Organic LETTERS

Letter

pubs.acs.org/OrgLett

Organocatalytic, Asymmetric Synthesis of Aza-Quaternary Center of Izidine Alkaloids: Synthesis of (−)-Tricyclic Skeleton of Cylindricine

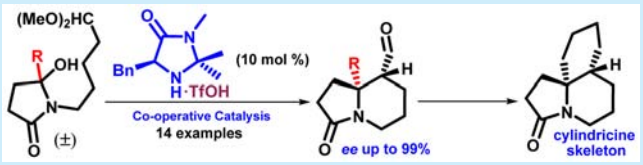
Kyatham Srinivas,[†] Nishant Singh,[†] Dinabandhu Das,[‡] and Dipankar Koley*[,†]

[†]Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute, Lucknow 226031, India

[‡]School of Physical Science, Jawaharlal Nehru University, New Delhi 110067, India

Supporting Information

ABSTRACT: We report a highly efficient, enantioselective, organocatalytic method for the synthesis of izidinone alkaloids containing a bridgehead aza-quaternary center using ketone-derived *N*,*O*-hemiaminal with a tethered acetal. Alkyl-, aryl-, and alkenyl-substituted substrates cyclize to the respective products with excellent enantioselectivities. Five- and seven-membered ring formation has also been established. Furthermore, synthesis of the tricyclic skeleton of cylindricine alkaloids has been achieved in high yield.



All-carbon quaternary stereogenic centers are widely present in many natural products, pharmaceuticals, and drugs (Figure 1).[1] Among these, natural products having a bridgehead aza-quaternary motif show diverse pharmacological properties, e.g., anticancer activity against non-small-cell lung cancer,[2] cytotoxic properties,[3] antiarrhythmic properties.[4] They have been found to reduce blood pressure in vivo in a rat model.[5] Recent data revealed that they block the cardiac muscle Kir channel.[4] Moreover, omacetaxine mepesuccinate (Myelostat) has been approved by the FDA to treat chronic myeloid leukemia. Therefore, synthesis of these scaffolds has become an important research area. While considerable efforts[6] have been pursued for the construction of these motifs, catalytic asymmetric synthesis of these sterically hindered motifs remains a significant challenge.[7]

The field of asymmetric organocatalysis has witnessed rapid and dramatic development in the efficient synthesis of structurally complex natural products and/or natural product like scaffolds from simple achiral substrates.[8] In this regard, many studies have been reported for the construction of asymmetric all-carbon quaternary stereocenters via organocatalytic activation (Scheme 1).[8g,9] However, there are few reports of asymmetric organocatalytic reactions for the development of bridgehead aza-quaternary centers.[10] Of relevance to this work, the first report was disclosed in 2007 by Jacobsen and co-workers[10a] in which thiourea-based chiral catalyst was employed to perform enantioselective Pictet–

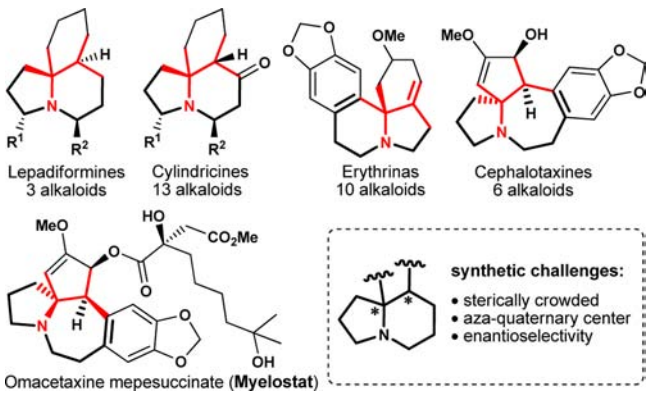
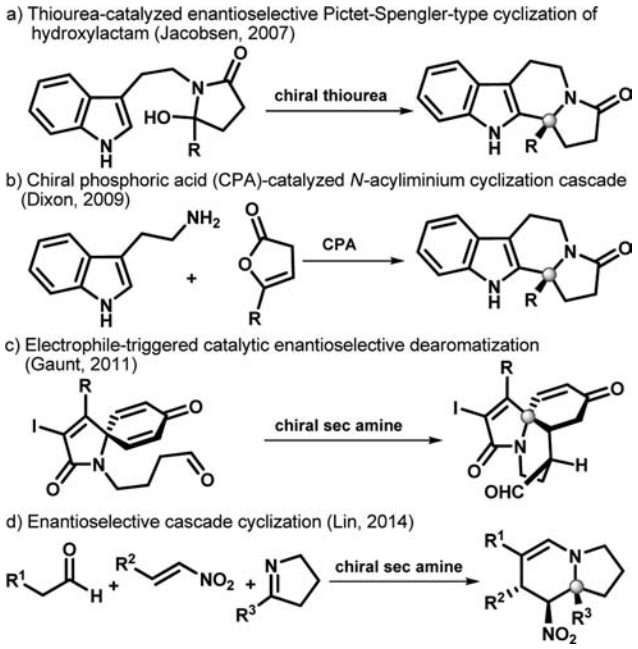


