Organic LETTERS

Letter

pubs.acs.org/OrgLett

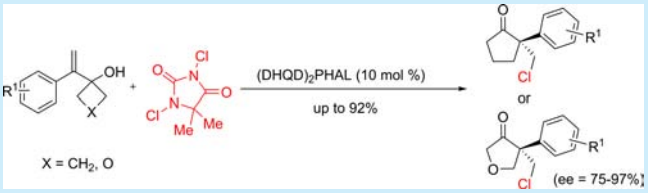
Asymmetric Chlorination/Ring Expansion for the Synthesis of α-Quaternary Cycloalkanones

Qin Yin and Shu-Li You*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China

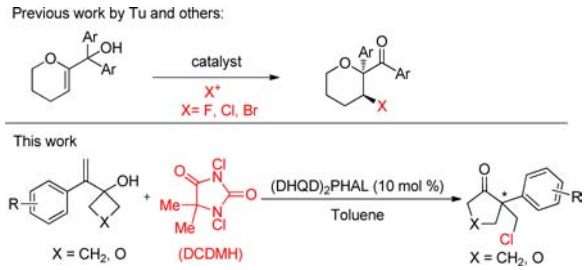
Supporting Information

ABSTRACT: A highly enantioselective chlorination/ring expansion cascade for the construction of cycloalkanones with an all-carbon quaternary center was realized (up to 97% ee). Oxa-cyclobutanol substrates were employed for the first time in the ring expansion reactions, affording the functionalized dihydrofuranones in excellent enantioselectivity.



Construction of chiral quaternary carbon centers, especially all-carbon quaternary centers, remains one of the most challenging subjects in contemporary synthetic chemistry.[1] Cycloalkanones with a chiral all-carbon quaternary center are attractive synthetic targets, as they are widely utilized intermediates for natural product syntheses.[2] For example, optically active 2-methyl-2-arylcyclopentanones have been employed as the key intermediates in the total synthesis of (−)-aphanorphine,[3a,b] (−)-isoeupamne,[3c] and tochiunyl acetate.[3d] Several catalytic enantioselective approaches have been developed for these synthetically useful building blocks. In this regard, Buchwald and co-workers have realized the Pd-catalyzed asymmetric α-arylation of alkyl-substituted cyclopentanones; however, installation of a blocking group at the less substituted α-carbon of 2-alkyl cyclopentanones is required.[4] Later, Shi and co-workers reported that enantioenriched 2-alkyl-2-aryl cyclopentanones could be obtained by asymmetric epoxidation of benzylidenecyclobutanes and subsequent epoxide rearrangement promoted by Et_2AlCl.[5] Despite notable advances, development of mild and straightforward methods for catalytic enantioselective syntheses of cycloalkanones with an α-all-carbon quaternary stereocenter is still in great demand.[6] On the other hand, catalytic asymmetric halofunctionalization of alkenes has witnessed rapid progress during the past several years.[7,8] Among them, relatively little attention has been focused toward catalytic asymmetric halogenation/semipinacol rearrangement cascade reactions though they have been proven to be highly efficient methods to construct chiral quaternary carbon centers.[9] Tu and co-workers recently reported highly enantioselective syntheses of α-oxa-quaternary ketones *via* chlorination, bromination, and fluorination-induced semipinacol rearrangement of electron-rich cyclic enol ethers (Scheme 1).[10] Inspired by these elegant works, we envisaged that catalytic enantioselective halogenation-initiated ring expansion might provide an efficient synthesis of chiral cycloalkanones.[11] Herein we report such an asymmetric synthesis of 2-alkyl-2-aryl cycloalkanones by a highly enantioselective chlorination/ring expansion cascade. Oxa-cyclobutanol substrates were found to be compatible for the first time in the ring expansion reactions.[12]

