Organic LETTERS

Letter

pubs.acs.org/OrgLett

Catalytic Asymmetric Construction of Pyrroloindolines via an in Situ Generated Magnesium Catalyst

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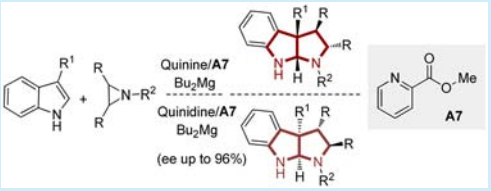
Supporting Information

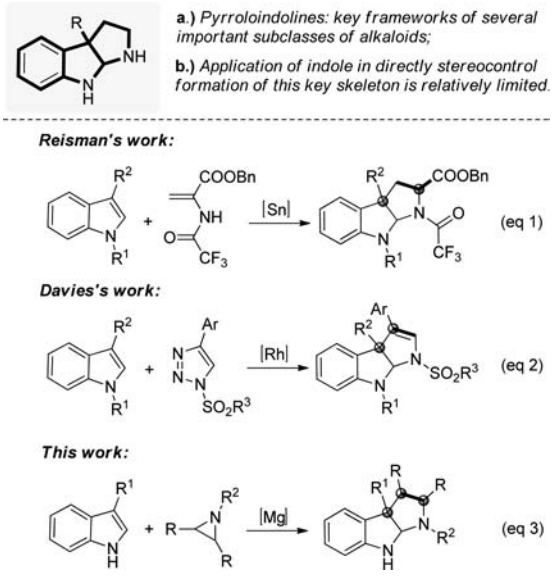
ABSTRACT: An asymmetric formal [3 + 2]-cycloaddition between *meso*-aziridines and C3-alkylindoles mediated by an in situ generated magnesium catalyst was developed for asymmetric construction of pyrroloindolines. A variety of pyrroloindolines could be obtained by employing commercial available ligands with the assistance of an easily prepared achiral ligand.



Using catalytic asymmetric reactions to construct key frameworks of natural products is a highly attractive research area. Pyrroloindolines bearing a C3 quaternary stereocenter are an important indole-derived heterocyclic motif of several important subclasses of alkaloids which exhibit promising biological properties.[1] Consequently, several catalytic enantioselective approaches have been developed for the formation of this hexahydropyrrolo[2,3-*b*]indole skeleton.[2] In this context, the catalytic asymmetric addition−cyclization reactions employing tryptamine as key precursor have proven to be successful strategies in the one-step construction of optically active pyrroloindoline structures.[3] The wide applications of carbon- or heteroatom-based electrophiles in this transformation provide a powerful platform for construction of pyrroloindolines bearing different types of C3 quaternary stereocenters which could be extended to enantioselective synthesis of natural products.

Despite the great success achieved in catalytic asymmetric synthesis of hexahydropyrrolo[2,3-*b*]indole core structures employing tryptamine derivatives as key precursors, the direct application of indole or C3-substituted indole in enantioselective formation of this key framework is relatively undeveloped. To date, there are only limited successful strategies that could realize this direct route. In 2010, Reisman and co-workers established a Binol·$SnCl_4$ catalyzed formal [3 + 2]-cycloaddition reaction of simple C3-substituted indoles and 2-amidoacrylate which could concisely furnish enantioenriched pyrroloindolines in one synthetic operation (Scheme 1, eq 1).[4] More recently, an interesting Rh(II)-catalyzed [3 + 2]-annulation between 4-aryl-1-sulfonyl-1,2,3-triazoles and C3-substituted indoles was described by Davies and co-workers to give didehydropyrroloindolines with excellent enantioselectivities (Scheme 1, eq 2).[5] Given these two well-established methods and based on our continuous interest in asymmetric Friedel−Crafts alkylations of indoles,[6] we report herein a direct and efficient method to synthesize pyrroloindolines by enantioselective desymmetrization of aziridines with C3-substituted indoles (Scheme 1, eq 3).

