ORGANIC LETTERS

2012
Vol. 14, No. 12
3154–3157

Rhodium-Catalyzed Asymmetric Formal Cycloadditions of Racemic Butadiene Monoxide with Imines

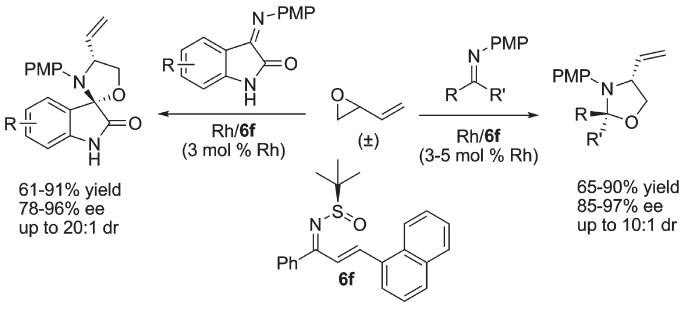
Zhaoqun Liu, Xiangqing Feng, and Haifeng Du*

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 May 7, 2012

ABSTRACT



A simple chiral sulfur−alkene hybrid ligand has proven to be highly effective for rhodium-catalyzed formal cycloaddition reactions of racemic butadiene monoxide and imines to furnish spirooxindole oxazolidines or 1,3-oxazolidines with high yields and stereoselectivities. A possible dynamic kinetic resolution as well as a kinetic resolution is considered to be involved in this catalytic process.

Rhodium catalysts can bring about a wide range of synthetic transformations,[1] and allylrhodium intermediates, involved in reactions, such as allylic substitution, are generally thought to involve σ-allylrhodium complexes rather than π-allylrhodium complexes.[2] Because of the relatively slow $\sigma-\pi-\sigma$ isomerization of σ-allylrhodium intermediates, the regio- and stereochemistry of the starting substrates can usually be well conserved in the products.[3] This substrate-controlled feature of rhodium catalysts appears to be incompatible with the catalyst-controlled asymmetric synthesis from racemic starting materials. Although there are very few reports on the use of chiral rhodium catalyst for such an asymmetric transformation, Pregosin,[4a] Hayashi,[4b] and Vireze[4c] have shown that racemic allylic acetates or carbonates can be converted to highly enantioenriched products, which clearly indicates that the $\sigma-\pi-\sigma$ isomerization can also occur in rhodium complexes under suitable conditions.

Very recently, Jarvo and co-workers described a Rh-catalyzed stereospecific reaction of (*R*)-butadiene monoxide (**2**) with arylimines **1** to provide synthetic and pharmaceutically important 1,3-oxazolidines **3** in high yields (Scheme 1).[5−7] Moreover, phosphine ligands were found to inhibit this Rh-catalyzed reaction.[5] Our own group has

(1) Evans, P. A. *Modern Rhodium-Catalyzed Organic Reactions*; Wiley-VCH: Weinheim, 2005.

(2) Minami, I.; Shimizu, I.; Tsuji, J. *J. Organomet. Chem.* **1985**, *296*, 269.

(3) (a) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581. (b) Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6761. (c) Fagnou, K.; Lautens, M. *Org. Lett.* **2000**, *2*, 2319. (d) Evans, P. A.; Uraguchi, D. *J. Am. Chem. Soc.* **2003**, *125*, 7158. (e) Evans, P. A.; Leahy., D. K. *J. Am. Chem. Soc.* **2003**, *125*, 8974. (f) Evans, P. A.; Lawler, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 8642. (g) Ashfeld, B. L.; Miller, K. A.; Martin, S. F. *Org. Lett.* **2004**, *6*, 1321. (h) Kazmaier, U.; Stolz, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 3072. (i) Menard, F.; Chapman, T. M.; Dockendorff, C.; Lautens, M. *Org. Lett.* **2006**, *8*, 4569. (j) Ashfeld, B. L.; Miller, K. A.; Smith, A. J.; Tran, K.; Martin, S. F. *J. Org. Chem.* **2007**, *72*, 9018.

