ORGANIC LETTERS

2010
Vol. 12, No. 23
5482−5485

Vicinal-Diamine-Based Chiral Chain Dienes as Ligands for Rhodium(I)-Catalyzed Highly Enantioselective Conjugated Additions

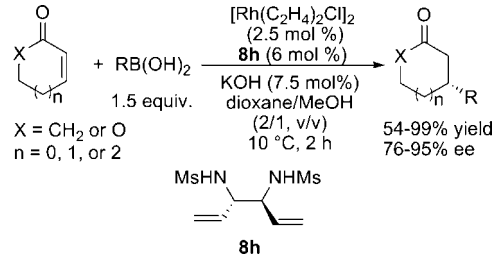
Yazhou Wang, Xichao Hu, and Haifeng Du*

Beijing National Laboratory of Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China

haifengdu@iccas.ac.cn

Received September 30, 2010

ABSTRACT



A variety of readily accessible vicinal-diamine-based chiral chain dienes were successfully synthesized and utilized as steering ligands for rhodium-catalyzed conjugated additions of organoboronic acids to α,β-unsaturated carbonyl compounds to afford the desired adducts in good to excellent yields and ee's.

Chiral dienes as highly effective steering ligands for transition-metal-catalyzed enantioselective reactions have attracted extensive attention since the pioneering studies by the groups of Hayashi and Carreira in 2003 and 2004, respectively.[1−5] Especially, in recent years, there has been rapid progress for both exploring novel diene ligands[6] and utilizing chiral diene ligands to achieve challenging asymmetric reactions,[7] which stand for the most important two subjects in this field. However, the types of chiral diene ligands are still very limited, and almost all of these ligands are bicyclic dienes.[2] The rigid bicyclic structures are important to produce high reactivities and enantioselectivities in catalytic asymmetric reactions, but the synthetic problems may partially restrict the wide application of these ligand systems. The development of novel, effective, easily synthesized and modified chiral diene ligands is still of prime importance. As part of our general interest in exploring acyclic chiral diene ligands which was inspired by the experimental result that flexible

(1) (a) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508. (b) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628.

(2) For reviews on chiral olefin ligands, see: (a) Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3364. (b) Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 840. (c) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482. (d) Shintani, R.; Hayashi, T. *Aldrichimica Acta* **2009**, *42*, 31.

(3) For leading references on chiral diene ligands, see: (a) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584. (b) Defieber, C.; Paquin, J.-F.; Serna, S.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 3873. (c) Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54. (d) Paquin, J.-F.; Stephenson, C. R. J.; Defieber, C.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 3821. (e) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850. (f) Shintani, R.; Duan, W.-L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628. (g) Aikawa, K.; Akutagawa, S.; Mikami, K. *J. Am. Chem. Soc.* **2006**, *128*, 12648. (h) Shintani, R.; Sannohe, Y.; Tsuji, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 7277. (i) Helbig, S.; Sauer, S.; Cramer, N.; Laschat, S.; Baro, A.; Frey, W. *Adv. Synth. Catal.* **2007**, *349*, 2331. (j) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336.

10.1021/ol1023536
Published on Web 11/01/2010

1,5-hexadiene can act as an efficient ligand for rhodium(I)-catalyzed asymmetric additions, we have successfully developed chiral ligands **1**−**3** (Figure 1) from readily available

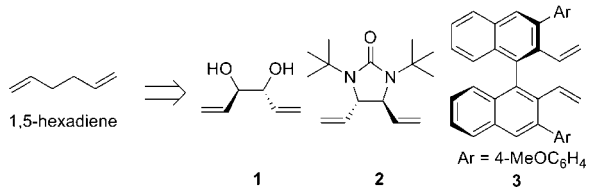
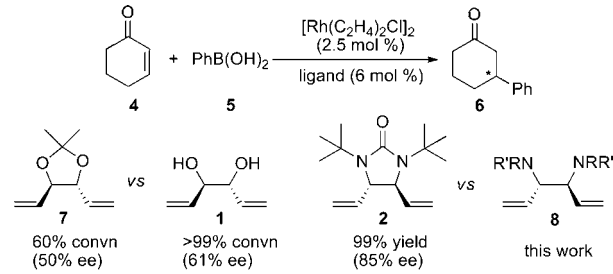


Figure 1. Development of acyclic chiral diene ligands for asymmetric catalysis.

starting materials.[8] Although encouraging results were obtained when employing these ligands in the catalytic asymmetric conjugated additions[8a,b,9] or arylations,[8c] the enantioselectivity (no more than 85% ee) is still not satisfactory. To achieve excellent enantioselectivity using flexible acyclic diene ligands is therefore a great interest.

