JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Asymmetric Fluorination of Enamides: Access to α-Fluoroimines Using an Anionic Chiral Phase-Transfer Catalyst

Robert J. Phipps, Kenichi Hiramatsu, and F. Dean Toste*

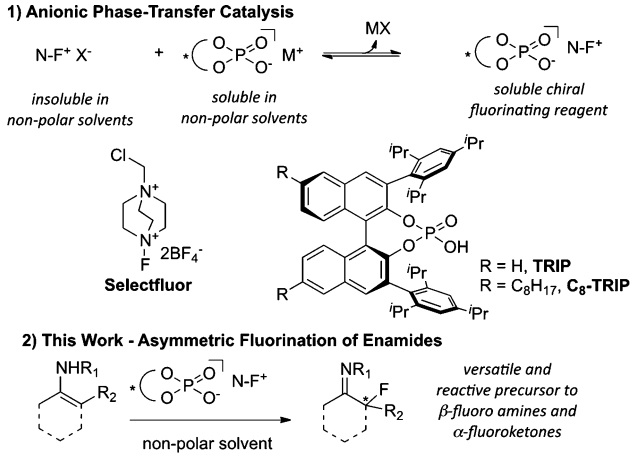
Department of Chemistry, University of California, Berkeley, California 94720, United States

Supporting Information

ABSTRACT: The use of a BINOL-derived phosphate as a chiral anionic phase-transfer catalyst in a nonpolar solvent allows the enantioselective fluorination of enamides using Selectfluor as the fluorinating reagent. We demonstrate that a wide range of stable and synthetically versatile α-(fluoro)benzoylimines can be readily accessed with high enantioselectivity. These compounds have the potential to be readily elaborated into a range of highly stereodefined β-fluoroamines, compounds that constitute highly valuable building blocks of particular importance in the synthesis of pharmaceuticals.

The prevalence of fluorine atoms in pharmaceutical agents[1] has driven the development of new methods for the enantioselective[2,3] introduction of fluorine into small molecules that may constitute basic building blocks for elaboration into biologically relevant molecules. In this context, the chiral β-fluoroamine motif is one of remarkable utility; the presence of a β-fluorine is well established to lower the pK_a of the amine nitrogen, impacting binding, metabolism, and other pharmacological properties.[1b,4] Nevertheless, there are few direct methods for the asymmetric synthesis of β-fluoroamines. Those that do exist often proceed through processes in which introduction of the fluorine is not itself asymmetric[5] or through α-fluorocarbonyl compounds generated by enantioselective fluorination of ketones and aldehydes.[6] Organocatalysis has provided a number of elegant protocols for this asymmetric α-fluorination reaction, including cinchona alkaloid-mediated transformations[3b,7] and those based on enamine catalysis.[8] We noted that the latter highly successful organocatalyic methods proceed via α-fluoroimine intermediates that are subsequently hydrolyzed for the necessary release of the secondary amine catalyst. We speculated that a methodology, distinct from enamine catalysis, in which an enantioenriched α-fluoroimine could be isolated would be highly versatile. These products could be elaborated through a number of well-precedented pathways to a wide variety of enantioenriched β-fluoroamines.[9]

Our laboratory has recently reported the enantioselective fluorocyclization of olefins using a cationic fluorinating agent, Selectfluor, and anionic phase-transfer catalysts based on chiral phosphoric acids, specifically TRIP and C_8-TRIP (eq 1).[10] As a powerful application of this new strategy we sought to apply this concept to the enantioselective synthesis of α-fluoroimines. Specifically, enamides and ene−carbamates have seen much recent use in asymmetric synthesis, and we sought to employ



these compounds as nucleophiles in our fluorination process (eq 2).[11] The success of this class of substrates as nucleophiles in a number of enantioselective phosphoric acid-catalyzed reactions was encouraging.[12] We were particularly encouraged by the reported stability of *N*-carbobenzyloxy (Cbz) ketimines, which made us optimistic that an α-fluoroimine may be stable and isolable, in line with our goal.[11b,12f] We commenced our studies by examining the fluorination of several ene−carbamates based on 2-methyltetralone (Table 1).