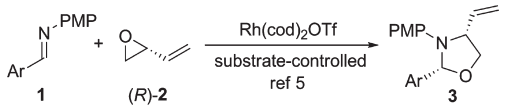
(4) (a) Selvakumar, K.; Valentini, M.; Pregosin, P. S. *Organometallics* **1999**, *18*, 4591. (b) Hayashi, T.; Okada, A.; Suzuka, T.; Kawatsura, T. *Org. Lett.* **2003**, *5*, 1713. (c) Vrieze, D. C.; Hoge, G. S.; Hoerter, P. Z.; Van Haitsma, J. T.; Samas, B. M. *Org. Lett.* **2009**, *11*, 3140.

(5) Shaghafi, M. B.; Grote, R. E.; Jarvo, E. R. *Org. Lett.* **2011**, *13*, 5188.

(6) For selected examples on oxazolidine synthesis by cycloadditions of vinyl epoxides, see: (a) Larksarp, C.; Alper, H. *J. Am. Chem. Soc.* **1997**, *119*, 3709. (b) Larksarp, C.; Alper, H. *J. Org. Chem.* **1998**, *63*, 6229. (c) Shim, J.-G.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 1053. (d) Shim, J.-G.; Yamamoto, Y. *Heterocycles* **2000**, *52*, 885.

10.1021/ol301248d
Published on Web 06/06/2012

Scheme 1. Rh-Catalyzed Stereospecific Reaction of Butadiene Monoxide with Imines[5]



been working on the development of novel chiral olefin ligands,[8−10] and in some cases, this type of ligand shows higher activity and selectivity than many other types of ligand. Because of this, we envisioned that the Rh-catalyzed asymmetric reaction of racemic butadiene monoxide (**2**) with imines could probably be achieved using chiral olefin ligands. Herein, we report our efforts in this area.

Initially, we selected the novel reaction of isatin imine **4a** with 1.2 equivalent of racemic butadiene monoxide (**2**) which would produce spirooxindole oxazolidines.[11,12] This would serve as the model reaction to test our hypothesis on

Scheme 2. Initial Study on Rh-Catalyzed Formal Cycloadditions with Chiral Sulfur/Alkene Ligands

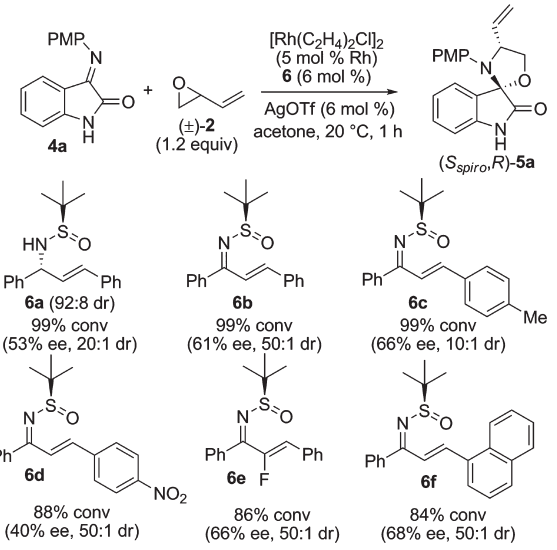


Table 1. Optimization of Reaction Conditions[a]

entry	(±)-**2** (equiv)	AgX	solvent	time (h)	conv[b] (%)	dr[b]	ee[c] (%)
1	1.2	AgOTf	acetone	1	84	50:1	68
2	1.2	$AgBF_4$	acetone	1	90	20:1	56
3	1.2	$AgPF_6$	acetone	1	80	50:1	60
4	1.2	$AgSbF_6$	acetone	1	99	20:1	42
5	1.2	AgOTf	EtOAc	2.5	74	10:1	84
6	1.2	AgOTf	EtOAc	12	83	10:1	65
7	2.0	AgOTf	EtOAc	1	99	10:1	84
8[d]	2.0	AgOTf	EtOAc	2.5	99	10:1	88
9[d]	**3.0**	**AgOTf**	**EtOAc**	**2.5**	**99**	**12:1**	**94**
10[d]	4.0	AgOTf	EtOAc	2.5	99	20:1	95
11[e]	3.0	AgOTf	EtOAc	12	86	20:1	95