Figure 1. Izidine alkaloids with aza-quaternary motif.

Scheme 1. Asymmetric Organocatalytic Synthesis of Bridgehead Aza-Quaternary Center

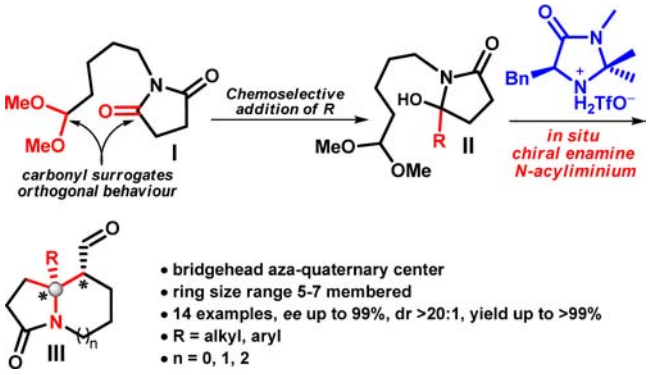


Received: December 2, 2016
Published: December 16, 2016

DOI: 10.1021/acs.orglett.6b03605
Org. Lett. 2017, 19, 274–277

Spengler-type cyclization of hydroxylactams to afford indolizidinone and quinolizidinone derivatives bearing an aza-quaternary motif. Subsequently, the *N*-acyliminium ion chemistry was exploited by Dixon and co-workers,[10b,c] however, by utilizing phosphoric acid based chiral catalyst. They reported coupling and cyclization between enol lactones and tryptamine derivatives to furnish aza-quaternary bicyclic alkaloids with high enantioselectivities. However, as the use of tryptamine derivatives was obligatory, and neither of these methods was directed to the synthesis of naturally available tricyclic izidine alkaloids. Interestingly, Gaunt et al.[10d] reported electrophile-triggered organocatalytic enantioselective dearomatization (ECED) of anisidine derivatives into a tricyclic scaffold containing an aza-quaternary stereogenic center. Recently, Lin and co-workers[10e] demonstrated a one-pot cascade reaction for the construction of indolizidine and quinolizidine alkaloids containing a bridghead aza-quaternary stereocenter. However, these methods are also substrate specific. As part of our interest[11] in izidine-based alkaloids, we have recently demonstrated[11b] that an acetal functional group could directly be used as a precursor of chiral enamine by treating it with MacMillan's imidazolidinone-based[12] chiral catalyst. Following this accomplishment, we further questioned whether a ketone-derived *N*,*O*-hemiaminal[13] substrate could be used as the precursor for such a cyclization. We envisioned that the chemoselective addition of Grignard reagents to the imide **I** (Scheme 2) would provide ketone-derived *N*,*O*-hemiaminal

