ACS Catalysis

Letter

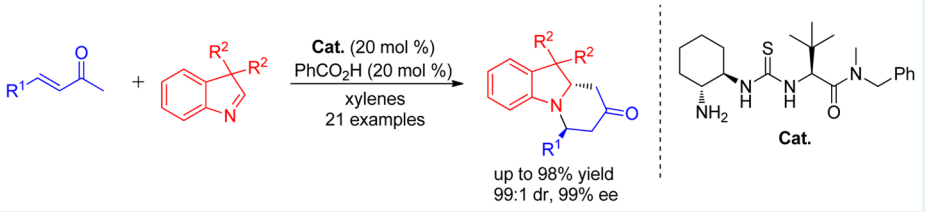
pubs.acs.org/acscatalysis

Catalytic Asymmetric Formal Aza-Diels–Alder Reactions of α,β-Unsaturated Ketones and 3*H*-Indoles

Haoxiang Hu,[†] Chunna Meng,[†] Yun Dong,[†] Xin Li,[†] and Jinxing Ye*[,†,‡]

[†]Engineering Research Centre of Pharmaceutical Process Chemistry, Ministry of Education, School of Pharmacy and [‡]Shanghai Key Laboratory of New Drug Design, School of Pharmacy, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China

Supporting Information



ABSTRACT: Asymmetric formal aza-Diels–Alder reactions with α,β-unsaturated ketones and 3*H*-indoles with disubstituted groups on the C3 position catalyzed by primary amine-thiourea bifunctional catalyst have been developed. The reactions produced chiral hexahydropyrido-[1,2-*a*]-indole-2-ones in high yields with excellent diastereo- and enantioselectivities.

KEYWORDS: *asymmetric catalysis, amine, aza-Diels–Alder, cycloaddition, piperidinone, bifunctional catalyst*

The Diels–Alder (DA) reaction participates as one of the most eminent, practical, and elegant synthetic strategies in organic chemistry, which demonstrates numerous applications in the total synthesis of natural products and drugs.[1] Its imine variant, the imino-Diels–Alder reaction, has recently attracted the attention of organic chemists on the synthesis of aza-heterocycles, such as piperidine derivatives. In the imino-Diels–Alder reactions, the imines may be employed as either dienes or dienophiles.[2] Alternatively, a tandem Mannich–Michael reaction of enone and imine, named the formal aza-Diels–Alder (FADA) reaction, provided a facile access to 4-piperidinone by employing Lewis acid, Brønsted acid, or organocatalyst. In 2003, Itoh, Ohsawa and co-workers reported a remarkable proline-catalyzed enantioselective FADA reaction (tandem Mannich–Michael reaction) between vinyl ketone and dihydro-β-carboline and its application in the total synthesis of *ent*-dihydrocorynantheol.[3] Recently, Jacobsen and co-workers reported a general and highly enantio- and diastereoselective FADA method between α,β-unsaturated ketones and dihydro-β-carbolines via a new bifunctional catalyst.[4] This cyclic (Z)-aldimine dihydro-β-carboline is treated as a versatile starting material in the various protocols of the synthesis of natural products. However, 3*H*-indoles,[5] another readily accessible cyclic (*Z*)-aldimines, have rarely been reported as reagents in asymmetric processes.[6] The structural skeleton of hexahydropyrido[1,2-*a*]-indole has been found in many natural products and potential biologically active compounds (Figure 1).[7] As is illustrated in Figure 1, the retrosynthetic analysis showed that the structural motif of pyrido[1,2-*a*]-indole-2-one might be synthesized from 3*H*-indole and trimethylsilyl dienol ether or dienamine (*N*-

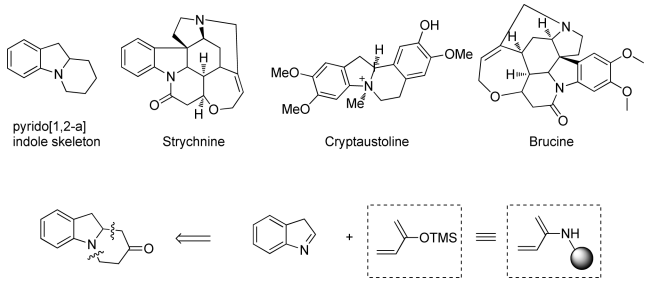


Figure 1. Selected natural products, pharmaceutically active molecules with the fragments of hexahydropyrido [1, 2-*a*] indole, and its retro-synthesis analysis.

