CHEMISTRY
A EUROPEAN JOURNAL

ChemPubSoc
Europe

DOI: 10.1002/chem.201200821

Mg-Catalyzed Enantioselective Benzylic C–H Bond Functionalization of Isoindolinones: Addition to Imines

Yudai Suzuki,[a] Motomu Kanai,*[a, b] and Shigeki Matsunaga*[a, b]

Dedicated to Professor Masakatsu Shibasaki on the occasion of his 65th birthday

Isoindolinones are an important structural motif in natural products and biologically active compounds.[1] Among them, chiral isoindolinones that bear a carbon substituent at the C3-position are particularly attractive in medicinal chemistry, because of their usefulness in many drug candidates, such as pazinaclone **1a** (an anxiolytic agent),[2a] cyclin-dependent kinase 1,2,4,6 inhibitor **1b**,[2b] PD172938 **1c** (a dopamine D4 receptor antagonist),[2c] and HIV-reverse transcriptase inhibitor **1d** (Figure 1).[2d] Although several synthetic methods for chiral 3-substituted isoindolinones have been reported over the past two decades, most of them are diastereoselective reactions by using stoichiometric amounts of chiral auxiliaries or chiral starting materials,[3] and the development of catalytic asymmetric methods is in high demand. Quite recently, a few catalytic asymmetric approaches have been reported.[4–6] Huang and co-workers reported a catalytic asymmetric tandem Michael/Mannich/cyclization reaction of Et_2Zn, chalcone derivatives, and an imine (methyl 2-[(tosylimino)methyl]benzoate) to form isoindolinone cores.[4] Wang et al.[5] and Zhou et al.[6] developed more straightforward approaches by using 3-hydroxy-substituted isoindolinones. A chiral Brønsted acid catalyst generated *N*-acyliminium intermediates in situ, and an asymmetric Friedel–Crafts reaction with indoles[5] and a reduction with a Hantzsch ester[6] gave chiral 3-substituted isoindolinones. In these methods, the isoindolinone cores were used as electrophiles. The use of isoindolinones as nucleophiles via carbanion formation is an alternative approach for chiral 3-substituted isoindolinones, but only chiral-auxiliary-based methods by using stoichiometric amounts of strong bases, such as sodium hexamethyl disilazide (NaHMDS) and lithium diisopropylamide (LDA), have been reported.[7] In striking contrast to the well-established catalytic asymmetric methods by using oxindoles as nucleophiles,[8,9] there are no reports of catalytic nucleophile formation directly from an isoindolinone core and catalytic asymmetric reactions by using isoindolinones as nucleophiles, possibly owing to the lower acidity of the benzylic proton in isoindolidinones than in oxindoles. Herein, we report the first catalytic enantioselective C–H bond functionalization of isoindolinones. A Bu_2Mg/Schiff base **2** catalyst (1:1; Figure 2) promoted the enantioselective addition of *N*-Boc-isoindolinones **3** to 2-thiophenesulfonyl imines **4**, giving 3-substituted functionalized isoindolinones in up to 98% *ee* and 91:9 d.r.

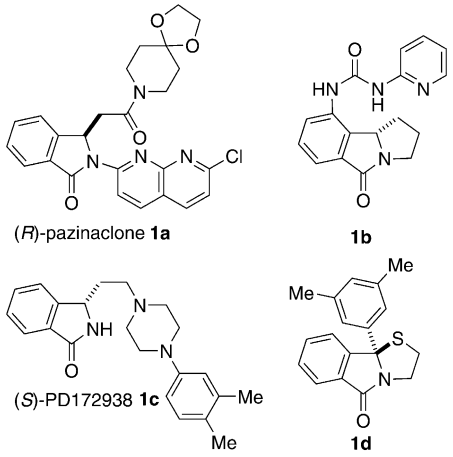


Figure 1. Structures of biologically active compounds with 3-substituted isoindolinone core.