[a] All of the reactions were carried out with **4a** (0.20 mmol), (±)-**2** as indicated, $[Rh(C_2H_4)_2Cl]_2$ (0.005 mmol), ligand **6f** (0.012 mmol), and AgX (0.012 mmol) in solvent (1.0 mL) at 20 °C unless other noted. [b] The conversion and dr were determined by crude ^1H NMR. [c] The ee was determined by chiral HPLC (Chiralcel OD-H column). [d] 3 mol % catalyst was used. [e] 1 mol % catalyst was used.

the utility of chiral alkene ligands for allylrhodium transformations. As shown in Scheme 2, a variety of easily accessible chiral sulfur/alkene ligands[10e,f,13] were found to be effective for this reaction to afford optically active spirooxindole oxazolidines **5a** with up to 68% ee and high diastereoselectivity, which indicated that the stereochemistry of this reaction is at least partially controlled by chiral rhodium catalysts.

To further improve the enantioselectivity, various conditions for the Rh-catalyzed reaction between **4a** and (±)-**2**, with the use of ligand **6f**, were thoroughly examined, and some results are summarized in Table 1. Studies on the influence of the counteranion on Rh center showed that

(7) For recent reviews on oxazolidine, see: (a) Scott, J. D.; William, R. M. *Chem. Rev.* **2002**, *102*, 1669. (b) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311. (c) Wu, G.; Huang, M. *Chem. Rev.* **2006**, *106*, 2596.

(8) For leading reviews on chiral alkene 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. (e) Tian, P.; Dong, H.-Q.; Lin, G.-Q. *ACS catal* **2012**, *2*, 95.

(9) For leading references on chiral alkene ligands, see: (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. (c) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336. (d) Gendrineau, T.; Chuzel, O.; Eijsberg, H.; Genet, J.-P.; Darses, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7669. (e) Luo, Y.; Carnell, A. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 2750. (f) Pattison, G.; Piraux, G.; Lam, H. W. *J. Am. Chem. Soc.* **2010**, *132*, 14373. (g) Maire, P.; Deblon, S.; Breher, F.; Geier, J.; Böhler, C.; Rüegger, H.; Schönberg, H.; Grützmacher, H. *Chem.—Eur. J.* **2004**, *10*, 4198. (h) Shintani, R.; Duan, W.-L.; Nagano, T.; Okada, A.; Hayashi, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 4611. (i) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139. (j) Maire, P.; Breher, F.; Schönberg, H.; Grützmacher, H. *Organometallics* **2005**, *24*, 3207. (k) Hahn, B. T.; Tewes, F.; Fröhlich, R.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 1143.

(10) For examples on alkene ligands developed by our group, see the following. Acyclic diene: (a) Hu, X.; Zhuang, M.; Cao, Z.; Du, H. *Org. Lett.* **2009**, *11*, 4744. P/alkene: (b) Liu, Z.; Du, H. *Org. Lett.* **2010**, *12*, 3054. S/alkene: (c) Feng, X.; Wang, Y.; Wei, B.; Yang, J.; Du, H. *Org. Lett.* **2011**, *13*, 3300. (d) Feng, X.; Wei, B.; Yang, J.; Du, H. *Org. Biomol. Chem.* **2011**, *9*, 5927. (e) Wang, Y.; Feng, X.; Du, H. *Org. Lett.* **2011**, *13*, 4954. (f) Feng, X.; Nie, Y.; Yang, J.; Du, H. *Org. Lett.* **2012**, *14*, 624.

(11) For recent reviews on spriooxindoles, see: (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (b) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127. (c) Galliord, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *47*, 8748. (d) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003.