substituted buta-1,3-dien-2-amine). In adopting one chiral amine catalyst, there is a possibility of modulating the stereochemical outcome of this FADA reaction of α,β-unsaturated ketone. As part of an ongoing program showing the potential application of enones in organocatalytic reactions, we describe here highly diastereo- and enantioselective FADA reactions of enones and 3*H*-indoles, which contained disubstituted groups on the C3 position by employing a small molecule chiral primary amine- thiourea.[8]

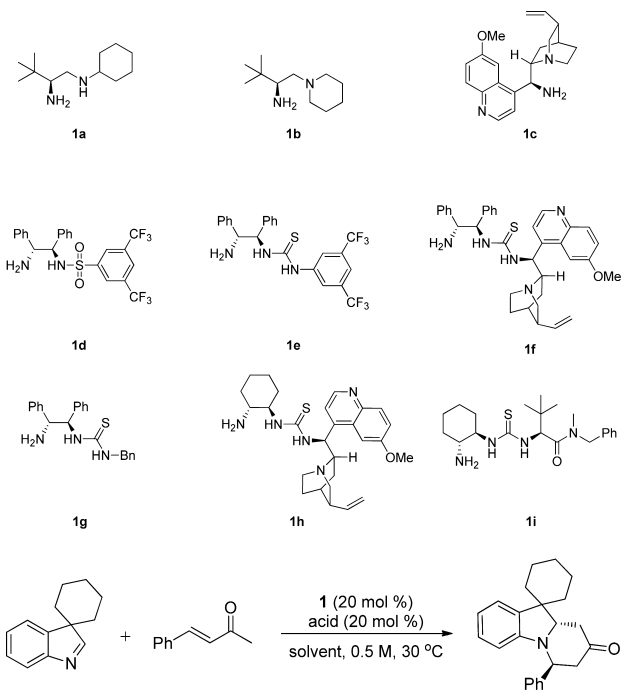
Initiating our work, we investigated the possible FADA reaction between the specified imine **2a** and α,β-unsaturated ketone **3a** in the presence of the bifunctional primary amine-secondary amine **1a** developed by our own group.[9] It was

Received: March 31, 2015
Revised: May 12, 2015
Published: May 13, 2015

DOI: 10.1021/acscatal.5b00680
ACS Catal. 2015, 5, 3700–3703

gratifying that the highly diastereoselective product **4a** was obtained with 60% conversion and 50% ee (Table 1, entry 1).

Table 1. Optimization of Reaction Parameters[a]



entry	cat	acid	solvent	conv (%)[b]	dr[c]	ee (%)[d]
1	**1a**	$PhCO_2H$	toluene	60	99:1	50
2	**1b**	$PhCO_2H$	toluene	--	--	--
3	**1c**	$PhCO_2H$	toluene	12	99:1	nd
4	**1d**	$PhCO_2H$	toluene	100	97:3	−37
5	**1e**	$PhCO_2H$	toluene	100	98:2	50
6	**1f**	$PhCO_2H$	toluene	25	98:2	77
7	**1g**	$PhCO_2H$	toluene	87	98:2	80
8[e]	**1h**	$PhCO_2H$	toluene	20	99:1	−8
9	**1i**	$PhCO_2H$	toluene	74	98:2	91
10[f]	**1i**	$PhCO_2H$	xylenes	100	99:1	92
11[f]	**1i**	*o*-F-$PhCO_2H$	xylenes	100	99:1	87
12[f]	**1i**	AcOH	xylenes	100	99:1	91
13[f]	**1i**	none	xylenes	9	99:1	nd
14[e]	**1i**	$PhCO_2H$	xylenes	100	99:1	88

[a]Unless otherwise stated, all reactions were carried out using 1.0 equiv of **3a** (0.1 mmol), 1.0 equiv of **2a** (0.1 mmol), 0.2 equiv of catalyst and 0.2 equiv of acid in solvent (0.2 mL) at 30 °C for 72 h. [b]Conversion was determined by GC. [c]Diastereomeric ratios (dr) were determined by GC. [d]Enantiomeric excess (ee) values were determined by chiral HPLC. [e]1.0 equiv of **3a** (0.1 mmol) and 3.0 equiv of **2a** (0.3 mmol) in solvent (0.2 mL) at 40 °C for 48 h. [f]1.0 equiv of **3a** (0.1 mmol) and 3.0 equiv of **2a** (0.3 mmol) in solvent (0.2 mL) at 30 °C for 72 h.