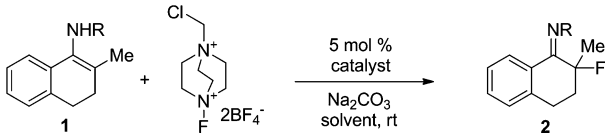
After 8h of reaction, the Cbz ene−carbamate **1a** was fluorinated to a very low degree in the absence of a catalyst (entry 1). Addition of our phase-transfer catalyst C_8-TRIP resulted in complete conversion to the fluorinated product in the same amount of time (entry 2). The α-fluoroimine product was stable and isolable, and the obtained product enantioselectivity of 55% was highly encouraging. The analogous methyl carbamate resulted in a similarly high yield but lower enantioselectivity (entry 3). Fluorination of *N*-acetylenamide **1c** was also clearly accelerated by our phase-transfer catalyst but resulted in a disappointingly low enantioselectivity (3% ee; entries 4 and 5). However, by progressing to the *N*-benzoylenamide **1d**, we were delighted to discover that the desired product could be obtained with excellent efficiency and selectivity (91% yield, 90% ee; entry 6). Notably, after the same reaction time in the absence of catalyst, only a 6% yield of fluorinated product was obtained (entry 7).

While the reaction was found to tolerate a number of apolar solvents, the highest enantioselectivity was obtained in hexane

Received: March 5, 2012
Published: May 11, 2012

dx.doi.org/10.1021/ja303959p | J. Am. Chem. Soc. 2012, 134, 8376−8379

Table 1. Optimization of the Enamide Fluorination Reaction



entry	R	catalyst	solvent, time	% yield **2**[a]	% ee **2**[b,c]
1	CO_2Bn (**1a**)	none	toluene, 8 h	14[d]	–
2	CO_2Bn	(*S*)-C_8-TRIP	toluene, 8 h	77	55 (*R*)
3	CO_2Me (**1b**)	(*S*)-C_8-TRIP	toluene, 8 h	75	22 (*R*)
4	Ac (**1c**)	none	toluene, 8 h	16[d]	–
5	Ac	(*S*)-C_8-TRIP	toluene, 8 h	84	3
6	Bz (**1d**)	(*S*)-C_8-TRIP	toluene, 8 h	91	90 (*R*)
7	Bz	none	toluene, 8 h	6[d]	–
8	Bz	(*S*)-C_8-TRIP	PhF, 24 h	87	90 (*R*)
9	Bz	(*S*)-C_8-TRIP	cyclohexane, 24 h	85	94 (*R*)
10	Bz	(*S*)-C_8-TRIP	hexane, 24 h	88	96 (*R*)
11	Bz	(*S*)-TRIP	toluene, 24 h	83	92 (*R*)
12	Bz	(*S*)-TRIP	hexane, 24 h	83	92 (*R*)
13[e]	Bz	(*S*)-TRIP	hexane, 24 h	13	11 (*R*)

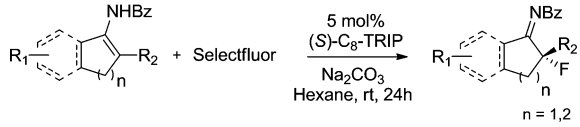
[a]Isolated yields after chromatography on silica gel, unless otherwise indicated. [b]Determined by HPLC. [c]Absolute configurations (in parentheses) were determined by hydrolysis and comparison of optical rotation with ref 13. [d]^{1}H NMR yield using 1,2-dimethoxyethane as an internal standard. [e]Reaction was run in the absence of Na_2CO_3.