In our previous study, we found that more flexible chiral diene **1** exhibited an obvious advantage over ligand **7** bearing a cyclic framework in both reactivity (>99% vs 60%) and enantioselectivity (61% vs 50%) for the Rh(I)-catalyzed conjugated addition of phenylboronic acid (**5**) to 2-cyclohexenone (**4**) under the same reaction conditions (Scheme 1),[8a] while

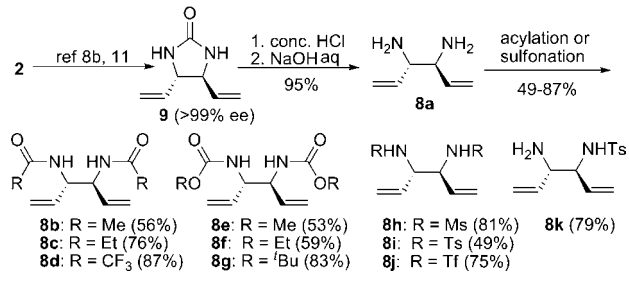
Scheme 1. Rh(I)/Diene Complex Catalyzed Asymmetric Conjugated Additions



chiral diene **2** bearing an imidazolin-2-one framework prepared from 1,5-hexadiene in only one step via Pd(0)-catalyzed asymmetric diamination[10,11] using di-*tert*-butyldiaziridinone[12] as the nitrogen source was found to promote the Rh(I)-catalyzed reactions of **4** and **5** efficiently to afford the corresponding adduct **6** in 99% yield and 85% ee (Scheme 1).[8b] We envisioned that deprotection of *tert*-butyl and carbonyl groups of **2** followed by introduction of different groups on the nitrogen atoms may provide a good opportunity to discover highly effective vicinal-diamine-based chiral chain diene ligands **8** (Scheme 1). Herein, we report our efforts on this subject.

Initially, the enantiopure compound (*S*,*S*)-**9** was prepared using diene (*S*,*S*)-**2** as a starting material according to the reported methods.[8b,11] After removal of the carbonyl group in concentrated hydrochloric acid and neutralization with aqueous sodium hydroxide solution, (3*S*,4*S*)-hexa-1,5-diene-3,4-diamine (**8a**) was obtained in 95% yield (Scheme 2).

Scheme 2. Synthesis of Vicinal-Diamine-Based Chiral Dienes



However, when subjecting **8a** to the Rh(I)-catalyzed reaction of 2-cyclohexenone (**4**) and phenylboronic acid (**5**), no desired product was observed (Table 1, entry 1) which may

(4) For leading references on phosphine−alkene hybrid ligands, see: (a) Maire, P.; Deblon, S.; Breher, F.; Geier, J.; Böhler, C.; Rüegger, H.; Schönberg, H.; Grützmacher, H. *Chem.*−*Eur. J.* **2004**, *10*, 4198. (b) Shintani, R.; Duan, W.-L.; Nagano, T.; Okada, A.; Hayashi, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 4611. (c) Duan, W.-L.; Iwamura, H.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 2130. (d) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139. (e) Stemmler, R. T.; Bolm, C. *Synlett* **2007**, *9*, 1365. (f) Minuth, T.; Boysen, M. M. K. *Org. Lett.* **2009**, *11*, 4212.

(5) For leading references on amine−alkene hybrid ligands, see: (a) Maire, P.; Breher, F.; Schönberg, H.; Grützmacher, H. *Organometallics* **2005**, *24*, 3207. (b) Hahn, B. T.; Tewes, F.; Fröhlich, R.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 1143.

(6) For leading references, see: (a) Feng, C.-G.; Wang, Z.-Q.; Shao, C.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2008**, *10*, 4101. (b) Gendrineau, T.; Chuzel, O.; Eijsberg, H.; Genet, J.-P.; Darses, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7669. (c) Nishimura, T.; Yasuhara, Y.; Nagaosa, M.; Hayashi, T. *Tetrahedron: Asymmetry* **2008**, *19*, 1778. (d) Okamoto, K.; Hayashi, T.; Rawal, V. H. *Org. Lett.* **2008**, *10*, 4387. (e) Okamoto, K.; Hayashi, T.; Rawal, V. H. *Chem. Commun.* **2009**, 4815. (f) Brown, M. K.; Corey, E. J. *Org. Lett.* **2010**, *12*, 172. (g) Luo, Y.; Carnell, A. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 2750. (h) Shao, C.; Yu, H.-J.; Wu, N.-Y.; Feng, C.-Q.; Lin, G.-Q. *Org. Lett.* **2010**, *12*, 3820.