Scheme 1. Designed Chlorination/Ring Expansion Cascade

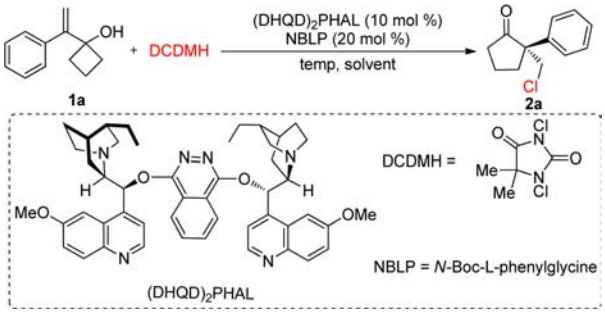


We began our study by testing the reaction of cyclobutanol **1a** with 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) under the catalysis of $(DHQD)_2PHAL$. To our delight, in the presence of 10 mol % of $(DHQD)_2PHAL$ and 20 mol % of *N*-Boc-L-phenylglycine (NBLP),[10b,13] the reaction could proceed smoothly in CCl_4 at 0 °C to give the desired cyclopentanone **2a** in 60% yield with 84% ee (Table 1, entry 1). Evaluation of the solvent effect was subsequently carried out. As shown in Table 1, product **2a** could be obtained in 72% yield in $CHCl_3$, with slightly decreased enantioselectivity (ee = 77%) (Table 1, entry 2). Other chlorine-containing solvents such as DCE and DCM gave low enantioselectivity (Table 1, entries 3−4). The desired product was obtained in almost racemic form when polar solvent CH_3CN was utilized (64% yield, ee = 5%) (Table 1, entry 5). Further screening of solvents displayed that **2a** could be obtained in a slightly increased yield with increased enantioselectivity in toluene (67% yield, ee = 86%) (Table 1, entry 6). However, evaluation of other less polar solvents did not give improved results (58−77% yield, ee = 50−64%) (Table 1, entries 7−10). Further screening displayed that a low reaction temperature could slightly increase the enantiocontrol

Received: February 20, 2014
Published: March 11, 2014

dx.doi.org/10.1021/ol5005565 | *Org. Lett.* 2014, 16, 1810−1813

Table 1. Evaluation of the Solvents[a]



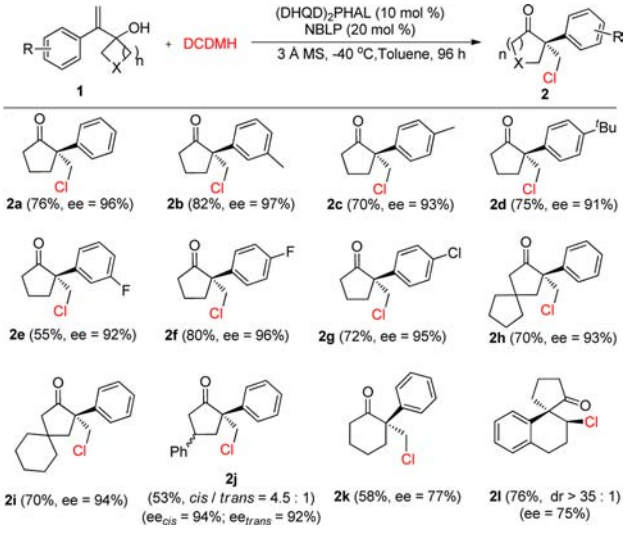
entry	solvent	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	CCl_4	0	1	60	84
2	$CHCl_3$	0	1	72	77
3	DCE	0	1	60	5
4	DCM	0	1	60	15
5	CH_3CN	0	1	64	5
6	toluene	0	2	67	86
7	xylene	0	2	58	50
8	*p*-xylene	0	2	67	51
9	*o*-xylene	0	2	72	51
10	PhF	0	2	77	64
11	toluene	−20	10	76	90
12[d]	toluene	−20	6	81	91
13[d]	toluene	−40	96	76	96

[a]Reactions were performed with **1a** (0.2 mmol), DCDMH (0.3 mmol), 20 mol % NBLP, and 10 mol % of $(DHQD)_2PHAL$. [b]Isolated yield. [c]Determined by HPLC analysis. [d]80 mg of 3 Å molecular sieves were utilized.

while addition of molecular sieves could accelerate the reaction and improve the yield (Table 1, entries 11−13). Finally, the desired product could be obtained in 76% yield and 96% ee at −40 °C (for complete optimization, see the Supporting Information).