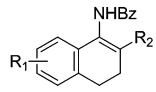
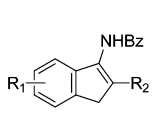
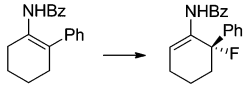
(entries 8–10). To evaluate the commercially available phosphoric acid catalyst TRIP in our process, we compared this catalyst with C_8-TRIP in two cases. In toluene, the enantioselectivity with the two catalysts was found to be similar (entries 6 and 11), but in hexane, C_8-TRIP was superior (entries 10 and 12). In the absence of an inorganic base, the fluorination proceeded to very low conversion with poor selectivity (entry 13). We speculate that the parent phosphoric acid is a very poor catalyst and that, in accordance with our proposal, the phosphate is required in order to undergo anion exchange with the Selectfluor reagent.

Having established the optimum conditions, we next examined the scope of the transformation. Gratifyingly, a range of cyclic enamides provided high yields of stable α-(fluoro)benzoylimines with high selectivities in this process (Table 2). Substitution on the enamide functionality was well-tolerated, as methyl, allyl, phenyl, and benzyl groups all gave high enantioselectivity, leading to products bearing a variety of diversely substituted quaternary fluorinated stereocenters (entries 1–3 and 6). In addition, these stereocenters bear a vicinal imine that is stable enough to isolate but poised to undergo a variety of further diastereoselective transformations. Indanone-derived enamides participated readily, and we used this scaffold to demonstrate that substrates with a variety of electronic characters are well-tolerated (entries 5–11). In the case of entry 4, in which the originally obtained enantioselectivity was lower (81% ee), we observed a beneficial effect of running the reaction in the presence of 5 equiv of 3-hexanol, which led to improved selectivity (94% ee).[15] The 2-phenylcyclohexanone-derived enamide **1o** gave slightly reduced but still synthetically useful enantioselectivity, with the versatile fluorinated enamide **2o** being isolated (entry 12). However, the corresponding 2-methylcyclohexanone-derived enamide revealed the present limitation (18% ee).[16]

We next turned our attention to enamides bearing no substitution (Table 3). Anticipating that product stability or racemization via tautomerization could be problematic, we were pleasantly surprised to find that tetralone-derived enamides delivered stable products with high enantiomeric excesses (**2q–s**). In addition, a benzosuberone-derived enamide was also amenable to our reaction (**2t**), and in two of the above cases, using 3-hexanol as an additive again led to improved selectivity. To assess the effectiveness of our reaction on a substrate with a

Table 2. Exploration of the Scope of Substituted Enamides

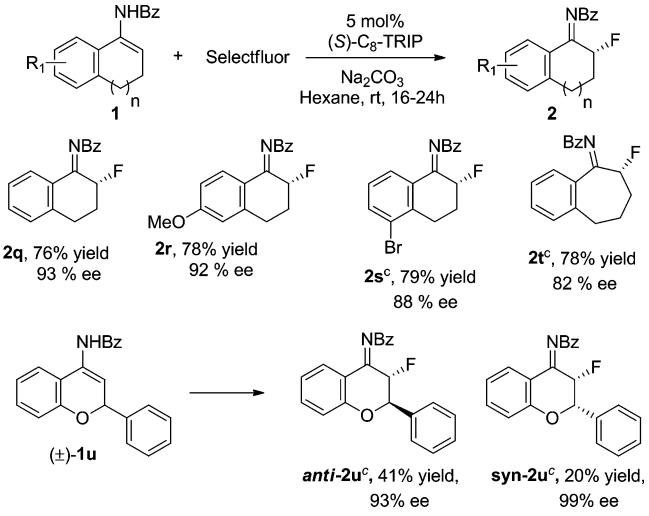


Entry	Substrate **1**	R_1	R_2	Product	% yield **2**[a]	%ee **2**[b,c]
1		H	Me	**2d**	88	96
2[d]		H	Allyl	**2e**	80	96
3		H	Bn	**2f**	92	99
4[e]		6-OMe	Me	**2g**	94	92
5		H	Me	**2h**	66	96
6[d,f]		H	Ph	**2i**	79	90
7		H	Bn	**2j**	84	98
8		5-OMe	Bn	**2k**	68	96
9[g]		5-F	Bn	**2l**	75	94
10[d]		5-Cl	Bn	**2m**	85	93
11		H	(3-OMe)Bn	**2n**	83	98
12[h]				**2o**	58	87