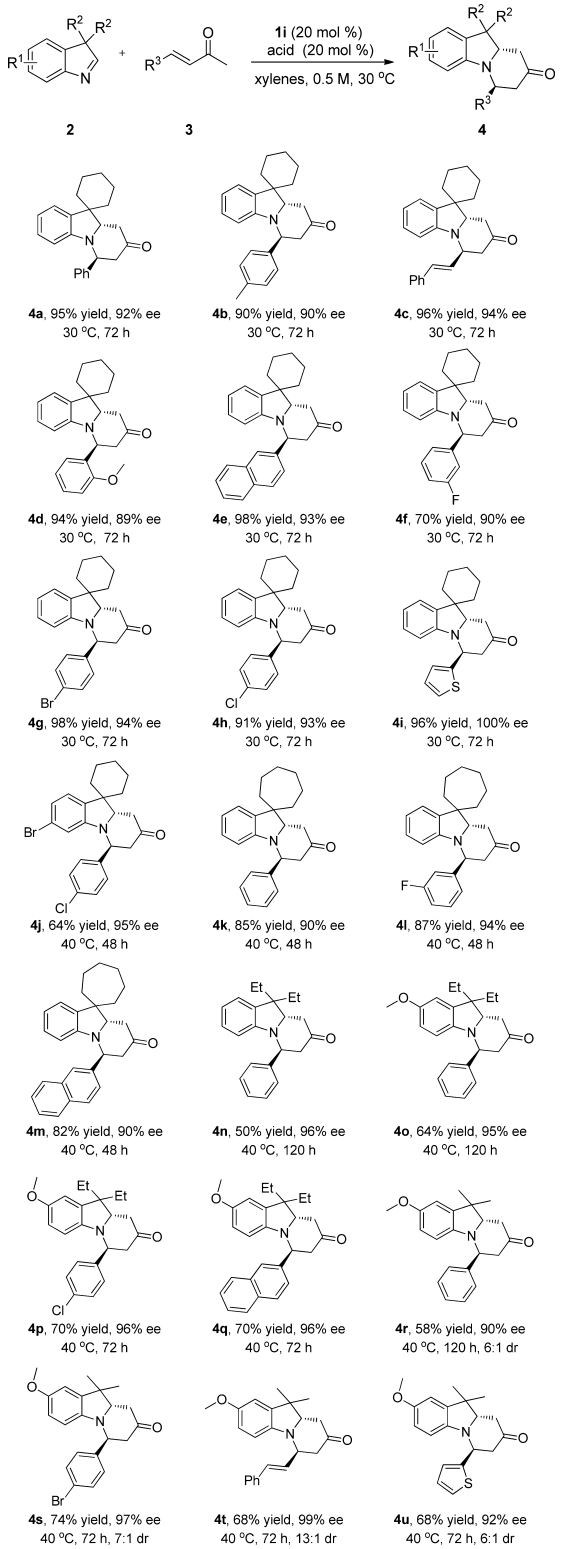
We considered the H-bond donated by secondary amine would activate the imine substrate, therefore, primary-tertiary amine **1b** derived from L-tert-leucine and 9-amino-9-deoxyepicinchonine **1c** were then employed in comparison (Table 1, entries 2−3). The inferior conversion demonstrated that the H-bond donor group was requisite in the sketch of catalysts. A library of primary amine/H-bond donor bifunctional asymmetric catalysts **1d**−**1i** was screened. With catalysts **1d** and **1e**, respectively possessing a 3,5-bis(trifluoromethyl)benzenesulfonamide and a 3,5-bis(trifluoromethyl)phenylthiourea, good reactivity was observed, but stereocontrol was moderate (Table 1, entries 4−5). The related trans-diphenyl-1,2-ethanediamine (DPEN) derivatives **1f** and **1g**, containing a more gentle thiourea motif, gave rise to better ee values and slightly lower conversion (Table 1, entries 6−7). On the other hand, primary amine/thiourea catalysts **1h** and **1i**, derived from trans-1,2-diaminocyclohexane (DACH), were competently embodied in diastereocontrol, especially when the Jacobsen's catalyst **1i** was adopted to both excellent diastereo- and enantiocontrol (Table 1, entries 8−9).[10] Increasing the weight ratio of imine **2a** to enone **3a** and screening the solvent, we detected the product with excellent conversion and ee value (Table 1, entry 10). A series of additives which might affect the outcome were screened successively (Table 1, entries 11−12). Then we investigated the reactivity of the FADA reaction without adding acid. That very trace of the product was detected demonstrating the acid was playing an important role in the formation of the intermediate (Table 1, entry 13). Finally, the temperature screen revealed 30 °C as the temperature of choice and the optimal condition employed the Jacobsen's catalyst (0.2 equiv) and benzoic acid (0.2 equiv) as the additive with the 3:1 ratio of imine to enone for 72 h (Table 1, entries 10 and 14). As is shown in Table 1, all the screened conditions represented excellent diastereoselectivities with 97:3 dr value at least.