(7) For leading references on expanding the application of chiral olefin ligands in asymmetric catalysis, see: (a) Nishimura, T.; Kumamoto, H.; Nagaosa, N.; Hayashi, T. *Chem. Commun.* **2009**, 5713. (b) Shintani, R.; Tsutsumi, Y.; Nagaosa, M.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2009**, *131*, 13588. (c) Gendrineau, T.; Genet, J.-P.; Darses, S. *Org. Lett.* **2010**, *12*, 308. (d) Nishimura, T.; Wang, J.; Nagaosa, M.; Okamoto, K.; Shintani, R.; Kwong, F.; Yu, W.; Chan, A. S. C.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 464. (e) Nishimura, T.; Kawamoto, T.; Nagaosa, M.; Kumanmoto, H.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 1638. (f) Shintani, R.; Isobe, S.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 3795. (g) Shintani, R.; Takeda, M.; Nishimura, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 3969. (h) Wang, Z.-Q.; Feng, C.-G.; Zhang, S.-S.; Xu, M.-H.; Lin, G.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 5780. (i) Nishimura, T.; Maeda, Y.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 7324. (j) Nishimura, T.; Yasuhara, Y.; Sawano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 7872. (k) Nishimura, T.; Makino, H.; Nagaosa, M.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 12865. (l) Shintani, R.; Takeda, M.; Tsuji, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 13168. (m) Pattison, G.; Piraux, G.; Lam, H. W. *J. Am. Chem. Soc.* **2010**, *132*, 14373.

(8) (a) Hu, X.; Zhuang, M.; Cao, Z.; Du, H. *Org. Lett.* **2009**, *11*, 4744. (b) Hu, X.; Cao, Z.; Liu, Z.; Wang, Y.; Du, H. *Adv. Synth. Catal.* **2010**, *352*, 651. (c) Cao, Z.; Du, H. *Org. Lett.* **2010**, *12*, 2602. For a reference on terminal−alkene phosphine hybrid ligand, see: (d) Liu, Z.; Du, H. *Org. Lett.* **2010**, *12*, 3054.

(9) For leading reviews on Rh-catalyzed asymmetric conjugated additions, see: (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (b) Gennari, C.; Monti, C.; Piarulli, U. *Pure Appl. Chem.* **2006**, *78*, 303. (c) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279. (d) Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chem. Soc. Rev.* **2010**, *39*, 2093.

Table 1. Evaluation of Chiral Diene Ligands and Optimization of Reaction Conditions[a]

entry	ligand	solvent[b]	temp (°C)	conv (%)[c]	ee (%)[d]
1	**8a**	dioxane/MeOH (2/1)	10	NR[e]	-
2	**8b**	dioxane/MeOH (2/1)	10	67	92
3	**8c**	dioxane/MeOH (2/1)	10	>99	89
4	**8d**	dioxane/MeOH (2/1)	10	>99	89
5	**8e**	dioxane/MeOH (2/1)	10	>99	90
6	**8f**	dioxane/MeOH (2/1)	10	>99	89
7	**8g**	dioxane/MeOH (2/1)	10	>99	90
8	**8h**	**dioxane/MeOH** (2/1)	**10**	**>99**	**95**
9	**8i**	dioxane/MeOH (2/1)	50	>99	78
10	**8j**	dioxane/MeOH (2/1)	50	16	78
11	**8k**	dioxane/MeOH (2/1)	10	NR[e]	-
12	**8h**	dioxane/H_2O (2/1)	10	93	95
13	**8h**	THF/MeOH (2/1)	10	73	95
14	**8h**	**benzene/MeOH** (2/1)	**10**	**>99**	**95**
15[f]	**8h**	dioxane/MeOH (2/1)	50	>99	89