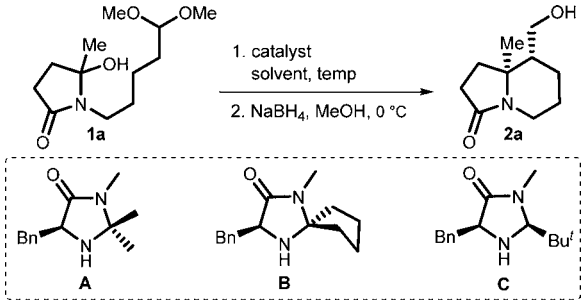
Scheme 2. Asymmetric Organocatalytic Synthesis of Bridgehead Aza-Quaternary Center



substrate **II**. Therefore, if substrate **II** having a tethered acetal would undergo cyclization via a one-pot catalytic acetal deprotection/enamine formation/*N*-acyl iminium pathway, an array of izidinone frameworks with an aza-quaternary motif could be obtained. Herein, we report the successful implementation of the hypothesis that provides efficient access to highly enantioenriched bicyclic alkaloids that contain a bridgehead aza-quaternary motif.

We began our study with the simplest possible *N*,*O*-hemiaminal ether derivative **1a** prepared via imide alkylation using MeMgBr. We were delighted to find that exposure of **1a** to 30 mol % of **A**·TfOH in acetone at 25 °C provided the bicyclic aza-quaternary moiety **2a** in 77% yield with excellent enantioselectivity (ee 98%) (Table 1, entry 1). A screening of various other imidazolidinone-based catalysts proved **A** was the optimal choice (entries 1−3). Next, various Bronsted acids were tested as additives,[14] and TfOH exhibited the highest efficiency (entries 1 and 4−7). Next, among the solvents

Table 1. Screening of Reaction Conditions for the Enantioselective Cyclization[a]



entry	catalyst	solvent	time (days)	yield[b] (%)	dr[c]	ee[d]
1	**A**·TfOH	acetone	2	77	>20:1	98
2	**B**·TfOH	acetone	2	23	>20:1	nd
3	**C**·TfOH	acetone	2	36	>20:1	nd
4	**A**·HCl	acetone	2	52	>20:1	98
5	**A**·PTSA	acetone	2	58	>20:1	98
6	**A**·TFA	acetone	2	44	>20:1	98
7	**A**·$HClO_4$	acetone	2	43	>20:1	98
8	**A**·TfOH	CH_2Cl_2	2	79	>20:1	98
9	**A**·TfOH	CH_3CN	2	86	>20:1	98
10	**A**·TfOH	THF	2	51	>20:1	98
11[e]	**A**·TfOH	CH_3CN	2	84	>20:1	98
12[f]	**A**·TfOH	CH_3CN	2	83	>20:1	98

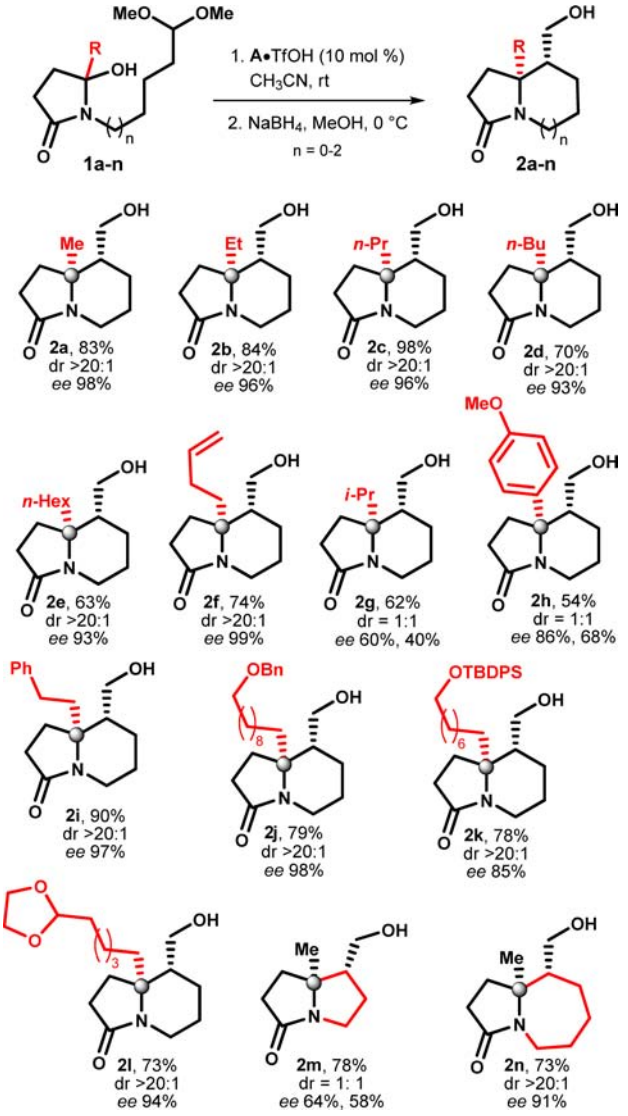
[a]Reaction conditions: 0.5 mmol of **1a**, 30 mol % catalyst, 3.0 mL of solvent at 25 °C. [b]Isolated yield of **2a** after silica gel column chromatography. [c]Determined by ^{1}H NMR of the crude alcohol. [d]Determined by HPLC on a chiral column of the benzoyl ester of **2a**. [e]20 mol % catalyst used. [f]10 mol % catalyst used. ee = enantiomeric excess.