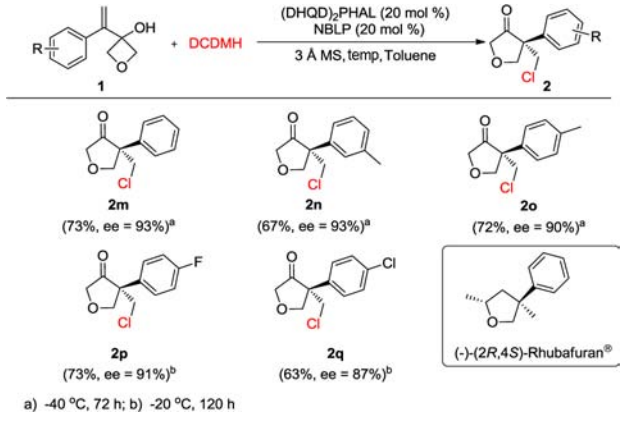
Under the optimized reaction conditions, the substrate scope of the chlorination/ring expansion cascade was explored. The results are summarized in Scheme 2. Either an electron-donating group (**2b**−**2d**) (70−82% yield, ee = 91−97%) or an electron-withdrawing group (**2e**−**2g**) (55−80% yield, ee = 92−96%) at the *meta* or *para* position of the benzene ring was well tolerated. The corresponding products could all be obtained in moderate to good yields with excellent enantioselectivity. To be noted, the incomplete conversion of substrate **1e** led to a moderate yield (55%). The 3,3-disubstituted cyclobutanols could give the corresponding spiro products in 70% yield with excellent enantioselectivity (**2h**−**2i**) (ee = 93−94%). Substrate **1j** (*cis*/*trans* = 2.7:1) with a phenyl group at the C3 position of the cyclobutanol moiety could also be well tolerated, affording product **2j** in 53% yield with a slightly increased diastereoselective ratio (4.5:1). Both of the diastereomers were obtained with excellent enantioselectivity (94% ee and 92% ee, respectively). We further tested the reaction between cyclopentanol derivative **1k** and DCDMH. The reaction gave the desired cyclohexanone **2k** in 58% yield and 77% ee. In addition, substrate **1l** derived from tetralone was also tested, and the desired spiro ketone **2l** could be obtained in 76% yield, 75% ee, and excellent diastereoselectivity.

Scheme 2. Chlorination/Ring Expansion of Cyclobutanols



Encouraged by the above results obtained for the cyclobutanols, we further explored whether oxa-cyclobutanols are suitable substrates. To the best of our knowledge, there is no previous report on the utilization of oxa-cyclobutanols in ring expansion while this method could provide a straightforward route to functionalized dihydrofuran-3(2*H*)-one. The 3,3-disubstituted tetrahydrofuran unit could be found in many functional molecules such as Rhubafuran, a commercially available odorous cyclic ether.[14] To our great delight, the ring expansion reaction proceeded smoothly for oxa-cyclobutanol substrates. As shown in Scheme 3, with 20 mol % of the catalyst, all the substituted oxa-cyclobutanol substrates tested could undergo the chlorination/ring expansion reactions, affording the desired products in excellent enantioselectivity (**2m**−**2q**) (63−73% yield, ee = 87−93%). To be noted, substrates (**2p**, **2q**) with a halogen atom on the benzene ring displayed decreased reactivity compared with electron-donating group containing substrates (**2n**, **2o**).

Scheme 3. Chlorination/Ring Expansion of Oxa-cyclobutanols

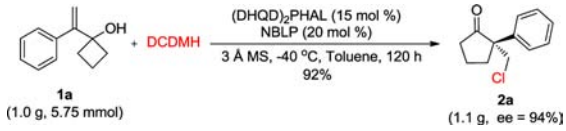


To evaluate the practicality of this catalytic process, a gram-scale reaction was carried out. As shown in Scheme 4, product **2a** could be obtained in 92% yield and 94% ee.