[a]Isolated yields after chromatography on silica gel. [b]Determined by HPLC. [c]The absolute configurations of **2d** and **2h** were determined by comparison of the optical rotations of their hydrolysis products with refs 13 and 14, and that of **2o** was determined by X-ray crystallography; absolute configurations of all the other compounds were tentatively assigned by analogy. [d]Toluene was used as the solvent. [e]Reaction was run in the presence of 5 equiv of 3-hexanol. [f](*S*)-TRIP was used as the catalyst. [g]Reaction time was 48 h. [h]See the Supporting Information for details.

dx.doi.org/10.1021/ja303959p | *J. Am. Chem. Soc.* 2012, 134, 8376–8379

Table 3. Fluorination of Unsubstituted Enamides[a,b]

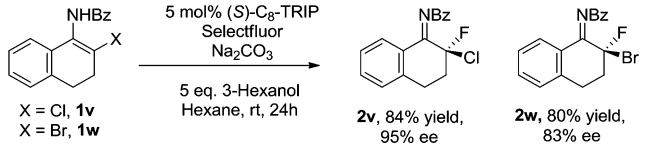


[a]Isolated yields after chromatography on silica gel. [b]ee's were determined by HPLC. [c]Reaction was run in the presence of 5 equiv of 3-hexanol.

pre-existing stereocenter, racemic flavanone-derived enamide **1u** was synthesized. Fluorination of this heterocyclic substrate resulted in an approximately equal ratio of separable anti and syn diastereomers, both with excellent enantioselectivity (93 and 99% ee; Table 3), although the instability of the syn diastereomer compromised the final isolated yield. This example illustrates the high selectivity of our catalytic system, regardless of the nature of an existing stereocenter.

To test the limits of our fluorination reaction, we applied it to chloro- and bromo-substituted enamides **1v** and **1w.** While there have been several reports on the catalytic asymmetric synthesis of geminal chlorofluoro compounds, compatible substrates have to date remained limited to activated methylene compounds, such as β-keto esters, and aldehydes.[17] Reports of chiral geminal fluorobromo compounds remain sparse, most likely because their asymmetric synthesis is challenging.[18] Accordingly, the extension of our methodology to encompass these classes of product (Scheme 1) is a testament to the future potential of this strategy for asymmetric fluorination: the geminal fluorochloro product **2v** was obtained in 95% ee and the novel chiral bromofluoro compound **2w** in 83% ee.

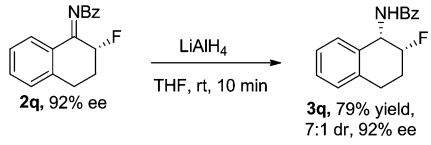
Scheme 1. Fluorination of Halo-Substituted Enamides



Finally, to demonstrate the surprisingly robust nature of product **2q** and in general the ready further transformation of our products, we showed that **2q** tolerates reduction with lithium aluminum hydride without any loss of stereochemical integrity (Scheme 2).