(12) For examples on spriooxindole oxazolidines, see: (a) Risitano, F.; Grassi, G.; Foti, F.; Bruno, G.; Rotondo, A. *Heterocycles* **2003**, *60*, 857. (b) Badillo, J. J.; Arevalo, G. E.; Fettinger, J. C.; Franz, A. K. *Org. Lett.* **2011**, *13*, 418.

(13) For examples on S/alkene hybrid ligands developed by other groups, see: (a) Thaler, T.; Guo, L.-N.; Steib, A. K.; Raducan, M.; Karaghiosoff, K.; Mayer, P.; Knochel, P. *Org. Lett.* **2011**, *13*, 3182. (b) Jin, S.-S.; Wang, H.; Xu, M.-H. *Chem. Commun.* **2011**, *47*, 7230. (c) Qi, W.-Y.; Zhu, T.-S.; Xu, M.-H. *Org. Lett.* **2011**, *13*, 3410. (d) Chen, G.; Gui, J.; Li, L.; Liao, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7681. (e) Xue, F.; Li, X.; Wan, B. *J. Org. Chem.* **2011**, *76*, 7256. (f) Zhu, T.-S.; Jin, S.-S.; Xu, M.-H. *Angew. Chem., Int. Ed.* **2012**, *51*, 780.

Scheme 3. Control Experiments with the Use of (*R*)-**2**

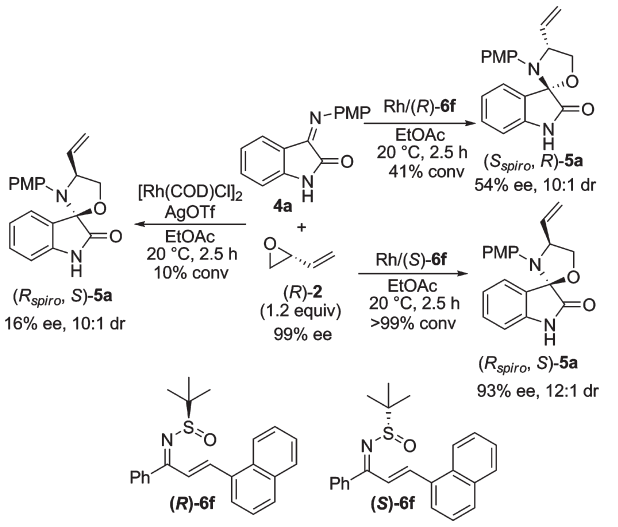
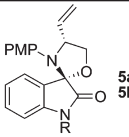
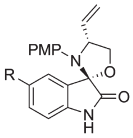
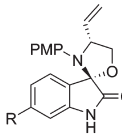
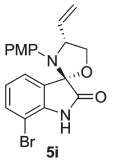


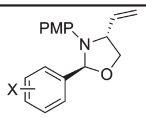
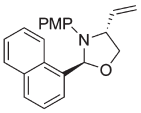
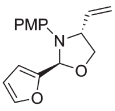
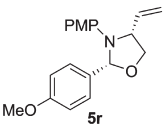
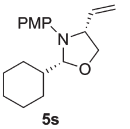
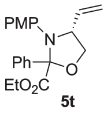
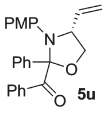
Table 2. Rh-Catalyzed Asymmetric Reaction of Isatin Imines **4** with Racemic Butadiene Monoxide **2**[a]

entry	product[b]	yield (%)[c]	dr[d]	ee (%)[e]
1	 **5a**: R = H	90	12:1	94
2	**5b**: R = PMB	61	12:1	96
3	 **5c**: R = F	82	20:1	82
4	**5d**: R = Cl	85	20:1	82
5	**5e**: R = Br	80	20:1	82
6	**5f**: R = OMe	90	10:1	78
7		90	20:1	88
8	**5g**: R = Cl **5h**: R = OMe	88	20:1	84
9	 **5i**	91	20:1	88

[a] All the reactions were carried out with **4** (0.4 mmol), (±)-**2** (1.2 mmol), $[Rh(C_2H_4)_2Cl]_2$ (0.006 mmol), ligand **6f** (0.0144 mmol), and AgOTf (0.0144 mmol) in ethyl acetate (2.0 mL) at 20 °C for 2.5 h. [b] The absolute configuration was tentatively assigned by analogy with **5i**. [c] Isolated yield. [d] The diastereoisomer ratio was determined by crude ^{1}H NMR. [e] The ee was determined by chiral HPLC.

