Organic LETTERS

Letter

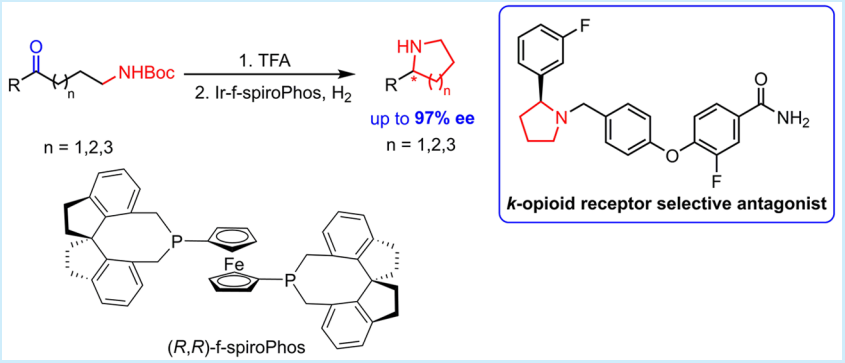
pubs.acs.org/OrgLett

# Enantioselective Direct Synthesis of Free Cyclic Amines via Intramolecular Reductive Amination

Ying Zhang, Qiaozhi Yan, Guofu Zi, and Guohua Hou*

Key Laboratory of Radiopharmaceuticals, College of Chemistry, Beijing Normal University, Beijing 100875, China

Supporting Information




**ABSTRACT:** Chiral cyclic amines can be prepared via intramolecular reductive amination of *N*-Boc-protected amino ketones in a one-pot process. With the complex of iridium and f-spiroPhos as the catalyst, a range of *N*-Boc-protected amino ketones are smoothly transformed into chiral cyclic free amines in high yields and excellent enantioselectivities (up to 97% ee). Moreover, this method can also be successfully applied to the synthesis of a κ-opioid receptor selective antagonist, (*S*)-**1**.

Chiral cyclic amines are ubiquitous and important structural motifs in natural products and pharmaceutical compounds.[1,2] In particular, chiral pyrrolidine and piperidine derivatives are widely present in many biological active molecules, for example, nicotine,[3] (−)-crispine,[4] (*S*)-**1**,[5] (*S*)-coniine,[6] PARP-1/2 inhibitor,[7] and solifenacin (Figure 1).[8]

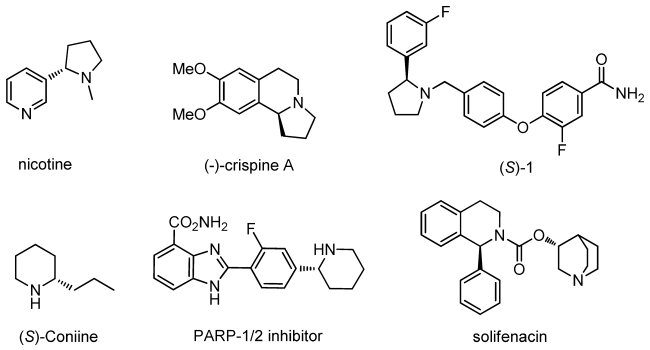



**Figure 1.** Structures of biologically active compounds and pharmaceutical drugs containing the chiral cyclic amine moiety.