The extensive previous efforts directed toward understanding the mechanism of BINOL-derived phosphoric acid-catalyzed reactions allow us to advance a plausible hypothesis as to the origin of the observed enantioselectivities. We have employed the model of Simón and Goodman regarding the reactions of

Scheme 2. Reduction of 2q without Racemization



ene–carbamates with *N*-acylimines[12f,h] and nitrosobenzene[12e] to provide a tentative rationalization of the absolute stereochemistry that we observed experimentally.[19] Utilizing the bifunctional nature of this class of catalysts, we anticipate that the phosphate anion is able to form an ion pair with the Selectfluor reagent on one oxygen atom while simultaneously activating the enamide through hydrogen bonding with the second. The enamide would reside so as to put the bulk of the tetralone in an "open" quadrant, with the amide group occupying a "closed" quadrant (Figure 1). We speculate that

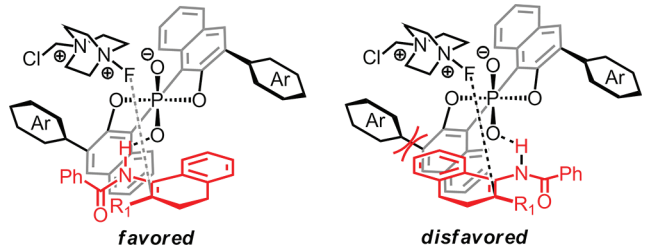


Figure 1. Mechanistic proposal for observed absolute stereochemistry.

the high tolerance of our reaction toward substitution on the enamide (Figure 1, R_1) as well as an existing stereocenter at the 3-position (Table 3, **2u**) may reflect the fact that these positions point away from the catalyst and thus have no effect on catalyst–substrate binding.[20] The remarkably high selectivity obtained with benzamide compared with other acyl groups is a focus of current investigation.

In summary, we have extended our concept of anionic phase-transfer catalysis[10,21] to encompass the enantioselective fluorination of cyclic enamides. The scope of this transformation is broad, and we have demonstrated the effectiveness of the reaction on five-, six-, and seven-membered rings as well as heterocyclic rings. Our future work will focus on gaining insight into the factors controlling the selectivity and, more generally, opening new avenues for this mode of catalysis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

fdtoste@berkeley.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank University of California, Berkeley and Amgen for financial support. R.J.P. is grateful to the European Commission for a Marie Curie International Outgoing Fellowship. K.H. gratefully acknowledges support from Asubio Pharma Co., Ltd.

REFERENCES

(1) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (b) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (c) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637. (d) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.

(2) (a) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119. (b) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1. (c) Lectard, S.; Hamashima, Y.; Sodeoka, M. *Adv. Synth. Catal.* **2010**, *352*, 2708.

(3) (a) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359. (b) Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10728. (c) Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530. (d) Paull, D. H.; Scerba, M. T.; Alden-Danforth, E.; Widger, L. R.; Lectka, T. *J. Am. Chem. Soc.* **2008**, *130*, 17260. (e) Suzuki, T.; Hamashima, Y.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 5435. (f) Cahard, D.; Xu, X.; Couve-Bonnaire, S.; Pannecoucke, X. *Chem. Soc. Rev.* **2010**, *39*, 558.

(4) (a) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell: Chichester, U.K., 2009. (b) Morgenthaler, M.; Schweizer, E.; Hoffmann-Röder, A.; Benini, F.; Martin, R. E.; Jaeschke, G.; Wagner, B.; Fischer, H.; Bendels, S.; Zimmerli, D.; Schneider, J.; Diederich, F.; Kansy, M.; Müller, K. *ChemMedChem* **2007**, *2*, 1100.

(5) (a) Duthion, B.; Pardo, D. G.; Cossy, J. *Org. Lett.* **2010**, *12*, 4620. (b) Kalow, J. A.; Schmitt, D. E.; Doyle, A. G. *J. Org. Chem.* **2012**, *77*, 4177.

(6) (a) Appayee, C.; Brenner-Moyer, S. E. *Org. Lett.* **2010**, *12*, 3356. (b) Fadeyi, O. O.; Lindsley, C. W. *Org. Lett.* **2009**, *11*, 943. (c) Schulte, M. L.; Lindsley, C. W. *Org. Lett.* **2011**, *13*, 5684.

(7) (a) Cahard, D.; Audouard, C.; Plaquevent, J.-C.; Roques, N. *Org. Lett.* **2000**, *2*, 3699. (b) Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123*, 7001. (c) Ishimaru, T.; Shibata, N.; Horikawa, T.; Yasuda, N.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4157.