OTf anion gave higher enantioselectivity (Table 1, entries 1−4). Ethyl acetate was a better solvent than acetone, giving a higher ee (Table 1, entries 1 vs 5). Increasing the amount of (±)-**2** and/or reducing the catalyst loading from 5.0 mol % to 3.0 mol % led to a complete conversion of the

Table 3. Rh-Catalyzed Asymmetric Reaction of Imines Derived from Aldehydes or Ketones with Racemic Butadiene Monoxide **2**[a]

entry	product	dr (*trans*:*cis*)[c]	yield (%)[g] (dr)[h]	ee (%)[i]
1[b]		3.5:1[d,e]	90 (3:1)	97 (*trans*)[j] 97 (*cis*)[j]
2		3.5:1[d]	70 (5:1)	93
3[b]	**5j**: X = H	3.5:1	76 (20:1)	86
4[b]	**5k**: X = 4-Cl **5l**: X = 4-Br	10:1	75 (10:1)	92
5	**5m**: X = 3-Cl	5:1	81 (10:1)	90
6	**5n**: X = 3-Br **5o**: X = 2-Cl	10:1	85 (8:1)	85
7[b]	 **5p**	2.3:1	80 (5:1)	96 (*trans*)[j] 98 (*cis*)[j]
8	 **5q**	2:1	72 (7:1)	97
9	 **5r**	1:1.5[d,e]	65 (1:7)	96
10	 **5s**	1:4[e,f]	78 (1:4)	89 (*cis*)[j] 89 (*trans*)[j]
11	 **5t**	4:1	81 (3:1)	94
12	 **5u**	7:1[e]	86 (7:1)	86 (*trans*)[j] 87 (*cis*)[j]

[a] All of the reactions were carried out with imine (0.4 mmol), (±)-**2** (1.2 mmol), $[Rh(C_2H_4)_2Cl]_2$ (0.010 mmol), ligand **6f** (0.024 mmol), and AgOTf (0.024 mmol) in ethyl acetate (2.0 mL) at 20 °C for 4.0 h unless other noted. [b] The reaction was performed with 3.0 mol % of catalyst for 2.5 h. [c] The diastereoisomer ratio was determined by crude ^{1}H NMR. [d] The relative stereochemistry was assigned according to ref 5. [e] The absolute configuration of allyl carbon was determined by comparing the optical rotation value of the hydrolysis product with that of ref 16. [f] The relative stereochemistry was assigned by NOE experiment. [g] Isolated yield. [h] The diastereoisomer ratio for isolated products. [i] The ee for major isomer was determined by chiral HPLC unless other noted. [j] The ee for both *trans*- and *cis*-isomers was determined.

isatin imine **4a** to give **5a** with up to 95% ee (Table 1, entries 7−10). Even with as low as a 1.0 mol % catalyst loading, high enantioselectivity could still be maintained with only a slight drop of conversion (Table 1, entry 11).

With excellent enantio- and diastereoselectivity in hand, a series of control experiments using enantiomerically pure butadiene monoxide[14] (**2**) as substrate were conducted in order to have better insight into the course of this reaction.

(14) (a) Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 2687. (b) Hunter, L.; O'Hagan, D.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2006**, *128*, 16422.