screened, acetonitrile gave the best result, generating the desired product in 86% yield with equal enantioselectivity (entries 1 and 8−10). Furthermore, there was no erosion of efficiency of this method when 10 mol % of catalyst **A**·TfOH was used (entries 11 and 12). It should be noted that the diastereomeric ratio was always in favor of the *cis*-isomer by >20:1 under either set of conditions.

Encouraged by these results, we first explored the generality of our protocol to elucidate the scope of the R group around the aza-quaternary center (Scheme 3). In line with our expectations, the reaction was very general for the substrates having the R group as methyl, ethyl, *n*-propyl, *n*-butyl, or *n*-hexyl (**2a**−**e**), and the desired products were obtained in very good yields with excellent diastereo- (>20:1) and enantioselectivities (ee 93−98%). Substrate obtained via the addition of homoallyl Grignard reagent cleanly yielded the product (**2f**) in good yield with excellent diastereo- and enantioselectivity (ee 99%). Allyl Grignard addition derivative did not furnish the desired product, and the conjugated diene product was obtained via elimination (data not shown). Substrate with a sterically hindered isopropyl group also furnished the product (**2g**), albeit with moderate yield and enantioselectivity. Hydroxylactam generated via arylation to imide was also found to be a suitable substrate and provided the product (**2h**) in good yield with excellent enantioselectivity (ee 86%). Substrate with an appended arene underwent the required Mannich cyclization without the formation of any undesired Pictet−Spengler derivative. The required product **2i** was obtained in 90% yield with excellent enantioselectivity (ee 97%). Substrates having functional groups like OBn (**1j**),

DOI: 10.1021/acs.orglett.6b03605
Org. Lett. 2017, 19, 274−277

Scheme 3. Scope of the Enantioselective Cyclization with Respect to R Rroup[a]



[a]Reactions conditions: 0.5 mmol of **1a**, 10 mol % of catalyst, 3.0 mL of solvent at 25 °C. Yields are isolated yields after silica gel column chromatography. dr measured by ^{1}H NMR of the crude alcohol; ee determined by HPLC on a chiral column of the benzoyl ester of the alcohol.

OTBDPS (**1k**), and 1,3-dioxolane (**1l**) were well tolerated in this method to afford orthogonally functionalized products (**2j**–**l**) with excellent enantioselectivities (ee 85–98%). Formation of the product **2l** having an untouched 1,3-dioxolane group demonstrated the highly chemoselective nature of the process. Having demonstrated the scope of the cyclization with a variety of R groups, we next focused our efforts on the formation of different ring sizes on the izidinone skeleton. Delightfully, the process furnished azabicyclo derivatives containing five- and seven-membered rings with good to excellent enantioselectivities (ee up to 91%). Eight-membered cyclization did not occur under the optimized conditions. Finally, the absolute configuration of **2c** (1*R*,8a*S*) was determined by X-ray crystallographic analysis of its derivative **3** (CCDC 1515316; Figure 2).