Scheme 1. Direct Enantioselective Construction of Pyrroloindolines



It could be predicted that catalytic enantioselective ring-opening reaction of *meso*-azairidines with C3-substituted indoles would provide straightforward access to pyrroloindolines. Although some racemic ring-opening reactions of this version have been reported to be promoted by Lewis acids,[7] catalytic asymmetric approaches have never been realized, which might be because there is still no effective catalyst to realize this transformation with good control of the enantiomeric discrimination during the C−C bond formation. Based on our recent work on magnesium-mediated enantioselective ring-opening reactions of aziridines and simple indoles,[8,9] we decided to

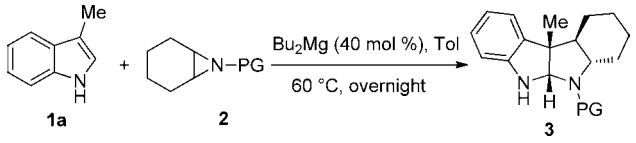
Received: September 9, 2014
Published: December 31, 2014

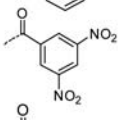
DOI: 10.1021/ol503455r
Org. Lett. 2015, 17, 176−179

applied this effective catalytic system to realize the present enantioselective [3 + 2]-annulation between *meso*-azairidines and C3-substituted indoles.

Our preliminary study of this formal [3 + 2]-cycloaddition focused on investigating the influence of the protecting group of aziridines. After a series of screenings, *N*-(2-picolinoyl)aziridine **2a** was identified as a potential substrate in the current ring-opening reaction,[10] and the reaction could afford the desired pyrroloindoline **3a** using Bu_2Mg as the catalyst. On the basis of the IR studies of the carbonyl group of different aziridines, it is known that the reactivity of aziridines is not dependent on the Lewis basicity of the protecting groups but relies on coordination ability of the substrates (Table 1). Next, we turned to the

Table 1. Preliminary Screening of the Protecting Groups and IR Study of the Carbonyl Group[a]



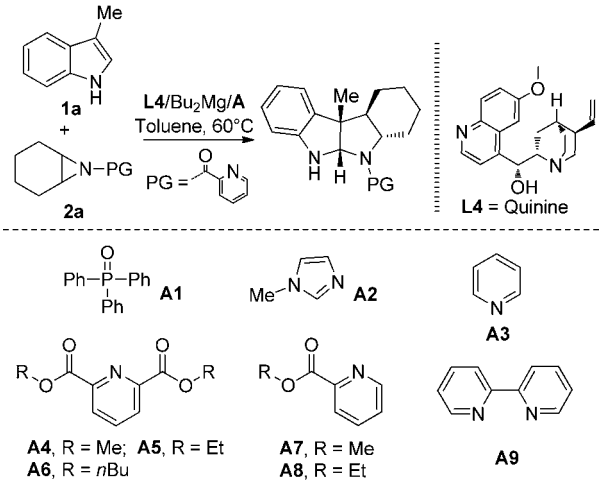
entry	PG	yield (%)	IR (λ/cm^{-1})
1		n.r.	1668.8
2		n.r.	1675.9
3		< 5%	1667.1
4		11%	1657.2
5		67%	1670.7
6		< 5%	-

[a]Reactions were performed with 0.20 mmol of **2a** and 0.40 mmol of **1a** in toluene (0.5 mL) in the presence of Bu_2Mg (40 mol %) at 60 °C overnight.

selection process of chiral ligands, and we found the optical active cyclization adduct **3a** could be generated when some commercially available chiral amino alcohols as ligand of Bu_2Mg were employed.[11] Fortunately, when some commercially available chiral amino alcohols, such as quinine **L4** or quinidine **L5** ,were introduced into our model reaction, the desired pyrroloindoline **3a** could be obtained with relative good enantioselectivies. After identification of promising chiral ligands that are easy to access, we focused our attention on improving the enantioselectivity of this present formal [3 + 2]-cycloaddition by employing different types of achiral coligands.[12] As illustrated in Table 2, after a careful screening process, we found that addition of *N,O*-bidentate ligands such as **A4** and **A7** could elevate the ee value of the reaction significantly (Table 2, entries 2−10). The enantioselectivity could be slightly enhanced to 94% ee when *p*-xylene was used as the solvent (Table 2, entry 11).[13]