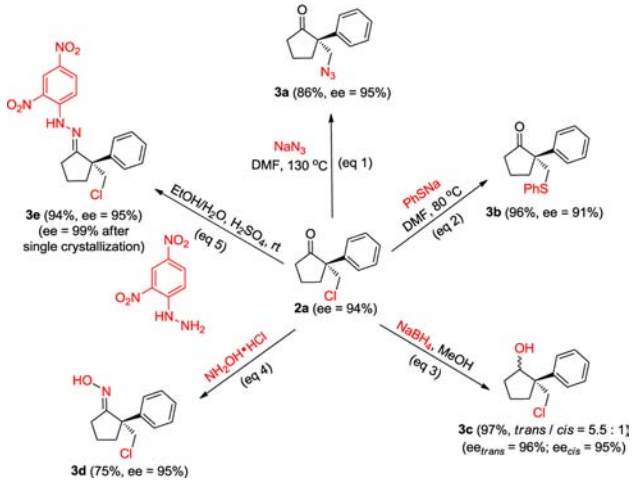
The products obtained here contain a carbonyl group and C−Cl bond that provide versatile handles for performing subsequent transformations. Several transformations have been carried out as shown in Scheme 5. Substitution of the chlorine atom with sodium azide and sodium benzenethiolate could

dx.doi.org/10.1021/ol5005565 | *Org. Lett.* 2014, 16, 1810−1813

Scheme 4. Gram-Scale Reaction



Scheme 5. Transformations of Product



provide the corresponding azide **3a** and thioether **3b** with good stereochemical integrity (Scheme 5, eqs 1−2). Cyclopentanol **3c** with continuous chiral centers could be obtained in 5.5:1 (*trans*/*cis*) dr when **2a** was subjected to $NaBH_4$ reduction (Scheme 5, eq 3). Furthermore, the chiral ketone could be converted to the corresponding oxime **3d** and hydrazine **3e** in good yields, without any loss of enantiopurity (Scheme 5, eqs 4−5). The absolute configuration of the α-quaternary chiral center was determined as *S* by an X-ray diffraction analysis of a single crystal of enantiopure **3e** (see the Supporting Information for details).

In summary, we have developed a highly enantioselective chlorination/ring expansion cascade for the construction of cycloalkanones with an all-carbon quaternary center. Notably, oxa-cyclobutanol substrates were used for the first time in the ring expansion reactions, affording the functionalized dihydrofuranones in excellent enantioselectivity. In addition, the gram-scale reaction and versatile transformations of the product would warrant the synthetic utility of this methodology.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analysis data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: slyou@sioc.ac.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Basic Research Program of China (973 Program 2010CB833300), the National Natural Science Foundation of China (21025209, 21121062, 21361140373), and the Chinese Academy of Sciences for generous financial support.

■ REFERENCES

(1) For recent reviews on the construction of chiral tetrasubstituted carbon centers, see: (a) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (b) Ramón, D. J.; Yus, M. *Curr. Org. Chem.* **2004**, *8*, 149. (c) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (d) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (e) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. (f) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873. (g) Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583. (h) Hawner, C.; Alexakis, A. *Chem. Commun.* **2010**, *46*, 7295. (i) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593.

(2) For a recent review, see: Hong, A. Y.; Stoltz, B. M. *Eur. J. Org. Chem.* **2013**, 2745.

(3) (a) Takano, S.; Inomata, K.; Sato, T.; Takahashi, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1990**, 290. (b) Tanaka, K.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 1049. (c) Tori, M.; Miyake, T.; Hamaguchi, T.; Sono, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2731. (d) Srikrishna, A.; Reddy, T. J. *Tetrahedron* **1998**, *54*, 8133.

(4) (a) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918. (b) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261.

(5) (a) Shen, Y.-M.; Wang, B.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 1429. (b) Shen, Y.-M.; Wang, B.; Shi, Y. *Tetrahedron Lett.* **2006**, *47*, 5455.