[a] All the reactions were carried out with 2-cyclohexenone (**4**) (0.20 mmol), phenylboronic acid (**5**) (0.30 mmol), KOH (0.015 mmol), $[RhCl(C_2H_4)_2]_2$ (0.005 mmol), and ligand **8** (0.012 mmol) at the indicated temperature in solvent (0.6 mL) under argon for 5 h unless otherwise stated. [b] The ratio was in volume. [c] The conversion was determined by crude ^1H NMR. [d] The ee was determined by chiral HPLC (Chiralpak AD-H column). [e] No reaction. [f] The catalyst loading was 1 mol %.

be due to the relatively stronger coordination ability of vicinal diamine moieties than that of diene moieties. Hence, acyl and sulfonyl groups were introduced to the nitrogen atoms to decrease the coordination ability of diamine groups, and a variety of diene ligands **8b**−**k** were afforded in 49−87% yields (Scheme 2).

Ligands **8b**−**k** (6.0 mol %) were then subjected to the reactions of 2-cyclohexenone (**4**) and phenylboronic acid (**5**) with $[RhCl(C_2H_4)_2]_2$ (2.5 mol %) in dioxane/methanol (2/1, v/v) using KOH (7.5 mol %) as base for 5 h. As shown in Table 1, we were pleased to find that the majority of Rh/diene complexes can promote this reaction efficiently to afford the desired product (*R*)-**6** in quantitative conversions and 89−95% ee's (Table 1, entries 2−8). Ligand **8i** gave 78% ee with a quantitative conversion at 50 °C (Table 1, entry 9), while ligand **8k** bearing only one 4-toluenesulfonyl (Ts) group on the nitrogen atom was not effective for this reaction (Table 1, entry 11). Overall, ligand **8h** gave the highest conversion and ee for this reaction (Table 1, entry 8). Further studies on the solvent effects showed that all these solvents gave the same ee's (Table 1, entries 8 vs 12−14), and benzene/methanol was found to be an alternative solvent for this reaction. Decreasing the loading amount of the Rh/**8h** complex from 5 to 1 mol %, the reaction still went

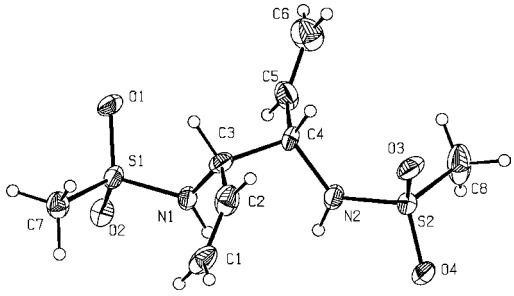
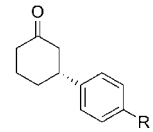
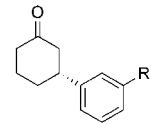
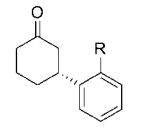
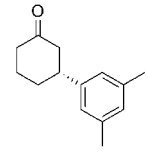
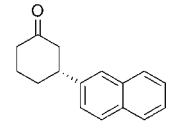
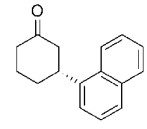
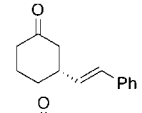
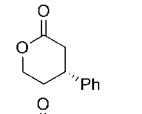
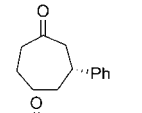
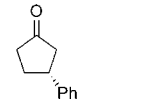


Figure 2. X-ray structure of chiral diene ligand **8h**.

Table 2. Enantioslective Conjugated Additions Catalyzed by the Rh(I)/**8h** Complex[a]

entry	organoboronic acid	product[b]	yield (%)[c]	ee (%)[d]
1	R = H		96	95
2	R = OMe		97	94
3	R = F		90	92
4	R = Me		99	94
5	R = Cl		84	93
6	R = OMe		97	82
7	R = Cl		96	84
8			99	94
9			94	95
10			98	82
11			54	90
12	$PhB(OH)_2$		95	90
13	$PhB(OH)_2$		93	84
14	$PhB(OH)_2$		81	76

[a] All the reactions were carried out with α,β-unsaturated carbonyl compound (0.40 mmol), organoboronic acid (0.60 mmol), $[RhCl(C_2H_4)_2]_2$ (0.01 mmol), KOH (0.030 mmol), and ligand **8h** (0.024 mmol) in dioxane/MeOH (2/1, v/v) (1.2 mL) at 10 °C under argon for 2 h. [b] The absolute configuration was determined by comparing the optical rotation with the reported one. [c] Isolated yield. [d] The ee was determined by chiral HPLC (Chiralpak AD-H column) unless otherwise stated. Chiralcel OD-H column for entries 8 and 11, Chiralcel OJ-H column for entries 10 and 13, Chiralcel OB-H column for entry 14, and Chiralcel AS-H column for entry 12.

