we successfully developed a rigid catalyst based on an indanol scaffold and identified suitable reaction conditions to perform the reaction smoothly. This study will encourage further development of chiral electrophilic selenium catalysts and their applications based on their broad reactivity,[4,5] as well as the use of chiral indanol scaffolds in other asymmetric catalyst designs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01462.

Crystallographic data (CIF)
Crystallographic data (CIF)
Crystallographic data (CIF)
Experimental details and characterization data for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*maruoka@kuchem.kyoto-u.ac.jp

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partially supported by a Grant-in-Aid for Scientific Research from the MEXT (Japan). Y.K. thanks a Grant-in-Aid for the Research Fellowship of JSPS for Young Scientists.

■ REFERENCES

(1) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*, Vols. *I–III*; Springer: Berlin, 1999.

(2) (a) Denmark, S. E.; Kornfilt, D. J. P.; Vogler, T. *J. Am. Chem. Soc.* **2011**, *133*, 15308. (b) Denmark, S. E.; Chi, H. M. *J. Am. Chem. Soc.* **2014**, *136*, 3655. (c) Denmark, S. E.; Chi, H. M. *J. Am. Chem. Soc.* **2014**, *136*, 8915. (d) Denmark, S. E.; Hartmann, E.; Kornfilt, D. J. P.; Wang, H. *Nat. Chem.* **2014**, *6*, 1056. (e) Denmark, S. E.; Jaunet, A. *J. Am. Chem. Soc.* **2013**, *135*, 6419. (f) Denmark, S. E.; Jaunet, A. *J. Org. Chem.* **2014**, *79*, 140.

(3) Chen, F.; Tan, C. K.; Yeung, Y. Y. *J. Am. Chem. Soc.* **2013**, *135*, 1232.

(4) (a) Wirth, T. *Organoselenium Chemistry: Synthesis and Reactions*; Wiley-VCH: Weinheim, Germany, 2012. (b) Browne, D. M.; Wirth, T. *Curr. Org. Chem.* **2006**, *10*, 1893. (c) Wirth, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 3740. (d) Wirth, T. *Tetrahedron* **1999**, *55*, 1. (e) Breder, A.; Ortgies, S. *Tetrahedron Lett.* **2015**, *56*, 2843.

(5) (a) Nicolaou, K. C.; Petasis, N. A. *Selenium in Natural Product Synthesis*; CIS: Philadelphia, 1984. (b) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: Oxford, 1986. (c) Liotta, D. *Organoselenium Chemistry*; Wiley Interscience: New York, 1987.

(6) (a) Fujita, K.; Iwaoka, M.; Tomoda, S. *Chem. Lett.* **1994**, 923. (b) Fukuzawa, S.-i.; Takahashi, K.; Kato, H.; Yamazaki, H. *J. Org. Chem.* **1997**, *62*, 7711. (c) Wirth, T.; Häuptli, S.; Leuenberger, M. *Tetrahedron: Asymmetry* **1998**, *9*, 547. (d) Tiecco, M.; Testaferri, L.; Santi, C.; Tomassini, C.; Marini, F.; Bagnoli, L.; Temperini, A. *Tetrahedron: Asymmetry* **2000**, *11*, 4645. (e) Tiecco, M.; Testaferri, L.; Santi, C.; Tomassini, C.; Marini, F.; Bagnoli, L.; Temperini, A. *Chem. - Eur. J.* **2002**, *8*, 1118. (f) Browne, D. M.; Niyomura, O.; Wirth, T. *Org. Lett.* **2007**, *9*, 3169.

(7) Mukherjee, A. J.; Zade, S. S.; Singh, H. B.; Sunoj, R. B. *Chem. Rev.* **2010**, *110*, 4357.

(8) (a) Guan, H.; Wang, H.; Huang, D.; Shi, Y. *Tetrahedron* **2012**, *68*, 2728. (b) Wei, Q.; Wang, Y.-Y.; Du, Y.-L.; Gong, L.-Z. *Beilstein J. Org. Chem.* **2013**, *9*, 1559.

(9) (a) Denmark, S. E.; Kalyani, D.; Collins, W. R. *J. Am. Chem. Soc.* **2010**, *132*, 15752. (b) Niu, W.; Yeung, Y.-Y. *Org. Lett.* **2015**, *17*, 1660.

(10) Zhang, H.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2014**, *136*, 16485.

(11) Use of tetralol as stoichiometric chiral selenylating reagents has been reported; see: (a) Wirth, T.; Fragale, G. *Chem. - Eur. J.* **1997**, *3*, 1894. (b) Wirth, T.; Fragale, G. *Synthesis* **1998**, *1998*, 162. (c) Uehlin, L.; Fragale, G.; Wirth, T. *Chem. - Eur. J.* **2002**, *8*, 1125.

(12) The non-bonding interaction between the selenium and indanol oxygen is considered to be small. Fragale, G.; Neuburger, M.; Wirth, T. *Chem. Commun.* **1998**, 1867.

(13) Hashimoto, T.; Kawamata, Yu.; Maruoka, K. *Nat. Chem.* **2014**, *6*, 702.

(14) The corresponding triselenide is known to be formed along with the target diselenide. Santi, C.; Fragale, G.; Wirth, T. *Tetrahedron: Asymmetry* **1998**, *9*, 3625.

(15) (a) Trenner, J.; Depken, C.; Weber, T.; Breder, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 8952. (b) Krätzschmar, F.; Kaßel, M.; Delony, D.; Breder, A. *Chem. - Eur. J.* **2015**, *21*, 7030. (c) Ortgies, S.; Breder, A. *Org. Lett.* **2015**, *17*, 2748. (d) Zhang, X.; Guo, R.; Zhao, X. *Org. Chem. Front.* **2015**, *2*, 1334. (e) Deng, Z.; Wei, J.; Liao, L.; Huang, H.; Zhao, X. *Org. Lett.* **2015**, *17*, 1834.

(16) (a) Shahzad, S. A.; Venin, C.; Wirth, T. *Eur. J. Org. Chem.* **2010**, *2010*, 3465. (b) Singh, F. V.; Wirth, T. *Org. Lett.* **2011**, *13*, 6504.

(17) The reaction of substrates with an additional alkene moiety was inefficient.

(18) The use of ***ent*-1a** as the catalyst resulted in the formation of ***epi*-6k** in 81% yield with 97:3 dr (see the Supporting Information for details).

(19) We assume that use of $TMSOCOCF_3$ generates a catalyst which has trifluoroacetate as a counteranion, thereby affecting the enantioselectivity slightly.

(20) Mao, B.; Geurts, K.; Fañanás-Mastral, M.; van Zijl, A. W.; Fletcher, S. P.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2011**, *13*, 948.

DOI: 10.1021/jacs.6b01462
J. Am. Chem. Soc. 2016, 138, 5206–5209