To realize catalytic benzylic C–H bond functionalization,[10] we screened various metal and ligand combinations by using *N*-Boc-isoindolinone (**3a**) and 2-thiophenesulfonyl imine **4a**[11,12] as model substrates. Among the ligands screened, Schiff base ligand **2a** afforded promising results.[13–15] The results of the optimization studies by using Schiff base ligands are summarized in Table 1. Because rare earth metal alkoxides failed to promote the reaction (entries 1 and 2), we screened more Brønsted basic Group 2 metal sources (entries 3–6). Although Group 2 metal alkoxides did not promote the reaction (entries 3–5),[16] a Bu_2Mg/

[a] Y. Suzuki, Prof. Dr. M. Kanai, Dr. S. Matsunaga
Graduate School of Pharmaceutical Sciences
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
Fax: (+81) 3-5684-5206
E-mail: kanai@mol.f.u-tokyo.ac.jp
smatsuna@mol.f.u-tokyo.ac.jp

[b] Prof. Dr. M. Kanai, Dr. S. Matsunaga
Kanai Life Science Catalysis Project, ERATO
Japan Science and Technology Agency
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201200821.

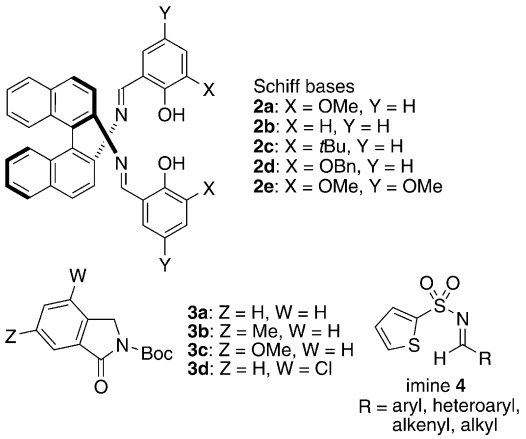
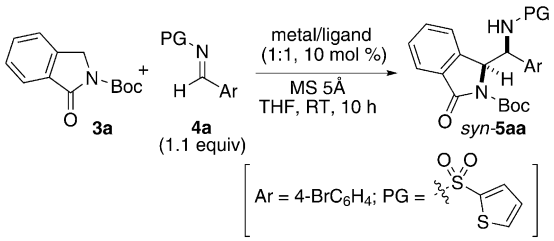


Figure 2. Structures of Schiff bases **2a**–**e**, *N*-Boc-isoindolinones **3a**–**d**, and 2-thiophenesulfonyl imines **4**.

Table 1. Optimization studies.



Entry	Metal	Ligand	Yield [%][a]	d.r.[b] (*syn/anti*)	*ee* [%][c] (*syn*)
1	$La(OiPr)_2$	**2a**	0	–	n.d.
2	$Sc(OiPr)_2$	**2a**	0	–	n.d.
3	$Ba(OiPr)_2$	**2a**	0	–	n.d.
4	$Sr(OiPr)_2$	**2a**	0	–	n.d.
5	$Mg(OiPr)_2$	**2a**	0	–	n.d.
6	Bu_2Mg	**2a**	40	86:14	88
7	Et_2Zn	**2a**	0	–	n.d.
8	Bu_2Mg	**2b**	0	–	n.d.
9	Bu_2Mg	**2c**	0	–	n.d.
10	Bu_2Mg	**2d**	14	86:14	83
11	Bu_2Mg	**2e**	>95	86:14	98

[a] Determined by ^{1}H NMR analysis with an internal standard. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase after removal of the Boc group. n.d. = not determined.

Schiff base **2a** complex (1:1) promoted the addition of **3a** to **4a**, giving product **5aa** in 40% yield, 86:14 d.r., and 88% *ee* after 10 h (entry 6). No reaction occurred when using another alkyl metal source, Et_2Zn (entry 7). The MeO group in Schiff base **2** was critical for both reactivity and selectivity, and Schiff bases **2b**, **c**, and **d** resulted in poor reactivity (entries 8–10). On the other hand, Schiff base **2e** with additional MeO groups gave much higher reactivity than **2a**, possibly owing to a difference in the Brønsted basicity of the Mg-aryloxide species. The enantioselectivity also improved with **2e**, and a Bu_2Mg/Schiff base **2e** catalyst (1:1) gave product **5aa** in >95% yield, 86:14 d.r., and 98% *ee* after 10 h (entry 11).