With optimal conditions in hand, the scope of the reaction in regards to both the imine and the *α,β*-unsaturated ketone was surveyed (Scheme 1). A number of aryl-substituted enones were first investigated. Irrespective of the electronic and steric demand of the aromatic ring within enone **3a**−**3h**, all reactions went to completion, affording the respective products **4a**−**4h** in excellent yields and diastereo- and enantioselectivities. Enone **3i** bearing a heteroaromatic ring also performed well in this formal aza-Diels−Alder reaction (Scheme 1, **4i**). A variety of aryl-substituted imines, which carried diverse bulky groups on the C3 position, were then studied.[11] Unexpectedly, we found that the stereocontrol of the product would be superior when the temperature was increased to 40 °C, while enantioselectivities would be slightly lower with 83% ee at most at 30 °C (Scheme 1, **4j**−**4m**). Meanwhile, imines with a diethyl substitution on the C3 position were synthesized, and reduced yields of the respective products were observed, in spite of the maintained excellent diastereo- and enantioselectivities (Scheme 1, **4n**−**4q**). Furthermore, electron-donating groups on the phenyl ring of imines, for example, 5-methoxy-substituted imines (**4o**, **4p**, **4q**), proved to be higher in reactivity and stability than the imine with no substitutions (**4n**). Finally, when dimethly was chosen to be the bulky group on the C3 position of imines, we measured that the diastereomeric ratios of the adducts were reduced to between 6:1 and 13:1 along with, respectively, excellent ee values and moderate yields (Scheme 1, **4r**−**4u**). The phenyl-substituted and thiofuran-substituted enones processed smoothly with a less hindered imine, irrespective of even higher ee values, yet moderate dr values (6:1−7:1) were obtained (**4r**, **4s**, **4u**). In addition, the styryl-substituted *α,β*-unsaturated ketone involved in this reaction with dimethyl substituted on the C3 position of imine revealed better stereocontrol than other ketones (**4t**).

On the basis of X-ray crystal structure analysis of product **4g** (Supporting Information), a potential transition-state structure was proposed.[12] As shown in Figure 2, the catalyst serves the dual function of activating both reaction partners. The primary amine of this catalyst combines with enone followed by the formation of dienamine, while the thiourea moiety binds and

DOI: 10.1021/acscatal.5b00680
ACS Catal. 2015, 5, 3700−3703

Scheme 1. Scope of FADA Reactions between Various α, β-Unsaturated Ketones and Imines[a]



[a]All reactions were carried out using 1.0 equiv of **3** (0.20 mmol), 3.0 equiv of imine **2** (0.60 mmol), and 0.20 equiv of the catalyst **1i** and benzoic acid in xylenes (0.4 mL). [b]All isolated yields were major diastereoisomer. [c]Determined by GC. [d]Determined by chiral HPLC. [e]Unless otherwise noted, diastereomeric ratios determined by GC were above 30:1 values.