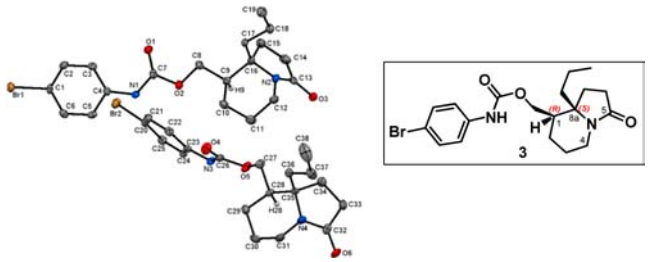
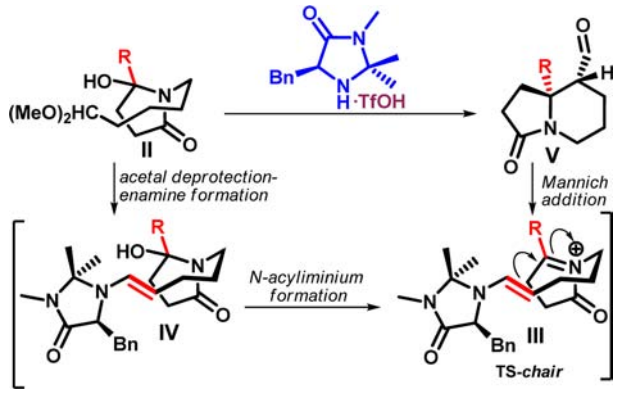


Figure 2. X-ray crystallographic analysis of **3** (CCDC 1515316). Thermal ellipsoids are shown at 60% probability.

On the basis of the results of the stereochemical outcome and our previous results,[11b] a plausible mechanism is proposed (Scheme 4). First, substrate **II** undergoes acetal deprotection

Scheme 4. Plausible Mechanistic Pathway



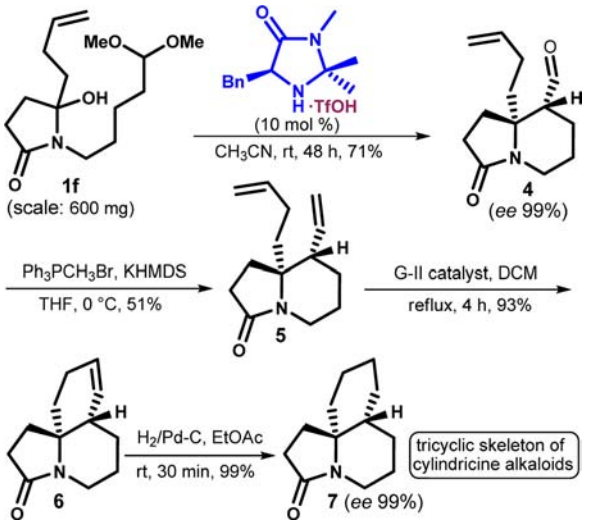
with the aid of acid additive followed by enamine formation to form *Re*-face-blocked *E*-enamine-hydroxylactam intermediate **IV**. Thereafter, acid-promoted dehydration furnished *N*-acyliminium–enamine intermediate **V**. The *Si*-face of enamine preferentially attacks the *Re*-face of *N*-acyliminium via a six-membered cyclic transition state (chair form) to yield the product **III**.

Finally, to demonstrate the utility of the newly developed asymmetric catalytic method, the tricyclic skeleton of cylindricine alkaloids was synthesized (Scheme 5). Following our developed protocol, a larger scale reaction of **1f** (600 mg, 2.1 mmol) delivered the azabicyclo aldehyde **4** in 71% yield with >99% enantioselectivity. This also demonstrates the effectiveness of the method for scaled up reactions. Methylenation[15] of the aldehyde **4** using Ph_3PCH_3Br and KHMDS in THF at 0 °C yielded diene **5** in moderate yield (51%). Ring-closing metathesis reaction[15] of the diene using Grubbs' second-generation catalyst (G-II) furnished the tricyclic skeleton **6** in excellent yield (93%). The desired tricyclic skeleton of cylindricine alkaloids was obtained via catalytic hydrogenation of **6** using Pd–C in EtOAc, delivering **7** in quantitative yields with 99% enantioselectivity. The spectral data of **7** were in good agreement with the literature value.[16]