The substrate scope and limitations of the Mg-catalyzed enantioselective addition of isoindolinones **3** to imines are summarized in Table 2. To simplify the purification process by silica gel column chromatography, the isolated yield (Table 2) was determined after removing the Boc group by treatment with TFA (trifluoroacetic acid). With isoindolinone **3a** and imine **4a**, the catalyst loading was successfully reduced to 5 mol%, and good yield and stereoselectivity were maintained (entry 2). With 2.5 mol% catalyst, the reaction was not complete, even after 72 h (entry 3). Isoindolinones **3b** and **3c** bearing an electron-donating group at the C6-position (Figure 2) gave products with excellent enantioselectivity (entries 4 and 5). The substituent at the C4-position of the isoindolinone core, which is close to the reaction site, was also compatible, and isoindolinone **3d** gave *syn*-**6da** in 91% *ee* (entry 6). The diastereoselectivity with **3d**, however, was slightly decreased. Next, the imine scope was investigated (entries 7–14). An electron-donating substituent at the *para* position of the imine's aromatic ring in **4c** and **4d** was compatible, giving products in 83:17 and 78:22 d.r. and 97 and 95% *ee*, respectively (entries 8 and 9). The diastereoselectivity strongly depended on the imine structure, and imines **4e**–**h** resulted in poor to moderate diastereoselectivity, while high enantioselectivity was observed for all entries (entries 10–13). It is worth noting that the present system was applicable to enolizable alkyl imines, and imine **4i** gave product **6ai** in high yield, diastereoselectivity, and enantioselectivity (entry 14). The result in entry 14 suggests that the Mg-catalyst chemoselectively activates the benzylic C–H bond of isoindolinone **3a**, while isomerization of imine **4i** to the enamide was suppressed. For imines affording moderate diastereoselectivity, the enantiomeric excess of both isomers was determined, and both isomers gave good to high enantioselectivity (84–98% *ee*; entries 10–13 in parentheses). The absolute configuration of both diastereomers was unequivocally determined by X-ray crystallographic analysis (Figure 3).[17] The results suggest that the catalyst clearly differentiates the enantiofacial selectivity of the isoindolinones, giving both diastereomers in high enantioselec-

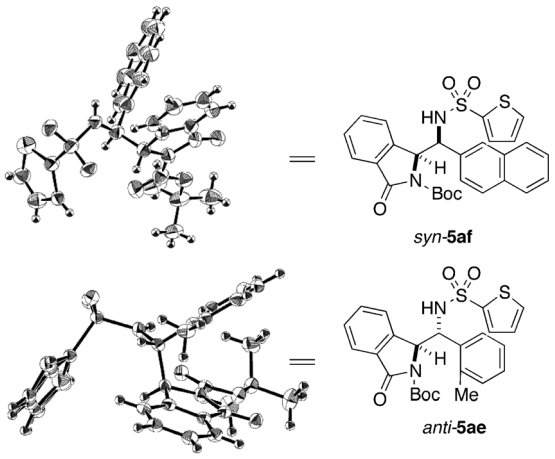
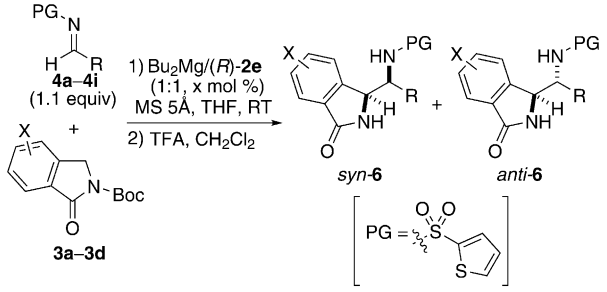


Figure 3. ORTEP plots of *syn*-**5af** and *anti*-**5ae**.

Table 2. Mg-catalyzed enantioselective addition of isoindolinones **3** to imines **4**.[a]



Entry	3	R	4	6	Cat. [mol %]	t [h]	Yield [%][b]	d.r.[c] (*syn/anti*)	*ee* [%][d] (*syn*)
1	**3a**	4-BrC_6H_4	**4a**	**6aa**	10	10	95	86:14	98
2	**3a**	4-BrC_6H_4	**4a**	**6aa**	5	36	94	82:18	97
3[e]	**3a**	4-BrC_6H_4	**4a**	**6aa**	2.5	72	76	83:17	99
4	**3b**	4-BrC_6H_4	**4a**	**6ba**	10	24	90	82:18	97
5	**3c**	4-BrC_6H_4	**4a**	**6ca**	10	48	77	80:20	97
6	**3d**	4-BrC_6H_4	**4a**	**6da**	10	24	78	76:24	91
7	**3a**	4-PhC_6H_4	**4b**	**6ab**	10	12	86	79:21	97
8	**3a**	4-MeOC_6H_4	**4c**	**6ac**	10	24	95	83:17	97
9	**3a**	4-MeC_6H_4	**4d**	**6ad**	10	12	86	78:22	95
10	**3a**	2-MeC_6H_4	**4e**	**6ae**	10	12	95	50:50	98(97)[f]
11	**3a**	2-naphthyl	**4f**	**6af**	10	12	87	58:42	97(98)[f]
12	**3a**	2-thienyl	**4g**	**6ag**	10	12	83	61:39	96(95)[f]
13	**3a**	(*E*)-PhCH=CH	**4h**	**6ah**	10	24	64	64:36	93(84)[f]
14	**3a**	cyclohexyl	**4i**	**6ai**	10	24	90	91:9	92