Consequently, asymmetric synthesis of chiral cyclic amines continuously attracts considerable attention from chemists, and many approaches to optical substituted pyrrolidines and piperidines have been developed[1a,3b,9] such as asymmetric reduction of cyclic imine or enamine by biocatalysis,[10] organocatalysis,[11] and transition-metal catalysis.[12] In addition, intramolecular asymmetric reductive amination (RA) is regarded as an efficient and concise alternative that is more direct for obtaining chiral cyclic amines while avoiding the problematic imine isolation.[1a,13−15] To our surprise, there have been few reports on this method for synthesis of chiral cyclic amines. Wills' group first reported the synthesis of piperidine and azepane derivatives by intramolecular RA under transfer hydrogenation conditions.[14] Although this strategy was efficient for the synthesis of chiral 1-methyl tetrahyroisoquinoline in high yields and good enantioselectivities, both 2-substituted piperidines and azepanes were provided as racemates, and it particularly failed to obtain 2-substituted pyrrolidines. Subsequently, Turner and co-workers reported dramatically improved results with a chem-enzymatic route.[10a] Fan and co-workers successfully synthesized chiral *N*-Boc-2-phenylpyrrolidine with 96% ee via a one-pot RA under asymmetric hydrogenation conditions, but the further complete neutralization of the resulted iminium and $(Boc)_2O$ were necessary for high reactivity and enantioselectivity.[15] To the best of our knowledge, the enantioselective direct synthesis of chiral free cyclic amines including 2-substituted pyrrolidines, piperidines, and azepanes via asymmetric intramolecular RA has not been explored and remains a great challenge so far.

Most recently, we developed a novel catalyst ferrocenyl ligand containing the privileged spirobiindane skeleton,[16] f-

**Received:** June 15, 2017

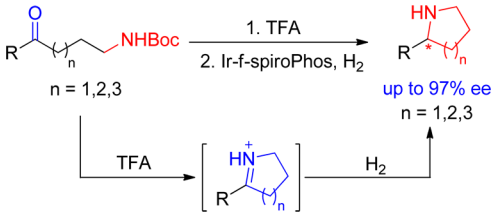




DOI: 10.1021/acs.orglett.7b01828
*Org. Lett.* XXXX, XXX, XXX−XXX

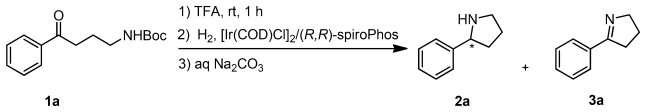
spiroPhos, which exhibited high efficiency and excellent enantioselectivity in asymmetric hydrogenation of various substrates including prochiral cyanoolefins, nitroolefins, unsaturated carboxylic, and imines.[17] Prompted by these promising results and excellent performance in the asymmetric hydrogenation of cyclic imines,[12g,17e] we hypothesize the enantioselective synthesis of chiral free pyrrolidines and piperidines via intramolecular RA catalyzed by Ir–f-spiroPhos complex. Herein we report the highly efficient intramolecular asymmetric RA of *N*-Boc-protected amino ketones under additive-free conditions for the direct preparation of free cyclic amines with up to 97% ee (Scheme 1).

**Scheme 1. Intramolecular RA of *N*-Boc-Protected Amino Ketones under Additive-Free Conditions**




The *N*-Boc-protected amino ketone **1a** was chosen as the model substrate for our initial studies, using the complex generated in situ by $[Ir(COD)Cl]_2$ and (*R*,*R*)-f-spiroPhos as the catalyst under 50 atm of $H_2$ at 50 °C in 1,4-dioxane in the presence of $Ti(O^iPr)_4$, TsOH, and $I_2$. To our delight, the desired chiral cyclic amine **2a** was obtained with 93% ee as the only product (Table 1, entry 1), which was not consistent with the results of the Ru–Ts-DPEN catalyst obtained by Will's group. It could be attributed to the formation of iminium avoiding the negative effect from the nitrogen lone pair on enantioselectivity.[14] Remarkably, in the absence of any additive, slightly higher enantioselectivity, 94% ee, and similar yield were still achieved (entry 2). It was revealed that additives had no obvious influence on either the formation of iminium intermediate or its reduction to chiral cyclic amine **2a**. Gratifyingly, this transformation could be completed in a shorter time with similar results (entry 3). Adjusting the reaction temperature, we found that lower temperature could lead to higher enantioselectivity, 95% ee (entry 4). In addition, under a lower hydrogen pressure of 10 atm, the full conversion was also achieved without any erosion of enantioselectivity (entry 5). However, much lower hydrogen pressure (5 atm) resulted in an incomplete conversion but maintained enantioselectivity (entry 6). Besides 1,4-dioxane, tetrahydrofuran (THF) was also suitable for this reaction and could provide full conversion and slightly better enantionselectivity, 96% ee (entry 7), whereas when dichloromethane, toluene, or methanol was used as the solvent only imine **3a** was afforded, and no reduced product **2a** was observed (entries 8–10). After careful investigation, it was found that the iminium **3a** could be dissolved in 1,4-dioxane and THF but not in $CH_2Cl_2$ or toluene, which meant that the solubility had a significant effect on the further conversion of **3a** and played the key role in the conversion of **3a** to **2a**. Finally, several other chiral phosphine ligands (Figure 2) including (*S*)-Binap, (*R*)-DM-segphos, (*R*)-