With the above optimal conditions established for the construction of pyrroloindoline **3a**, we next explored the scope of this enantioselective [3 + 2]-annulation with respect to different C3-alkylindoles (Table 3). The reactions could furnish

Table 2. Screening of the Achiral Additives for the [3 + 2]-Cycloaddition[a]



entry	A	yield[b] (%)	dr[c]	ee[d] (%)
1		67	9:1	79
2	**A1**	65	11:1	87
3	**A2**	21	9:1	68
4	**A3**	62	9:1	84
5	**A4**	57	13:1	91
6	**A5**	62	13:1	87
7	**A6**	45	10:1	81
8	**A7**	69	12:1	93
9	**A8**	70	12:1	86
10	**A9**	64	9:1	89
11[e]	**A7**	70	12:1	94

[a]Reactions were performed with 0.20 mmol of **2a** and 0.40 mmol of **1a** in toluene (0.5 mL) in the presence of **L4** (20 mol %), **A** (20 mol %), and Bu_2Mg (20 mol %) at 60 °C for 36 h. [b]Isolated yield. [c]Diastereomeric ratios were determined by ^{1}H NMR (300 MHz). [d]Enantiomeric excesses were determined by chiral stationary-phase HPLC. [e]The reaction was carried out in *p*-xylene.

desired cyclization adducts in moderate yields and high levels of diastereoselectivities and enantioselectivities when substituents with different electronic nature were located at the C4-, C5-, or C6-position of the C3-methylindoles **3a**−**g** (Table 3). However, the C7-substituted indole proved to be inefficient in this tansformation resulting in lower chemical yield (**3h**). Furthermore, different C3-alkyl substituted indoles were tested in the transformation, and some functional groups such as silyl ether and azide equipped in the C3-aliphatic chain were also tolerable in the reaction (**3k,l**).

Then, the same set of reaction conditions was applied to explore the scope of various aziridines with C3-alkylindoles. These results are summarized in Table 4. Reactions of other six-membered *meso*-aziridines afforded the cyclization products with excellent enantioselectivities under the standard reaction conditions (**3m,n**). With regard to seven-membered aziridine, the transformation needs higher catalyst loading to generate product **3o**. Unfortunately, the corresponding five-membered aziridines failed to react with C3-methylindole. On the other hand, aziridines containing acyclic aryl and aliphatic substituents were proven to be good substrates with respect to the chemical yields and enantioselectivities (**3p**, **3q**). Moreover, to our delight, the relative enantiomers of these polycyclic products could also be obtained by employing quinidine as a chiral ligand with the assistance of achiral coligand **A7** (**3a′**,**m′**−**q′**). Futhermore, two

DOI: 10.1021/ol503455r
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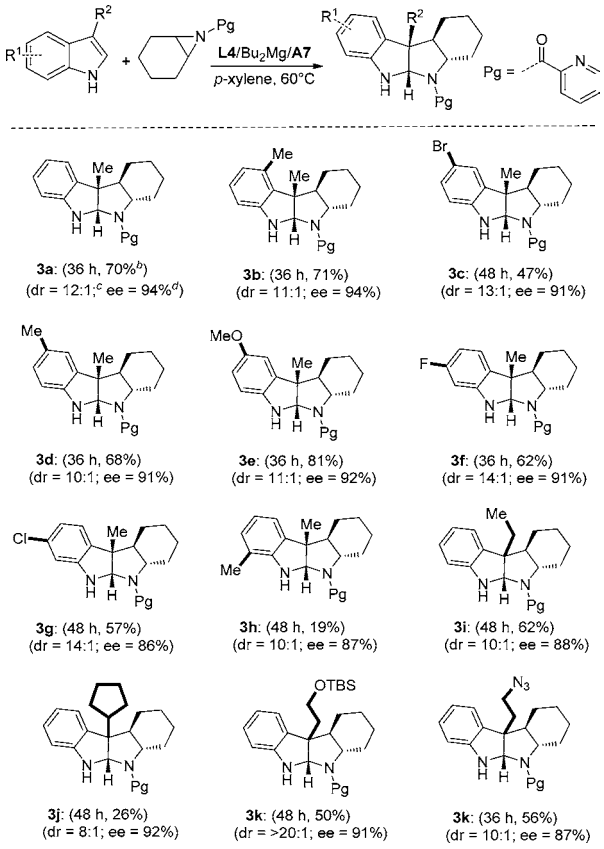
Table 3. Substrate Scope of the [3 + 2]-Cycloaddition with Respect to C3-Alkylindoles[a]