[a] Reaction was run by using isoindolinone **3** (0.20 mmol), imine **4** in THF (1.1 equiv, 0.50 M), Bu_2Mg (10 mol %), and Schiff base **2e** (10 mol %) with MS 5 Å (17.2 mg), unless otherwise noted. [b] Isolated yield of **6** in two steps after purification by silica gel column chromatography. [c] Determined by ^{1}H NMR analysis of the crude mixture of **5** after the addition to imine **4**. [d] Determined by HPLC analysis using a chiral stationary phase. [e] Reaction was run by using isoindolinone **3a** (0.4 mmol). [f] The value in parenthesis is the enantiomeric excess of *anti*-**6**.

tivity. Low diastereoselectivity in some imines was due to poor facial selectivity of the imine part.[18]

In summary, we developed a Mg-catalyzed enantioselective benzylic C–H bond functionalization of isoindolinones. A Bu_2Mg/Schiff base catalyst (1:1) promoted the enantioselective addition of *N*-Boc-isoindolinones to aryl, heteroaryl, alkenyl, and enolizable alkyl imines, giving 3-substituted isoindolinones in 84–99 % *ee* and 50:50–91:9 d.r. In comparison with previous methods,[4–6] the present method provides a complementary catalytic asymmetric access to chiral isoindolinones. Trials to improve the diastereoselectivity through ligand modifications and applications of the present method for the design and synthesis of biologically active compounds are ongoing.

Experimental Section

A test tube charged with MS 5 Å (17.2 mg) was flame dried under reduced pressure (around 1.0 kPa). After cooling down to RT, argon was refilled and (*R*)-**2e** (12.3 mg, 0.020 mmol), THF (0.47 mL), and then Bu_2Mg (1.0 M in heptane, 20 μL, 0.020 mmol) were added. After stirring for 30 min at RT, THF was removed under reduced pressure and *N*-Boc-isoindolinone **3** (0.20 mmol), imine **4** (0.22 mmol, 1.1 equiv), and THF (0.40 mL) were added to the test tube. The resulting mixture was stirred at RT for the indicated time (Table 2) and quenched by adding silica gel and diluted with AcOEt. The diastereoselectivity was determined by ^{1}H NMR analysis of the crude mixture at this stage. After evaporation, the residue was dissolved in CH_2Cl_2 (2.0 mL) and TFA (5 equiv) was added at 0 °C. The resulting mixture was stirred at RT for 3 h. After evaporation, the crude mixture was purified by flash silica gel column chromatography (AcOEt/hexane) to afford **6**. The *ee* value of **6** was determined by HPLC analysis using a chiral stationary phase.

Acknowledgements

We thank Dr. H. Sato at RIGAKU for technical support on X-ray analysis. This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis" from MEXT, ERATO from JST, Grant-in-Aid for Young Scientist (A) from JSPS, Inoue Foundation for Science, and the Naito Foundation.

Keywords: asymmetric catalysis · C–H activation · imines · isoindolinones · magnesium

[1] a) E. C. Lawson, D. K. Luci, S. Ghosh, W. A. Kinney, C. H. Reynolds, J. Qi, C. E. Smith, Y. Wang, L. K. Minor, B. J. Haertlein, T. J. Parry, B. P. Damiano, B. E. Maryanoff, *J. Med. Chem.* **2009**, *52*, 7432; b) E.-Y. Moon, J.-M. Oh, Y.-H. Kim, I.-J. Ryoo, I.-D. Yoo, *Biol. Pharm. Bull.* **2009**, *32*, 1689; c) H. M. Botero Cid, C. Tränkle, K. Baumann, R. Pick, E. Mies-Klomfass, E. Kostenis, K. Mohr, U. Holzgrabe, *J. Med. Chem.* **2000**, *43*, 2155; d) Z.-P. Zhuang, M.-P. Kung, M. Mu, H. F. Kung, *J. Med. Chem.* **1998**, *41*, 157; e) J. L. Wood, B. M. Stoltz, S. N. Goodman, *J. Am. Chem. Soc.* **1996**, *118*, 10656.