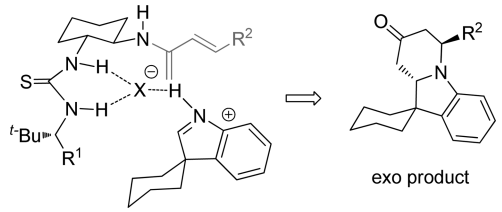


Figure 2. Proposed transition state.

activates the imine through hydrogen bonds. The bulky group on the imine and R^1 group of catalyst share space leading to single-face attack of imines to dienamine in below with *exo* product achieved.

Moreover, we checked the potential scalability of this methodology. According to Figure 3, the reaction between

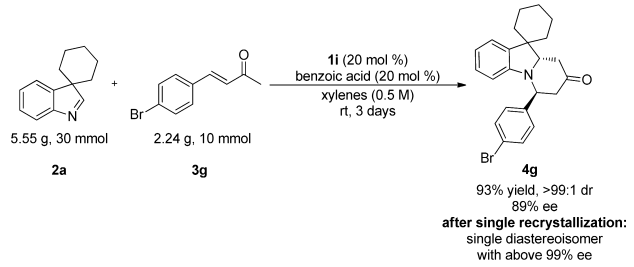


Figure 3. Gram scale synthesis.

enone **3g** loading on a 10 mmol scale and imine **2a** loading on a 30 mmol scale was performed in specified conditions providing product **4g** in 93% yield with >99:1 dr and 89% ee value.[13] After a single recrystallization, we achieved a single diastereoisomer with 75% yield and above 99% ee.

In summary, we have developed a highly diastereo- and enantioselective catalytic formal aza-Diels–Alder reaction of 3*H*-indole with *α,β*-unsaturated ketone. The bulky groups on the C3 position of imines are treated as hindrance in collaboration with a chiral catalyst. A new type of five-membered cyclic imines were introduced in the FADA reactions with covalently bound dienamines intermediate. The reactivity has been demonstrated in the synthesis of chiral hexahydropyrido [1,2-*a*] indoles or chiral 4-piperidinones. In general, the corresponding products were achieved in high yields and excellent dr values and ee values. We provided an adoptable way for the synthesis of alkaloids, which broaden the range of the substrates reported by Jacobsen.[14]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b00680.

Experimental procedures and characterization data of the products, and copies of the ^{1}H and ^{13}C spectra and the HPLC traces (PDF)

Crystallographic data for **4g** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yejx@ecust.edu.cn.

Notes

The authors declare no competing financial interest.

DOI: 10.1021/acscatal.5b00680
ACS Catal. 2015, 5, 3700–3703

■ ACKNOWLEDGMENTS

This work was supported by National Natural Science Foundation of China (21272068), Innovation Program of Shanghai Municipal Education Commission (11ZZ56), and the Fundamental Research Funds for the Central Universities.

■ REFERENCES

(1) (a) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650−1667. (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698. (c) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779−807.

(2) For selected examples of aza-Diels−Alder reactions, see: (a) Tambar, U. K.; Lee, S. K.; Leighton, J. L. *J. Am. Chem. Soc.* **2010**, *132*, 10248−10250. (b) Mancheño, O. G.; Arrayās, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 456−457. (c) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520−10524. (d) Memeo, M. G.; Quadrelli, P. *Chem. - Eur. J.* **2012**, *18*, 12554−12582. (e) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4796−4798. (f) Yao, S.; Johannsen, M.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 3121−3124. (g) Xie, M.; Chen, X.; Zhu, Y.; Gao, B.; Lin, L.; Liu, X.; Feng, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 3799−3802.

(3) For selected examples of aza-Diels−Alder reactions between imines and enones, see: (a) Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2003**, *5*, 4301−4304. (b) Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2006**, *8*, 1533−1535. (c) Sunden, H.; Ibrahem, I.; Eriksson, L.; CÓrdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4877−4880. (d) Rueping, M.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7832−7835. (e) Liu, H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2006**, *8*, 6023−6026. (f) Jiang, X.; Shi, X.; Wang, S.; Sun, T.; Cao, Y.; Wang, R. *Angew. Chem., Int. Ed.* **2012**, *51*, 2084−2087. (g) Liu, Y.; Kang, T.-R.; Liu, Q.-Z.; Chen, L.-M.; Wang, Y.-C.; Liu, J.; Xie, Y.-M.; Yang, J.-L.; He, L. *Org. Lett.* **2013**, *15*, 6090−6093.

(4) Lalonde, M. P.; McGowan, M. A.; Rajapaksa, N. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2013**, *135*, 1891−1894.