**Table 1. Optimization of Reaction Conditions**[a]




| entry | ligand | solvent | $T$ (°C) | $P_{H_2}$ (atm) | **2a**/**3a**[d] | ee[e] (%) |
|---|---|---|---|---|---|---|
| 1[b,c] | **L1** | dioxane | 50 | 50 | >99:1 | 93 |
| 2[c] | **L1** | dioxane | 50 | 50 | >99:1 | 94 |
| 3 | **L1** | dioxane | 50 | 50 | >99:1 | 93 |
| 4 | **L1** | dioxane | 30 | 50 | >99:1 | 95 |
| 5 | **L1** | dioxane | 30 | 10 | >99:1 | 95 |
| 6 | **L1** | dioxane | 30 | 5 | 75:25 | 96 |
| **7** | L1 | **THF** | **30** | **10** | **>99:1** | **96** |
| 8 | **L1** | $CH_2Cl_2$ | 30 | 10 | <1:99 | ND |
| 9 | **L1** | toluene | 30 | 10 | <1:99 | ND |
| 10 | **L1** | MeOH | 30 | 10 | <1:99 | ND |
| 11 | **L2** | THF | 30 | 10 | 26:74 | 88 |
| 12 | **L3** | THF | 30 | 10 | 82:18 | 92 |
| 13 | **L4** | THF | 30 | 10 | <1:99 | ND |
| 14 | **L5** | THF | 30 | 10 | 63:37 | 54 |
| 15 | **L6** | THF | 30 | 10 | <1:99 | ND |
| 16[c,f] | **L1** | THF | 50 | 50 | >99:1 | 90 |

[a]Unless otherwise mentioned, all reactions were carried out for 10 h with a $[Ir(COD)Cl]_2$/ligand/substrate ratio of 0.5:1.1:100, and **1a** was completely converted. [b]$Ti(OiPr)_4$ (1.1 equiv), TsOH (0.1 equiv), $I_2$ (0.1 equiv). [c]24 h. [d]Determined by $^1H$ NMR. [e]Determined by GC analysis after the cyclic amine was converted into the corresponding trifluoroacetamide. [f]S/C = 500.