[2] a) Z. Hussein, D. J. Mulford, B. A. Bopp, G. R. Granneman, *Br. J. Clin. Pharmacol.* **1993**, *36*, 357; b) N. Kawanishi, T. Sugimoto, J. Shibata, K. Nakamura, K. Masutani, M. Ikuta, H. Hirai, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5122; c) T. R. Belliotti, W. A. Brink, S. R. Kesten, J. R. Rubin, D. J. Wustrow, K. T. Zoski, S. Z. Whetzel, A. E. Corbin, T. A. Pugsley, T. G. Heffner, L. D. Wise, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1499; d) J. Ren, R. M. Esnouf, A. L. Hopkins, D. I. Stuart, D. K. Stammers, *J. Med. Chem.* **1999**, *42*, 3845.

[3] a) R. Grigg, M. J. R. Dorrity, J. F. Malone, T. Mongkolaussavaratana, W. D. J. A. Norbert, V. Sridharan, *Tetrahedron Lett.* **1990**, *31*, 3075; b) S. M. Allin, C. J. Northfield, M. I. Page, A. M. Z. Slawin, *Tetrahedron Lett.* **1997**, *38*, 3627; c) D. Enders, V. Braig, G. Raabe, *Can. J. Chem.* **2001**, *79*, 1528; d) H. McAlonan, J. P. Murphy, M. Nieuwenhuyzen, K. Reynolds, P. K. S. Sarma, P. J. Stevenson, N. Thompson, *J. Chem. Soc., Perkin Trans. 1* **2002**, 69; e) E. Deniau, D. Enders, A. Couture, P. Grandclaudon, *Tetrahedron: Asymmetry* **2005**, *16*, 875; f) M. Lamblin, A. Couture, E. Deniau, P. Grandclaudon, *Tetrahedron: Asymmetry* **2008**, *19*, 111; see also ref. [7].

[4] S. Guo, Y. Xie, X. Hu, C. Xia, H. Huang, *Angew. Chem.* **2010**, *122*, 2788; *Angew. Chem. Int. Ed.* **2010**, *49*, 2728.

[5] a) X. Yu, A. Lu, Y. Wang, G. Wu, H. Song, Z. Zhou, C. Tang, *Eur. J. Org. Chem.* **2011**, 892; b) X. Yu, Y. Wang, G. Wu, H. Song, Z. Zhou, C. Tang, *Eur. J. Org. Chem.* **2011**, 3060.

[6] M.-W. Chen, Q.-A. Chen, Y. Duan, Z.-S. Ye, Y.-G. Zhou, *Chem. Commun.* **2012**, *48*, 1698.

[7] a) D. L. Comins, S. Schilling, Y. Zhang, *Org. Lett.* **2005**, *7*, 95; b) D. L. Comins, A.-C. Hiebel, *Tetrahedron Lett.* **2005**, *46*, 5639; c) J. Pérard-Viret, T. Prangé, A. Tomas, J. Royer, *Tetrahedron* **2002**, *58*, 5103; for racemic reactions of isoindolinones with aldehydes via benzylic carbanion formation with stoichiometric amounts of LDA

(LDA = lithium diisopropylamide), see: d) A. Couture, E. Deniau, P. Grandclaudon, C. Hoarau, V. Rys, *Tetrahedron Lett.* **2002**, *43*, 2207.

[8] For a general review on enantioselective synthesis of tetrasubstituted oxindoles, see: a) F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381;for selected leading examples using oxindoles for asymmetric C–C bond formation, see: b) B. M. Trost, J. Xie, J. D. Sieber, *J. Am. Chem. Soc.* **2011**, *133*, 20611, and references therein; c) S. Ma, X. Han, S. Krishnan, S. C. Virgil, B. M. Stoltz, *Angew. Chem.* **2009**, *121*, 8181; *Angew. Chem. Int. Ed.* **2009**, *48*, 8037; d) R. He, S. Shirakawa, K. Maruoka, *J. Am. Chem. Soc.* **2009**, *131*, 16620; e) T. Bui, S. Syed, C. F. Barbas, III, *J. Am. Chem. Soc.* **2009**, *131*, 8758; f) B. M. Trost, Y. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 4590.