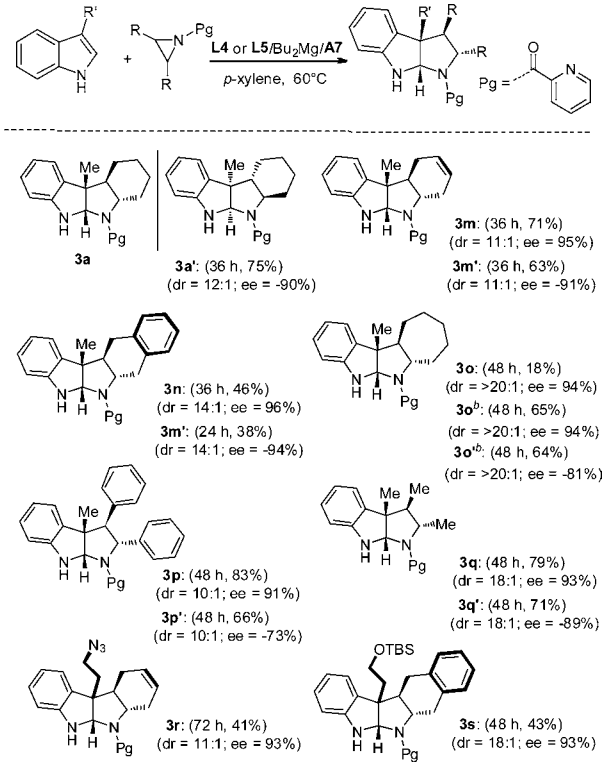
[a]Reactions were performed with 0.20 mmol of aziridine and 0.40 mmol of indoles in *p*-xylene (0.5 mL) in the presence of L4 (20 mol %), A7 (20 mol %), and Bu_2Mg (20 mol %) at 60 °C. [b]Sum yield of the both diastereoisomers due to difficult separation. [c]Diastereomeric ratios were determined by ^1H NMR (300 MHz). [d]Enantiomeric excesses were analyzed by chiral stationary-phase HPLC.

representative aziridines were also tested in cross reactions with bulkier C3-substituted indoles and the cyclization adducts could be obtained in relatively lower yields with excellent enantioselectivities (**3r,s**).

A reasonable mechanism was proposed on the basis of a series of control experiments.[14] As summarized in Scheme 2, the precatalyst A could be generated after a deprotonation process of quinine **L4** and Bu_2Mg. Then C3-methylindole was activated by the precatalyst and finished the formal cyclization process after the aziridine coordinates to the magnesium center (**B**, **C**). A protonation exchange with an incoming C3-methylindole released the product **3a** and reformed the activation process. In this process, it is speculated that the achiral ligand **A7**'s same coordination ability with aziridines would lead itself coordinated to the metal center during the reaction process that could result in generation of a more beneficial chiral environment.