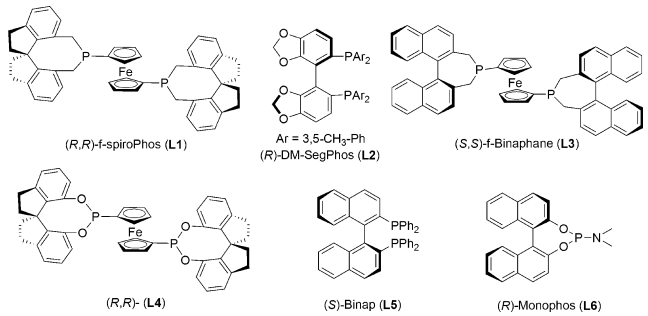



**Figure 2.** Structure of chiral phosphine ligands screened.

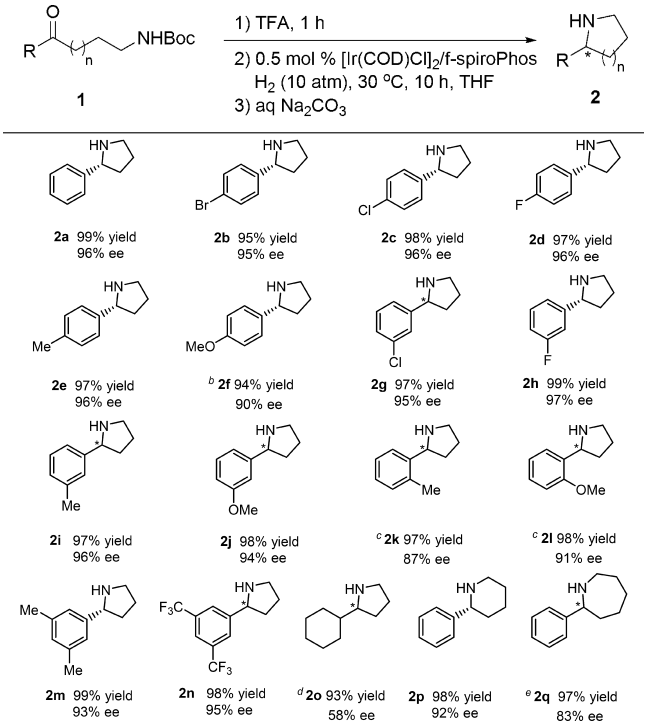
Monophos, (*S*,*S*)-f-Binaphane, and chiral ferrocenyl phosphite **L4** were also evaluated, but incomplete conversions of iminium **3a** were observed albeit with good to high enantioselectivities (entries 11–15). These results demonstrated that both electron-donating and sterically hindered rigid properties of ligands were presumably critical for the conversion and enantioselectivity in this transformation. Furthermore, when the catalyst loading was decreased to 0.2 mol %, the reaction still proceeded smoothly but a slightly lower enantioselectivity was obtained, 90% ee (entry 16).

To study the utility of the catalytic system, a range of *N*-Boc-protected amino ketones **1** were prepared and applied to this intramolecular RA under the optimized reaction conditions (Scheme 2). In general, both the electronic properties and steric hindrance of the substituent at the *para*- or *meta*-position of the phenyl ring had no evident influence on reactivity and enantioselectivity. For example, all of the substrates bearing a Br, Cl, F, or methyl group at the *para*- or *meta*-position (**1b–j**) could be converted to the corresponding desired products **2b–j** in high yields with excellent enantioselectivities of up to 97% ee. In comparison, the *ortho*-substituted substrates **1k** and **1l** exhibited lower reactivity and enantioselectivity to provide