[9] For early reports using oxindoles as nucleophiles by our group in collaboration with Prof. Shibasaki, see: a) Y. Kato, M. Furutachi, Z. Chen, H. Mitsunuma, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 9168; b) S. Mouri, Z. Chen, H. Mitsunuma, M. Furutachi, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 1255; c) H. Mitsunuma, S. Matsunaga, *Chem. Commun.* **2011**, *47*, 469; d) S. Mouri, Z. Chen, S. Matsunaga, M. Shibasaki, *Heterocycles* **2012**, *84*, 879; e) H. Mitsunuma, M. Shibasaki, M. Kanai, S. Matsunaga, S. *Angew. Chem. Int. Ed.* , DOI: 10.1002/anie.201201132.

[10] For a review on C(sp^3)–H bond functionalization, see: M. Tobisu, N. Chatani, *Angew. Chem.* **2006**, *118*, 1713; *Angew. Chem. Int. Ed.* **2006**, *45*, 1683.

[11] For selected leading examples using *N*-heteroarenesulfonyl imines, see: a) A. S. González, R. Gómez Arrayás, J. C. Carretero, *Org. Lett.* **2006**, *8*, 2977; b) J. Esquivias, R. Gómez Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2007**, *129*, 1480, and references therein; c) S. Nakamura, H. Nakashima, H. Sugimoto, N. Shibata, T. Toru, *Tetrahedron Lett.* **2006**, *47*, 7599; d) S. Nakamura, H. Nakashima, H. Sugimoto, H. Sano, M. Hattori, N. Shibata, T. Toru, *Chem. Eur. J.* **2008**, *14*, 2145, and references therein; e) H. Morimoto, G. Lu, N. Aoyama, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2007**, *129*, 9588; f) G. Lu, H. Morimoto, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2008**, *120*, 6953; *Angew. Chem. Int. Ed.* **2008**, *47*, 6847.

[12] Other imines, such as Ts-imine (Ts = *p*-toluenesulfonyl), 2-pyridinesulfonyl imine, diphenylphosphinoyl imine, and Boc-imine resulted in much less satisfactory yield and/or enantioselectivity when using Bu_2Mg/Schiff base catalysts.

[13] For the utility of MeO-substituted Schiff base **2a** and related ligands in asymmetric catalysis, see: a) B. Wu, J. C. Gallucci, J. R. Parquette, T. V. RajanBabu, *Angew. Chem.* **2009**, *121*, 1146; *Angew. Chem. Int. Ed.* **2009**, *48*, 1126; b) H. Mihara, Y. Xu, N. E. Shepherd, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 8384; c) Y. Xu, L. Lin, M. Kanai, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2011**, *133*, 5791.

[14] For the utility of Mg/Schiff base **2e** catalyst in other reactions, see: a) T. Yoshino, H. Morimoto, G. Lu. S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 17082; b) G. Lu, T. Yoshino, H. Morimoto, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2011**, *123*, 4474; *Angew. Chem. Int. Ed.* **2011**, *50*, 4382; c) S. Matsunaga, T. Yoshino, *Chem. Rec.* **2011**, *11*, 260.

[15] Other chiral ligands, such as BINOL derivatives (BINOL = 1,1'-bi-2-naphthol) and chiral bis-sulfonamides, resulted in poor reactivity and/or stereoselectivity.

[16] The difference in reactivity between Mg-alkoxide and dialkyl magnesium can be ascribed to the difference in solubility under the reaction conditions.

[17] CCDC-870068 (*syn*-**5af**) and CCDC-870069 (*anti*-**5ae**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[18] Because the structure of the catalyst, prepared from Bu_2Mg/Schiff base **2** (Figure 2) in a ratio of 1:1, has not been clarified, it is difficult to propose the transition state model to explain the stereochemistry of products. The Bu_2Mg/Schiff base **2** 1:1 mixture is speculated to have an oligomeric structure, see ref. [14b].

Received: March 11, 2012
Published online: May 21, 2012