(6) For asymmetric Heck arylations by a chiral auxiliary, see: (a) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2003**, *125*, 3430. (b) Datta, G. K.; Larhed, M. *Org. Biomol. Chem.* **2008**, *6*, 674. For examples of asymmetric synthesis of 2-methyl-2-aryl indanones, see: (c) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446. (d) Chen, G.; Kwong, F. Y.; Chan, H. O.; Yu, W.-Y.; Chan, A. S. C. *Chem. Commun.* **2006**, 1413. (e) Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195. (f) Ge, S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 16330. (g) Richter, C.; Ranganath, K. V. S.; Glorius, F. *Adv. Synth. Catal.* **2012**, *354*, 377.

(7) For recent reviews on asymmetric halogenation of olefins, see: (a) Chen, G.; Ma, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 8306. (b) Tan, C. K.; Zhou, L.; Yeung, Y.-Y. *Synlett* **2011**, 1335. (c) Castellanos, A.; Fletcher, S. P. *Chem.—Eur. J.* **2011**, *17*, 5766. (d) Hennecke, U. *Chem.—Asian J.* **2012**, *7*, 456. (e) Denmark, S. E.; Kuester, W. E.; Burk, M. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10938. (f) Murai, K.; Fujioka, H. *Heterocycles* **2013**, *87*, 763. (g) Tan, C. K.; Yeung, Y.-Y. *Chem. Commun.* **2013**, *49*, 7985. (h) Cheng, Y. A.; Yu, W. Z.; Yeung, Y.-Y. *Org. Biomol. Chem.* **2014**, 12, DOI: 10.1039/C3OB42335B.

(8) For selected asymmetric halofunctionalization of olefins, see: (a) Zhou, L.; Tan, C. K.; Jiang, X.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 15474. (b) Veitch, G. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 7332. (c) Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 9174. (d) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. *J. Am. Chem. Soc.* **2010**, *132*, 3664. (e) Cai, Y.; Liu, X.; Hui, Y.; Jiang, J.; Wang, W.; Chen, W.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 6160. (f) Nicolaou, K. C.; Simmons, N. L.; Ying, Y.; Heretsch, P. M.; Chen, J. S. *J. Am. Chem. Soc.* **2011**, *133*, 8134. (g) Lozano, O.; Blessley, G.; Martinez del Campo, T.; Thompson, A. L.; Giuffredi, G. T.; Bettati, M.; Walker, M.; Borman, R.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2011**, *50*, 8105. (h) Zhou, L.; Chen, J.; Tan, C. K.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2011**, *133*, 9164. (i) Jaganathan, A.; Garzan, A.; Whitehead, D. C.; Staples, R. J.; Borhan, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2593. (j) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681. (k) Hennecke, U.; Müller, C. H.; Fröhlich, R. *Org. Lett.* **2011**, *13*, 860. (l) Denmark, S. E.; Burk, M. T. *Org. Lett.* **2012**, *14*, 256. (m) Tungen, J. E.; Nolsøe, J. M. J.; Hansen, T. V. *Org. Lett.* **2012**, *14*, 5884. (n) Ikeuchi, K.; Ido, S.; Yoshimura, S.; Asakawa, T.; Inai, M.; Hamashima, Y.; Kan, T. *Org. Lett.* **2012**, *14*, 6016. (o) Dobish, M. C.; Johnston, J. N. *J. Am. Chem. Soc.*

2012, *134*, 6068. (p) Paull, D. H.; Fang, C.; Donald, J. R.; Pansick, A. D.; Martin, S. F. *J. Am. Chem. Soc.* **2012**, *134*, 11128. (q) Wang, Y.-M.; Wu, J.; Hoong, C.; Rauniyar, V.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 12928. (r) Alix, A.; Lalli, C.; Retailleau, P.; Masson, G. *J. Am. Chem. Soc.* **2012**, *134*, 10389. (s) Zhao, Y.; Jiang, X.; Yeung, Y.-Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 8597. (t) Chen, F.; Tan, C. K.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2013**, *135*, 1232. (u) Brindle, C. S.; Yeung, C. S.; Jacobsen, E. N. *Chem. Sci.* **2013**, *4*, 2100. (v) Huang, D.; Liu, X.; Li, L.; Cai, Y.; Liu, W.; Shi, Y. *J. Am. Chem. Soc.* **2013**, *135*, 8101. (w) Tripathi, C. B.; Mukherjee, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 8450. (x) Xie, W.; Jiang, G.; Liu, H.; Hu, J.; Pan, X.; Zhang, H.; Wan, X.; Lai, Y.; Ma, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 12924. (y) Jaganathan, A.; Staples, R. J.; Borhan, B. *J. Am. Chem. Soc.* **2013**, *135*, 14806.