DOI: 10.1021/acs.orglett.7b01828
Org. Lett. XXXX, XXX, XXX–XXX

**Scheme 2. Substrates Scope**[a]



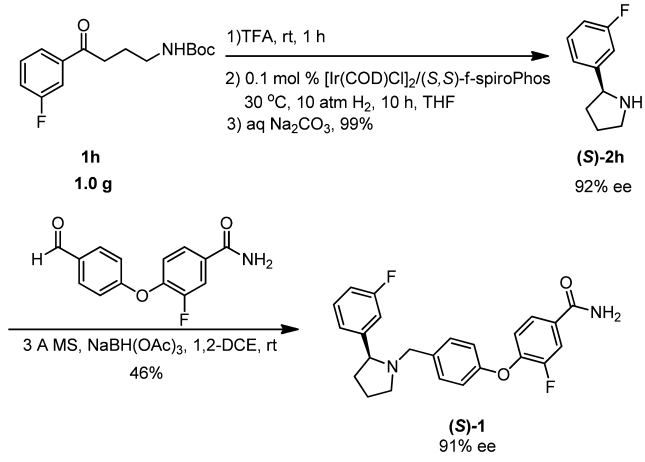

[a]Unless otherwise mentioned, substrates **1** were fully converted into corresponding **2** monitored by $^1$H NMR, and all ee values were determined by chiral GC analysis after the cyclic amines were converted into the corresponding trifluoroacetamides or HPLC analysis using a chiral stationary phase after the cyclic amine was converted into the corresponding *N*-Boc-protected product. [b]24 h. [c]2.0 mol % catalyst loading, 24 h. [d]40 °C, 30 atm of $H_2$, 24 h. [e]50 °C, 24 h.

chiral cyclic amines **2k** and **2l** with 87% ee and 91% ee, respectively, under higher catalyst loading of 2.0 mol %, which was perhaps due to steric hindrance. The *meta*-disubstituted substrates **1m** and **1n** were also evaluated, and both of them were fully converted to the corresponding chiral cyclic amines **2m** and **2n** with 93% ee and 95% ee, respectively. When the phenyl ring was replaced with a cyclohexyl group (**1o**), only moderate enantioselectivity was observed, which was possibly attributed to the flexibility of the alkyl group. Notably, chiral six-membered amine **2p** could also be obtained with comparable yield and enantioselectivity of 92% ee from the corresponding *N*-Boc-protected amino ketone **1p** by this intramolecular RA. However, the seven-membered substrate **1q** only achieved decreased enantioselectivity of 83% ee.

To demonstrate the further application of this approach, we carried out the experiment on a gram scale using the substrate **1h** under a lower catalyst loading of 0.2 mol %, and the free cyclic amine (*S*)-**2h** was smoothly afforded in high yield and enantioselectivity, 92% ee, which was subsequently converted to a potent selective antagonist of κ-opioid receptor (*S*)-**1** for treatment of schizophrenia and other psychotic disorders with retained enantioselectivity (Scheme 3).[5]

In summary, an enantioselective direct synthesis of free cyclic amines via intramolecular reductive amination catalyzed by the Ir-f-spiroPhos complex under additive-free conditions has been developed. A range of *N*-Boc-protected amino ketones were smoothly transformed into free chiral cyclic amines in high yields and excellent enantioselectivities of up to 97% ee.

**Scheme 3. Larger Scale Reductive Amination of 1h and Synthesis of (*S*)-1**




Moreover, this method could be successfully applied to the asymmetric synthesis of a potent selective antagonist of κ-opioid receptor (*S*)-**1**.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01828.

Experimental procedures, compound characterization data, and analysis of enantioselectivities of products (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: ghhou@bnu.edu.cn.

### ORCID

Guofu Zi: 0000-0002-7455-460X

Guohua Hou: 0000-0002-3571-456X


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (Grant Nos. 21672024, 21272026, and 21472013) and Beijing Municipal Commission of Education for generous financial support.

## ■ REFERENCES

(1) (a) Nugent, T. C.; El-Shazly, M. *Adv. Synth. Catal.* **2010**, *352*, 753. (b) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. *Chem. Rev.* **2012**, *112*, 2557. (c) Zhang, Z.; Butt, N. A.; Zhang, W. *Chem. Rev.* **2016**, *116*, 14769.

(2) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, *2003*, 3693.

(3) (a) Buchhalter, A. R.; Fant, R. V.; Henningfield, J. E. In *Handbook of Contemporary Neuropharmacology*; Sibley, D., Hanin, I., Kuhar, M., Skolnick, P., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, 2007. (b) Guo, C.; Sun, D.-W.; Yang, S.; Mao, S.-J.; Xu, X.-H.; Zhu, S.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2015**, *137*, 90.

(4) Rotte, S. C. K.; Chittiboyina, A. G.; Khan, I. A. *Eur. J. Org. Chem.* **2013**, *2013*, 6355.