smoothly at 50 °C to give the corresponding adduct (*R*)-**6** in >99% conversion but with a slightly lower ee (Table 1, entry 15). One single crystal of ligand **8h** was obtained, and its X-ray structure is shown in Figure 2. To clarify the binding mode between **8h** and rhodium, ligand **8h** was hydrogenated and then subjected to the reaction, but no desired product was observed, which indicates that ligand **8h** is likely binding to rhodium through the olefins rather than the sulfonamides. To have a better insight into the coordination mode between **8h** and rhodium, NMR studies were carried out by using C_6D_6/CD_3OD as solvent. However, to our surprise, only slight changes were observed for all the proton signals of ligand **8h** (see Supporting Information) which suggests that the complex formed between Rh and **8h** has the possibility to be less stable, and a very fast coordination/dissociation process may be involved, even though the Rh/**8h** complex still displays enough activity to promote this reaction to afford up to 95% ee with excellent yields which is interesting and awaits further study.

With the best ligand **8h**, the substrate scope was then investigated. Some of the results are summarized in Table 2. We were pleased to find that the asymmetric conjugated additions under the catalysis of Rh/**8h** (5 mol %) in dioxane/methanol (2/1, v/v) at 10 °C for 2 h proceeded smoothly to give the corresponding adducts in 54−99% yields with 76−95% ee's. The reactions of *meta*- or *para*-substituted aryboronic acids and 2-cyclohexenone (**4**) afforded excellent yields and ee's (Table 2, entries 2−5, 8, and 9), while using *ortho*-substituted arylboronic acids as substrates gave high yields but with lower ee's (Table 2, entries 6, 7, and 10). (*E*)-Styrylboronic acid was also an effective substrate for this reaction to give 90% ee with 54% yield (Table 2, entry 11). The Rh/**8h** complex was found to be an efficient catalyst for the reactions of other α,β-unsaturated carbonyl compounds and phenylboronic acid (**5**) to give 81−95% yields with 76−90% ee's (Table 2, entries 12−14).

In summary, a variety of novel vicinal-diamine-based chiral chain diene ligands were easily prepared in reasonable yields through a straightforward synthetic route. Ligand **8h** was found to be a highly effective steering ligand for rhodium-catalyzed asymmetric conjugated additions to give promising results (up to 95% ee). It is encouraging that such a simple and flexible diene can be utilized as a ligand in asymmetric reactions to achieve excellent reactivities and enantioselectivities which will benefit the development of accessible diene ligands in the future. Searching for more effective acyclic diene ligands, exploring their application in other asymmetric reactions, and understanding the detailed coordination mode are currently underway in our laboratory.

Acknowledgment. We are grateful to the generous financial support from the National Science Foundation of China (20802079, 21072194), the National Basic Research Program of China (973 program, 2010CB833300), and the Ministry of Science and Technology (2009ZX09501-018).

Supporting Information Available: The procedure for the synthesis of chiral dienes, rhodium-catalyzed conjugated additions, characterization of diene ligands and adducts, NMR study for the Rh/**8h** complex, and data for the determination of enantiomeric excesses of adducts along with NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1023536

(10) For leading reviews on diamination, see: (a) Lucet, D.; Gall, T. L.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580. (b) Mortensen, M. S.; O'Doherty, G. A. *Chemtracts: Org. Chem.* **2005**, *18*, 555. (c) Kotti, S. R. S. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101. (d) de Figueiredo, R. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1190. (e) Cardona, F.; Goti, A. *Nature Chem.* **2009**, *1*, 269.

(11) For leading references on Pd(0)-catalyzed diamination, see: (a) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762. (b) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 7496. (c) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 11688. (d) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 8590. (e) Wang, B.; Du, H.; Shi, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 8224. (f) Zhao, B.; Du, H.; Cui, S.; Shi, Y. *J. Am. Chem. Soc.* **2010**, *132*, 3523.

(12) (a) Greene, F. D.; Stowell, J. C.; Bergmark, W. R. *J. Org. Chem.* **1969**, *34*, 2254. (b) Du, H.; Zhao, B.; Shi, Y. *Org. Synth.* **2009**, *86*, 315.