The reaction of isatin imine **4a** and (*R*)-**2** (1.2 equiv) in ethyl acetate, catalyzed by the combination of $[Rh(COD)Cl]_2$ and AgOTf, furnished the desired product **5a** in only 10% conversion and with 16% ee (Scheme 3), which suggested that a $\sigma-\pi-\sigma$ isomerization was occurring under the current conditions. Ligand (*R*)-**6f** seems to be mismatched with the substrate, giving the product **5a** in 41% conversion with 54% ee, while matched ligand (*S*)-**6f** led to a complete conversion of isatin imine **4a** to **5a** in 93% ee (Scheme 3). On the basis of the aforementioned results, some interesting features for this reaction were concluded: (i) sulfur/alkene ligands can greatly accelerate this reaction; (ii) the absolute configuration of products is dependent on that of chiral ligand; (iii) a dynamic kinetic resolution as well as a kinetic resolution is probably involved in the reaction of imine **4a** with excess (±)-**2**. Moreover, it is noteworthy that the configuration at the stereogenic center of butadiene monoxide is reversed. Although the reason remains unclear, we suppose that the step of C−N bond formation is through a reductive elimination instead of a nucleophilic substitution.[3i,15]

Subsequently, we examined the scope to isatin imines **4** in this formal [3 + 2] cycloaddition. We were pleased to find that a variety of isatin imines **4** possessing either electron-donating or electron-withdrawing groups were well tolerated in this reaction, furnishing the desired spirooxindole oxazolidines **5a**−**i** in 61−91% yield with 78−96% ee and 10:1−20:1 dr (Table 2, entries 1−9). A single crystal of product **5i** was obtained, and the absolute configuration was determined accordingly.

Since isatin imines proved suitable substrates, we next examined the imines derived from simple aldehydes or ketones, for this reaction. In the presence of 3.0−5.0 mol % of rhodium catalyst, a wide range of aldimines reacted with racemic butadiene monoxide (**2**) efficiently to give the corresponding 1,3-oxazolindines **5j**−**s** with excellent enantioselectivities but relatively low diastereoselectivities (Table 3, entries 1−10). It should be noted that *trans*-oxazolidines were obtained as major products, instead of more stable *cis*-oxazolidines, except for imines derived from 4-methoxybenzaldehyde and cyclohexanecarbox-aldehyde (Table 3, entries 1−8 vs 9 and 10), which was distinct from the reported results.[5,6c,6d] An epimerization is supposed to exist under the reaction conditions on the basis of similar ee values being obtained for *trans*- and *cis*-isomers (Table 3, entries 1, 7, 10, and 12) and an observed isomerizaion of *trans*-**5k** to *cis*-**5k** after being kept at room temperature for several weeks. Moreover, imines derived from ethyl benzoylformate and benzil were also suitable substrates, affording the desired products with quaternary stereocenters (Table 3, entries 11 and 12).

In summary, Rh-catalyzed formal [3 + 2] cycloaddition between racemic butadiene monoxide and imines has been successfully achieved with the use of a simple and easily accessible chiral sulfur/alkene ligand. A possible dynamic kinetic resolution, besides a kinetic resolution, is presumed to operate in this catalytic process. A wide range of imines derived from isatins, simple aldehydes, and ketones were tolerated in this reaction and highly enantioenriched spirooxindole oxazolidines or 1,3-oxazolidines were formed in high yields with good to excellent diastereoselectivities.

Acknowledgment. We are thankful for the financial support from the National Natural Science Foundation of China (21072194, 21172222) and 973 program (2010-CB833300).

Supporting Information Available. Procedure for rhodium-catalyzed reactions, characterization of products, data for the determination of enantiomeric excesses, X-ray data for **5i**, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(15) (a) Matsushita, H.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1982**, 160. (b) Fiaud, J.-C.; Legros, J.-Y. *J. Org. Chem.* **1987**, *52*, 1907. (c) Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 4435. (d) Kar, A.; Argade, N. P. *Synthesis* **2005**, 2995.

(16) Gnamm, C.; Franck, G.; Miller, N.; Stork, T.; Brödner, K.; Helmchen, G. *Synthesis* **2008**, 3331.