DOI: 10.1021/acs.orglett.7b01828
*Org. Lett.* XXXX, XXX, XXX−XXX

(5) (a) Mitch, C. H.; Quimby, S. J.; Diaz, N.; Pedregal, C.; de la Torre, M. G.; Jimenez, A.; Shi, Q.; Canada, E. J.; Kahl, S. D.; Statnick, M. A.; McKinzie, D. L.; Benesh, D. R.; Rash, K. S.; Barth, V. N. *J. Med. Chem.* **2011**, *54*, 8000. (b) Wang, J.; Song, Q.; Xu, A.; Bao, Y.; Xu, Y.; Zhu, Q. *Eur. J. Med. Chem.* **2017**, *130*, 15.
(6) (a) Lee, S. T.; Green, B. T.; Welch, K. D.; Pfister, J. A.; Panter, K. E. *Chem. Res. Toxicol.* **2008**, *21*, 2061. (b) Arihan, O.; Boz, M.; Iskit, A. B.; Ilhan, M. *J. Ethnopharmacol.* **2009**, *125*, 274.
(7) Wang, L.; Mason, K. A.; Ang, K. K.; Buchholz, T.; Valdecanas, D.; Mathur, A.; Buser-Doepner, C.; Toniatti, C.; Milas, L. *Invest. New Drugs* **2012**, *30*, 2113.
(8) Hoebeke, P.; De Pooter, J.; De Caestecker, K.; Raes, A.; Dehoorne, J.; Van Laecke, E.; Vande Walle, J. *J. Urol.* **2009**, *182*, 2040.
(9) (a) Felpin; Girard, S.; Vo-Thanh, G.; Robins, R. J.; Villiéras, J.; Lebreton, J. *J. Org. Chem.* **2001**, *66*, 6305. (b) Escolano, C.; Amat, M.; Bosch, J. *Chem. - Eur. J.* **2006**, *12*, 8198.
(10) (a) Dunsmore, C. J.; Carr, R.; Fleming, T.; Turner, N. J. *J. Am. Chem. Soc.* **2006**, *128*, 2224. (b) Leipold, F.; Hussain, S.; Ghislieri, D.; Turner, N. J. *ChemCatChem* **2013**, *5*, 3505. (c) Ghislieri, D.; Houghton, D.; Green, A. P.; Willies, S. C.; Turner, N. J. *ACS Catal.* **2013**, *3*, 2869. (d) Ghislieri, D.; Green, A. P.; Pontini, M.; Willies, S. C.; Rowles, I.; Frank, A.; Grogan, G.; Turner, N. J. *J. Am. Chem. Soc.* **2013**, *135*, 10863. (e) Hussain, S.; Leipold, F.; Man, H.; Wells, E.; France, S. P.; Mulholland, K. R.; Grogan, G.; Turner, N. J. *ChemCatChem* **2015**, *7*, 579. (f) Aleku, G. A.; Man, H.; France, S. P.; Leipold, F.; Hussain, S.; Toca-Gonzalez, L.; Marchington, R.; Hart, S.; Turkenburg, J. P.; Grogan, G.; Turner, N. J. *ACS Catal.* **2016**, *6*, 3880.
(11) (a) Hunt, J. C. A.; Laurent, P.; Moody, C. J. *Chem. Commun.* **2000**, 1771. (b) Guizzetti, S.; Benaglia, M.; Cozzi, F.; Annunziata, R. *Tetrahedron* **2009**, *65*, 6354. (c) Liu, Y.; Du, H. *J. Am. Chem. Soc.* **2013**, *135*, 12968.