In summary, we have developed an acyl-Mannich cyclization process that enables highly enantioselective conversion of ketone-derived hemiaminal ether derivatives having pendant acetal into an azabicyclic skeleton featuring a bridgehead aza-quaternary stereogenic center. The reaction is very simple and delivers the products with excellent enantioselectivity. The method is applicable for the synthesis of five-, six-, and seven-membered rings. The developed methodology has paved a

DOI: 10.1021/acs.orglett.6b03605
Org. Lett. 2017, 19, 274–277

Scheme 5. Synthesis of the Tricyclic Skeleton of Cylindricine



pathway for the synthesis of the tricyclic skeleton of cylindricine alkaloids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03605.

Full experimental details, characterization data for new compounds, and NMR and HPLC spectra (PDF)

X-ray data for **3** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dkoley@cdri.res.in.

ORCID

Dipankar Koley: 0000-0002-4861-7232

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from DST-SERB (EMR/2016/000613) and CSIR-New Delhi (senior Research Fellowship to K.S. and N.S.) is gratefully acknowledged. We thank the SAIF division for analytical support. CDRI Communication No. 9396.

■ REFERENCES

(1) For selected reviews, see: (a) Büschleb, M.; Dorich, S.; Hanessian, S.; Tao, D.; Schenthal, K. B.; Overman, L. E. *Angew. Chem., Int. Ed.* **2016**, *55*, 4156. (b) Ling, T.; Rivas, F. *Tetrahedron* **2016**, *72*, 6729. (c) Chen, W.; Zhang, H. *Sci. China: Chem.* **2016**, *59*, 1065.

(2) Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691.

(3) Dutta, S.; Abe, H.; Aoyagi, S.; Kibayashi, C.; Gates, K. S. *J. Am. Chem. Soc.* **2005**, *127*, 15004.

(4) Sauviat, M. P.; Vercauteren, J.; Grimaud, N.; Juge, M.; Nabil, M.; Petit, J. Y.; Biard, J. F. *J. Nat. Prod.* **2006**, *69*, 558.

(5) Juge, M.; Grimaud, N.; Biard, J. F.; Sauviat, M. P.; Nabil, M.; Verbist, J. F.; Petit, J. Y. *Toxicon* **2001**, *39*, 1231.

(6) (a) Christoffers, J., Baro, A., Eds. *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Wiley-VCH: Weinheim, 2005. (b) For a review, see: Weinreb, S. M. *Chem. Rev.* **2006**, *106*, 2531.

(7) For a review, see: (a) Perreault, S.; Rovis, T. *Chem. Soc. Rev.* **2009**, *38*, 3149. For selected recent examples, see: (b) Yu, R. T.; Friedman, R. K.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 13250. (c) Oinen, M. E.; Yu, R. T.; Rovis, T. *Org. Lett.* **2009**, *11*, 4934. (d) Friedman, R. K.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10775. (e) Dalton, D. M.; Rovis, T. *Org. Lett.* **2013**, *15*, 2346. (f) Xu, H.-D.; Jia, Z.-H.; Xu, K.; Zhou, H.; Shen, M.-H. *Org. Lett.* **2015**, *17*, 66. (g) Coombs, T. C.; Zhang, Y.; Garnier-Amblard, E. C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2009**, *131*, 876. (h) Pandey, G.; Janakiram, V. *Chem. - Eur. J.* **2015**, *21*, 13120.

(8) For review, see: (a) Sun, B.-F. *Tetrahedron Lett.* **2015**, *56*, 2133. For selected recent examples, see: (b) Ren, Y.; Presset, M.; Godemert, J.; Vanthuyne, N.; Naubron, J.-V.; Giorgi, M.; Rodriguez, J.; Coquerel, Y. *Chem. Commun.* **2016**, *52*, 6565. (c) Hayashi, Y.; Ogasawara, S. *Org. Lett.* **2016**, *18*, 3426. (d) Chen, X.; Duan, S.; Tao, C.; Zhai, H.; Qiu, F. G. *Nat. Commun.* **2015**, *6*, 7204. (e) Hayashi, Y.; Aikawa, T.; Shimasaki, Y.; Okamoto, H.; Tomioka, Y.; Miki, T.; Takeda, M.; Ikemoto, T. *Org. Process Res. Dev.* **2016**, *20*, 1615. (f) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183. (g) Horning, B. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 6442.