(9) For recent reviews on semipinacol rearrangements, see: (a) Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523. (b) Wang, B.; Tu, Y. Q. *Acc. Chem. Res.* **2011**, *44*, 1207. (c) Wang, S.-H.; Li, B.-S.; Tu, Y.-Q. *Chem. Commun* **2014**, *50*, 2393. For selected examples on enantioselective construction of cycloalkanones with a quaternary carbon stereocenter by asymmetric semipinacol rearrangements, see: (d) Trost, B. M.; Yasukata, T. *J. Am. Chem. Soc.* **2001**, *123*, 7162. (e) Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2006**, *128*, 6044. (f) Zhang, Q.-W.; Fan, C.-A.; Zhang, H.-J.; Tu, Y.-Q.; Zhao, Y.-M.; Gu, P.; Chen, Z.-M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8572. (g) Kleinbeck, F.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 9178. (h) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2011**, *133*, 8834. (i) Chai, Z.; Rainey, T. J. *J. Am. Chem. Soc.* **2012**, *134*, 3615.

(10) For catalytic asymmetric halogenation-initiated semipinacol rearrangements, see: (a) Wang, M.; Wang, B. M.; Shi, L.; Tu, Y. Q.; Fan, C.-A.; Wang, S. H.; Hu, X. D.; Zhang, S. Y. *Chem. Commun.* **2005**, 5580. (b) Chen, Z.-M.; Zhang, Q.-W.; Chen, Z.-H.; Li, H.; Tu, Y.-Q.; Zhang, F.-M.; Tian, J.-M. *J. Am. Chem. Soc.* **2011**, *133*, 8818. (c) Müller, C. H.; Wilking, M.; Rühlmann, A.; Wibbeling, B.; Hennecke, U. *Synlett* **2011**, 2043. (d) Li, H.; Zhang, F.-M.; Tu, Y.-Q.; Zhang, Q.-W.; Chen, Z.-M.; Chen, Z.-H.; Li, J. *Chem. Sci.* **2011**, *2*, 1839. (e) Chen, Z.-M.; Yang, B.-M.; Chen, Z.-H.; Zhang, Q.-W.; Wang, M.; Tu, Y.-Q. *Chem.—Eur. J.* **2012**, *18*, 12950.

(11) During the preparation of this manuscript, elegant enantioselective fluorination or iodination-induced semipinacol rearrangements were reported; see: (a) Romanov-Michailidis, F.; Guénéé, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 9266. (b) Romanov-Michailidis, F.; Guénéé, L.; Alexakis, A. *Org. Lett.* **2013**, *15*, 5890.

(12) For examples of halofunctionalization of olefins from this group, see: (a) Yin, Q.; You, S.-L. *Org. Lett.* **2012**, *14*, 3526. (b) Yin, Q.; You, S.-L. *Org. Lett.* **2013**, *15*, 4266. (c) Cai, Q.; Yin, Q.; You, S.-L. *Asian J. Org. Chem.* **2013**, *3*, DOI: 10.1002/ajoc.201300146.

(13) *N*-Boc-L-phenylglycine was first utilized in asymmetric halogenation by Tu; see ref 10b.

(14) For an asymmetric synthesis of Rhubafuran, see: Abate, A.; Brenna, E.; Fronza, G.; Fuganti, C.; Gatti, F. G.; Serra, S.; Zardoni, E. *Helv. Chim. Acta* **2004**, *87*, 765.