(12) For selected examples on asymmetric reduction of cyclic imines and enamines, see: (a) Church, T. L.; Andersson, P. G. In *Chiral Amine Synthesis*; Nugent, T. C., Ed.; Wiley-VCH: Weinheim, 2010; pp 179−223. (b) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. *Chem. Rev.* **2011**, *111*, 1713. (c) Willoughby, C. A.; Buchwald, S. L. *J. Org. Chem.* **1993**, *58*, 7627. (d) Verdaguer, X.; Lange, U. E. W.; Reding, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 6784. (e) Li, C.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 13208. (f) Chang, M.; Li, W.; Hou, G.; Zhang, X. *Adv. Synth. Catal.* **2010**, *352*, 3121. (g) Zhang, Y.; Kong, D.; Wang, R.; Hou, G. *Org. Biomol. Chem.* **2017**, *15*, 3006. (h) Hou, G.-H.; Xie, J.-H.; Yan, P.-C.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2009**, *131*, 1366.
(13) (a) Wang, C.; Xiao, J. *Stereoselective Formation of Amines*; Li, W., Zhang, X., Eds.; Springer: Berlin, 2014; pp 261−282. (b) Blaser, H.-U.; Buser, H.-P.; Jalett, H.-P.; Pugin, B.; Spindler, F. *Synlett* **1999**, *1999*, 867. (c) Kadyrov, R.; Riermeier, T. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5472. (d) Chi, Y.; Zhou, Y.-G.; Zhang, X. *J. Org. Chem.* **2003**, *68*, 4120. (e) Kadyrov, R.; Riermeier, T. H.; Dingerdissen, U.; Tararov, V.; Börner, A. *J. Org. Chem.* **2003**, *68*, 4067. (f) Rubio-Pérez, L.; Pérez-Flores, F. J.; Sharma, P.; Velasco, L.; Cabrera, A. *Org. Lett.* **2009**, *11*, 265. (g) Li, C.; Villa-Marcos, B.; Xiao, J. *J. Am. Chem. Soc.* **2009**, *131*, 6967. (h) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84. (i) Chang, M.; Liu, S.; Huang, K.; Zhang, X. *Org. Lett.* **2013**, *15*, 4354. (j) Song, B.; Ji, Y.; Hu, S.-B.; Yu, C.-B.; Zhou, Y.-G. *Tetrahedron Lett.* **2017**, *58*, 1528. (k) Zhou, H.; Liu, Y.; Yang, S.; Zhou, L.; Chang, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 2725.
(14) Williams, G. D.; Pike, R. A.; Wade, C. E.; Wills, M. *Org. Lett.* **2003**, *5*, 4227.
(15) Chen, F.; Ding, Z.; Qin, J.; Wang, T.; He, Y.; Fan, Q.-H. *Org. Lett.* **2011**, *13*, 4348.
(16) (a) *Privileged Chiral Ligands and Catalysts*; Zhou, Q.-L., Ed.; Wiley-VCH: Weinheim, 2011. (b) Xie, J.-H.; Zhou, Q.-L. *Acc. Chem. Res.* **2008**, *41*, 581. (c) Ding, K.; Han, Z.; Wang, Z. *Chem. - Asian J.* **2009**, *4*, 32. (d) Xie, J.-H.; Zhou, Q.-L. *Huaxue Xuebao* **2014**, *72*, 778.
(17) (a) Yan, Q.; Kong, D.; Li, M.; Hou, G.; Zi, G. *J. Am. Chem. Soc.* **2015**, *137*, 10177. (b) Kong, D.; Li, M.; Wang, R.; Zi, G.; Hou, G. *Org. Biomol. Chem.* **2016**, *14*, 1216. (c) Kong, D.; Li, M.; Zi, G.; Hou, G. *Org. Biomol. Chem.* **2016**, *14*, 4046. (d) Yan, Q.; Kong, D.; Zhao, W.; Zi, G.; Hou, G. *J. Org. Chem.* **2016**, *81*, 2070. (e) Kong, D.; Li, M.; Zi, G.; Hou, G.; He, Y. *J. Org. Chem.* **2016**, *81*, 6640.



DOI: 10.1021/acs.orglett.7b01828
*Org. Lett.* XXXX, XXX, XXX−XXX