(9) For selected reviews, see: (a) Tian, L.; Luo, Y.-C.; Hu, X.-Q.; Xu, P.-F. *Asian J. Org. Chem.* **2016**, *5*, 580. (b) Kotsuki, H.; Sasakura, N. *New and Future Developments in Catalysis; Catalysis for Remediation and Environmental Concerns*; Suib, S. L., Ed.; Elsevier: Amsterdam, 2013, Chapter 19, p 563. (c) Mase, N.; Tanaka, F.; Barbas, C. F., III *Angew. Chem.* **2004**, *116*, 2474. (d) Inokoishi, Y.; Sasakura, N.; Nakano, K.; Ichikawa, Y.; Kotsuki, H. *Org. Lett.* **2010**, *12*, 1616. (e) Yao, L.; Liu, K.; Tao, H.-Y.; Qiu, G.-F.; Zhou, X.; Wang, C.-J. *Chem. Commun.* **2013**, *49*, 6078. (f) Guo, L.-D.; Huang, X.-Z.; Luo, S.-P.; Cao, W.-S.; Ruan, Y.-P.; Ye, J.-L.; Huang, P.-Q. *Angew. Chem., Int. Ed.* **2016**, *55*, 4064. (g) Zou, C.; Zeng, C.; Liu, Z.; Lu, M.; Sun, X.; Ye, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 14257.

(10) (a) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. (b) Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 10796. (c) Holloway, C. A.; Muratore, M. E.; Storer, R. I.; Dixon, D. J. *Org. Lett.* **2010**, *12*, 4720. (d) Leon, R.; Jawalekar, A.; Redert, T.; Gaunt, M. J. *Chem. Sci.* **2011**, *2*, 1487. (e) Tan, Y.; Chen, Y.-J.; Lin, H.; Luan, H.-L.; Sun, X.-W.; Yang, X.-D.; Lin, G.-Q. *Chem. Commun.* **2014**, *50*, 15913. (f) Zhao, Y.-L.; Wang, Y.; Cao, J.; Liang, Y.-M.; Xu, P.-F. *Org. Lett.* **2014**, *16*, 2438.

(11) (a) Koley, D.; Srinivas, K.; Krishna, Y.; Gupta, A. *RSC Adv.* **2014**, *4*, 3934. (b) Koley, D.; Krishna, Y.; Srinivas, K.; Khan, A. A.; Kant, R. *Angew. Chem., Int. Ed.* **2014**, *53*, 13196.

(12) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

(13) *N,O*-Hemiaminal in asymmetric catalysis; for a review, see: Huang, Y.-Y.; Cai, C.; Yang, X.; Lv, Z.-C; Schneider, U. *ACS Catal.* **2016**, *6*, 5747.

(14) Role of additive in organocatalysis; for review, see: (a) Hong, L.; Sun, W.; Yang, D.; Li, G.; Wang, R. *Chem. Rev.* **2016**, *116*, 4006. For selected examples, see: (b) Moteki, S. A.; Han, J.; Arimitsu, S.; Akakura, M.; Nakaya-ma, K.; Maruoka, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 1187. (c) Cozzi, P. G.; Benfatti, F.; Zoli, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 1313. (d) Weng, Z.-T.; Li, Y.; Tian, S.-K. *J. Org. Chem.* **2011**, *76*, 8095.

(15) Singh, N.; Pulukuri, K. K.; Chakraborty, T. K. *Tetrahedron* **2015**, *71*, 4608.

(16) Zheng, X.; He, J.; Li, H.-H.; Wang, A.; Dai, X.-J.; Wang, A.-E.; Huang, P.-Q. *Angew. Chem., Int. Ed.* **2015**, *54*, 13739.

DOI: 10.1021/acs.orglett.6b03605
Org. Lett. 2017, 19, 274–277