(8) (a) Kwiatkowski, P.; Beeson, T. D.; Conrad, J. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 1738. (b) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826. (c) Enders, D.; Hüttl, M. R. M. *Synlett* **2005**, 0991. (d) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703. (e) Steiner, D. D.; Mase, N.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2005**, *44*, 3706.

(9) Petrini, M.; Torregiani, E. *Synthesis* **2007**, 159.

(10) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681.

(11) (a) Carbery, D. R. *Org. Biomol. Chem.* **2008**, *6*, 3455. (b) Matsubara, R.; Kobayashi, S. *Acc. Chem. Res.* **2008**, *41*, 292. (c) Nugent, T. C.; El-Shazly, M. *Adv. Synth. Catal.* **2010**, *352*, 753.

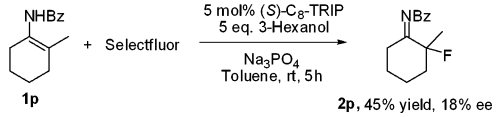
(12) (a) Dagousset, G.; Drouet, F.; Masson, G.; Zhu, J. *Org. Lett.* **2009**, *11*, 5546. (b) Dagousset, G.; Zhu, J.; Masson, G. *J. Am. Chem. Soc.* **2011**, *133*, 14804. (c) Guo, Q.-X.; Peng, Y.-G.; Zhang, J.-W.; Song, L.; Feng, Z.; Gong, L.-Z. *Org. Lett.* **2009**, *11*, 4620. (d) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. *J. Am. Chem. Soc.* **2009**, *131*, 4598. (e) Lu, M.; Lu, Y.; Zhu, D.; Zeng, X.; Li, X.; Zhong, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 8588. (f) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2254. (g) Terada, M.; Machioka, K.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 10336. (h) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 2553. (i) Drouet, F.; Lalli, C.; Liu, H.; Masson, G.; Zhu, J. *Org. Lett.* **2011**, *13*, 94.

(13) Davis, F. A.; Zhou, P.; Murphy, C. K.; Sundarababu, G.; Qi, H.; Han, W.; Przeslawski, R. M.; Chen, B.-C.; Carroll, P. J. *J. Org. Chem.* **1998**, *63*, 2273.

(14) Takeuchi, Y.; Suzuki, T.; Satoh, A.; Shiragami, T.; Shibata, N. *J. Org. Chem.* **1999**, *64*, 5708.

(15) The use of isopropanol as an additive has previously been observed to give higher enantioselecitivy in the organocatalytic fluorination of aldehydes (see ref 8b). In our case, we found 3-hexanol to be preferable, and we speculate that isopropanol may result in undesirable solubilization of the Selectfluor reagent. Investigations into the reasons for this improvement are underway.

(16) Enamide **1p** derived from 2-methylcyclohexanone gave fluorinated benzoylimine **2p** in 18% ee:



(17) (a) Frantz, R.; Hintermann, L.; Perseghini, M.; Broggini, D.; Togni, A. *Org. Lett.* **2003**, *5*, 1709. (b) Kang, S. H.; Kim, D. Y. *Adv. Synth. Catal.* **2010**, *352*, 2783. (c) Shibatomi, K.; Narayama, A.; Soga, Y.; Muto, T.; Iwasa, S. *Org. Lett.* **2011**, *13*, 2944. (d) Shibatomi, K.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5796.

(18) Iseki, K.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron* **1999**, *55*, 2225.

(19) Simón, L.; Goodman, J. M. *J. Org. Chem.* **2011**, *76*, 1775.

(20) It is possible that the lower selectivity observed with cyclohexanone-derived enamide **1o** may reflect the importance of $\pi-\pi$ interactions between the substrate and the catalyst, and we thank a referee for this suggestion.

(21) Hamilton, G. L.; Kanai, T.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 14984.