(5) For preparation of imines, see: (a) Rodriguez, J. G.; Benito, Y.; Temprano, F. *J. Heterocycl. Chem.* **1985**, *22*, 1207−1210. (b) Liu, K. G.; Robichaud, A. J. *Tetrahedron Lett.* **2007**, *48*, 461−463.

(6) Shao, Y.-D.; Tian, S.-K. *Chem. Commun.* **2012**, *48*, 4899−4901.

(7) (a) Larsen, N. K.; Jensen, A. A.; Kehler, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5431−5433. (b) Nicolaou, K. C.; Roecker, A. J.; Hughes, R.; van Summeren, R.; Pfefferkorn, J. A.; Winssinger, N. *Bioorg. Med. Chem.* **2003**, *11*, 465−476. (c) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045−1075. (d) Meyers, A. I.; Slelecki, T. M.; Crans, D. C.; Marshman, R. W.; Nguyen, T. H. *J. Am. Chem. Soc.* **1992**, *114*, 8483−8489. (e) Jiao, J.; Zhang, Y.; Flowers, R. A., II *Synlett* **2006**, *2006* (19), 3355−3357.

(8) For selected examples of the influence of the bulky group in stereocontrol, see: (a) Inoue, M.; Sato, T.; Hirama, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 4843−4848. (b) Meninno, S.; Croce, G.; Lattanzi, A. *Org. Lett.* **2013**, *15*, 3436−3439. (c) Fang, X.; Li, J.; Wang, C.-J. *Org. Lett.* **2013**, *15*, 3448−3451. (d) Bastida, D.; Liu, Y.; Tian, X.; Escudero-Adán, E.; Melchiorre, P. *Org. Lett.* **2013**, *15*, 220−223.

(9) For selected examples of the application of catalyst **1a**, see: (a) Wu, W.; Huang, H.; Yuan, X.; Zhu, K.; Ye, J. *Chem. Commun.* **2012**, *48*, 9180−9182. (b) Huang, H.; Wu, W.; Zhu, K.; Hu, J.; Ye, J. *Chem. - Eur. J.* **2013**, *19*, 3838−3841. (c) Wu, W.; Li, X.; Huang, H.; Yuan, X.; Lu, J.; Zhu, K.; Ye, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 1743−1747. (d) Wu, W.; Yuan, X.; Hu, J.; Wu, X.; Wei, Y.; Liu, Z.; Lu, J.; Ye, J. *Org. Lett.* **2013**, *15*, 4524−4527. (e) Gu, X.; Dai, Y.; Guo, T.; Franchino, A.; Dixon, D. J.; Ye, J. *Org. Lett.* **2015**, *17*, 1505−1508.

(10) For selected examples of the application of catalyst **1i**, see: (a) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170−7171. (b) Yamagata, A. D. G.; Datta, S.; Jackson, K. E.; Stegbauer, L.; Paton, R. S.; Dixon, D. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 4899−4903. (c) Retini, M.; Bergonzini, G.; Melchiorre, P. *Chem. Commun.* **2012**, *48*, 3336−3338.

(11) Sluder, A.; Shah, S.; Cassayre, J.; Clover, R.; Maienfisch, P.; Molleyres, L. P.; Hirst, E. A.; Flemming, A. J.; Shi, M.; Cutler, P.; Stanger, C.; Roberts, R. S.; Hughes, D. J.; Flury, T.; Robinson, M. P.; Hillesheim, E.; Pitterna, T.; Cederbaum, F.; Worthington, P. A.; Crossthwaite, A. J.; Windass, J. D.; Currie, R. A.; Earley, F. G. P. *PLoS One* **2012**, *7*, e34712.

(12) For a review, see: Girling, P. R.; Kiyoi, T.; Whiting, A. *Org. Biomol. Chem.* **2011**, *9*, 3105−3121.

(13) Corbett, M. T.; Johnson, J. S. *Chem. Sci.* **2013**, *4*, 2828−2832.

(14) Rajapaksa, N. S.; McGowan, M. A.; Rienzo, M.; Jacobsen, E. N. *Org. Lett.* **2013**, *15*, 706−709.

DOI: 10.1021/acscatal.5b00680
ACS Catal. 2015, 5, 3700−3703