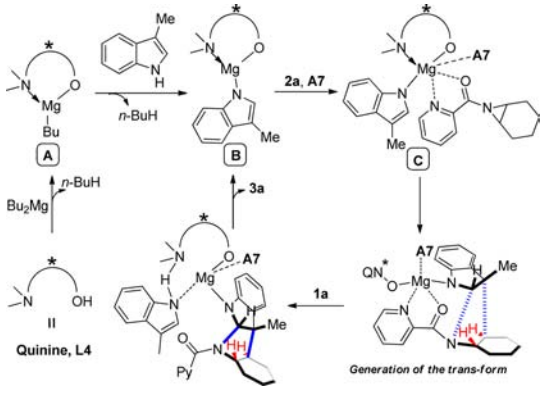
In summary, we have developed a successful strategy for catalytic enantioselective synthesis of pyrroloindolines with high diatereoselectivity and enantioselectivity mediated by a magnesium catalyst employing commercially available ligands with the assistance of an achiral coligand. Study of the mechanism of the magnesium-mediated enantioselective [3 + 2]-cycloaddition and the synthetic methodology are underway in our laboratory.

Table 4. Substrate Scope of the [3 + 2]-Annulation[a]



[a]These reactions were using quinidine (L5, 20 mol %) as chiral ligand to generate the relative enantiomers. [b]The reactions were performed under 50 mol % catalyst.

Scheme 2. Hypothesized Mechanism



■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

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Author Contributions

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Notes

The authors declare no competing financial interest.

DOI: 10.1021/ol503455r
Org. Lett. 2015, 17, 176−179

■ ACKNOWLEDGMENTS

This work was supported by the NSFC (91213302, 21272102, 81473095, 21432003), National S&T Major Project of China (2012ZX09504001-003), and Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT: IRT1137)

■ REFERENCES

(1) Anthoni, U.; Christophersen, C.; Nielsen, P. H. *Naturally Occurring Cyclotryptophans and Cyclotryptamines. In Alkaloids: Chemical & Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, 1999; Vol. *13*, pp 163.

(2) For recent reviews: (a) Repka, L. M.; Reisman, S. E. *J. Org. Chem.* **2013**, *78*, 12314. (b) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447. (c) Loh, C. C. J.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 46. (d) Zhuo, C.-X.; Zhang, W.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 12662.

(3) (a) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482. (b) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314. (c) Jones, S. B.; Simmons, B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 13606. (d) Zhu, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 10815. (e) Knowles, R. R.; Carpenter, J.; Blakey, S. B.; Kayano, A.; Mangion, I. K.; Sinz, C. J.; MacMillan, D. W. C. *Chem. Sci.* **2011**, *2*, 308. (f) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183. (g) Zhang, Z.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2012**, *51*, 11778. (h) Cai, Q.; Liu, C.; Liang, X.-W.; You, S.-L. *Org. Lett.* **2012**, *14*, 4588. (i) Horning, B. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 6442. (j) Laforteza, B. N.; Pickworth, M.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 11269. (k) 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. (l) 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. (m) Nelson, H. M.; Reisberg, S. H.; Shunatona, H. P.; Patel, J. S.; Toste, F. D. *Angew. Chem., Int. Ed.* **2014**, *53*, 5600.

(4) (a) Repka, L. M.; Ni, J.; Reisman, S. E. *J. Am. Chem. Soc.* **2010**, *132*, 14418. (b) Ni, J.; Wang, H.; Reisman, S. E. *Tetrahedron.* **2013**, *69*, 5622. (c) Wang, H.; Reisman, S. E. *Angew. Chem., Int. Ed.* **2014**, *53*, 6206.

(5) Spangler, J. E.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 6802.

(6) (a) Zhang, H.; Hong, L.; Kang, H.; Wang, R. *J. Am. Chem. Soc.* **2013**, *135*, 14098. (b) Feng, J.; Yan, W.; Wang, D.; Li, P.; Sun, Q.; Wang, R. *Chem. Commun.* **2012**, *48*, 8003. (c) Hong, L.; Sun, W.; Liu, C.; Wang, L.; Wong, K.; Wang, R. *Chem.—Eur. J.* **2009**, *15*, 11105. (d) Hong, L.; Liu, C.; Sun, W.; Wang, L.; Wong, K.; Wang, R. *Org. Lett.* **2009**, *11*, 2177.

(7) Nakagawa, M.; Kawahara, M. *Org. Lett.* **2000**, *2*, 953.

(8) Yang, D.; Wang, L.; Han, F.; Li, D.; Zhao, D.; Cao, Y.; Ma, Y.; Kong, W.; Sun, Q.; Wang, R. *Chem.—Eur. J.* **2014**, *20*, 16478.

(9) For recent examples on asymmetric ring-opening reactions using indoles as nucleophiles, see: (a) Bandini, M.; Cozzi, P.; G. Melchiorre, P.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 84. (b) Boudou, M.; Ogawa, C.; Kobayashi, S. *Adv. Synth. Catal.* **2006**, *348*, 2585. (c) Kokubo, M.; Naito, T.; Kobayashi, S. *Tetrahedron* **2010**, *66*, 1111. (d) Lin, S.; Jacobsen, E. N. *Nat. Chem.* **2012**, *4*, 817. (e) Plancq, B.; Lafantaisie, M.; Companys, S.; Maroun, C.; Ollevier, T. *Org. Biomol. Chem.* **2013**, *11*, 7463. (f) Xiong, H.; Xu, H.; Liao, S.; Xie, Z.; Tang, Y. *J. Am. Chem. Soc.* **2013**, *135*, 7851. (g) Wales, S. M.; Walker, M. M.; Johnson, J. S. *Org. Lett.* **2013**, *15*, 2558.

(10) For selected examples of asymmetric ring-opening reactions of aziridines, see: (a) Ohmatsu, K.; Hamajima, Y.; Ooi, T. *J. Am. Chem. Soc.* **2012**, *134*, 8794. (b) Xu, Y.-J.; Lin, L.-Q.; Kanai, M.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2011**, *133*, 5791. (c) Cao, Y.-M.; Zhang, F.-T.; Shen, F.-F.; Wang, R. *Chem.—Eur. J.* **2013**, *19*, 9476. (d) Peruncheralathan, S.; Teller, H.; Schneider, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 4849. (e) Rowland, E. B.; Rowland, G. B.; Rivera-Otero, E.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 12084. (f) Ohta, S. K.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2007**, *129*, 8103. (g) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312. (h) Mita, T.; Fujimori, I.; Wada, R.; Wen, J.-F.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 11252. (i) Müller, P.; Nury, P. *Org. Lett.* **1999**, *1*, 439. (j) Li, Z.; Fernández, M.; Jacobsen, E. N. *Org. Lett.* **1999**, *1*, 1611. For asymmetric ring-opening works of *N*-(2-picolinoyl)aziridines, there is still limited work: (k) Kalow, J. A.; Schmitt, D. E.; Doyle, A. G. *J. Org. Chem.* **2012**, *77*, 4177. (l) Hayashi, M.; Shiomi, N.; Funahashi, Y.; Nakamura, S. *J. Am. Chem. Soc.* **2012**, *134*, 19366. (m) Kalow, J. A.; Doyle, A. G. *Tetrahedron* **2013**, *69*, 5702. (l) Li, J.; Liao, Y.; Zhang, Y.; Liu, X.; Lin, L.; Feng, X. *Chem. Commun.* **2014**, *50*, 6672.

(11) See the Supporting Information for the results of preliminary screen of chiral ligands.

(12) For selected examples of our work on achiral ligands, see: (a) Zhao, D.; Mao, L.; Wang, Y.; Yang, D.; Zhang, Q.; Wang, R. *Org. Lett.* **2010**, *12*, 1880. (b) Zhao, D.; Mao, L.; Yang, D.; Wang, R. *J. Org. Chem.* **2010**, *75*, 6756. (c) Zhao, D.; Wang, L.; Yang, D.; Zhang, Y.; Wang, R. *Angew. Chem., Int. Ed.* **2012**, *51*, 7523.

(13) See the Supporting Information for the results of preliminary screen of solvents.

(14) See the Supporting Information for the results of control experiments.

DOI: 10.1021/ol503455r
Org. Lett. 2015, 17, 176−179