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Direct Allylation of Aldimines Catalyzed by C_2-Symmetric *N*,*N*′-Dioxide–Sc^{III} Complexes: Highly Enantioselective Synthesis of Homoallylic Amines

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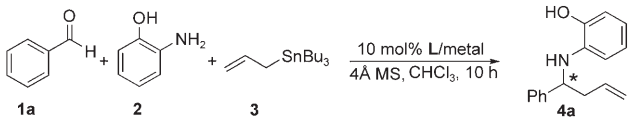
Optically active homoallylic amines are useful intermediates for the preparation of bioactive natural products and relevant compounds.[1] The asymmetric allylation of imines provides direct access to them and considerable efforts have been devoted to devising enantioselective versions of this transformation.[2–4] Among these methods, catalytic asymmetric allylation of imines, as a more efficient method, has made significant progress.[5–8] Despite these creative efforts, the development of new methods, the design and synthesis of new catalysts remain considerable challenge. Simplified and environmentally friendly multicomponent strategy[9] has been successfully adopted in the synthesis of racemic homoallylic amines.[10] Herein, we reported an efficient catalytic asymmetric direct allylation of aldimines promoted by readily accessible and tuneable C_2-symmetric *N*,*N*′-dioxide-Sc^{III} complexes under mild conditions.

As a versatile catalyst, chiral *N*,*N*′-dioxide compounds[11–12] and their complexes[13] with different metals have showed superiority in the enantioselective reactions of carbonyl compounds and imines. In our study of chiral *N*,*N*′-dioxide-metal complexes in catalytic asymmetric reactions, they have exhibited good ability for the activation of allylstannane reagent and 2-aminophenol-derived aldimines.[13] We sought to take advantage of the activation abilities of this kind of catalysts for the asymmetric allylation of 2-aminophenol-derived aldimines, which has been extensively documented well in the allylation by Kobayashi,[6] Leighton[3c,d] and Tsogoeva[4d,e] et al. With the three-component reaction of benzaldehyde, 2-aminophenol and allyltributyltin as benchmark,[14] catalytic ability of different metals complexed with L-proline-derived *N*,*N*′-dioxide **L1** was tested. The significant effect of the central metal on both reactivity and enantioselectivity was observed, as shown in Table 1. When $Zr(OiPr)_4$[6] and $Pd(OAc)_2$[5b–d] were adopted, the reaction did not take place (Table 1, entries 1, 2). Racemic products were obtained with good yields in the presence of $Cu(OTf)_2$[5h] and $In(OTf)_3$ (Table 1, entries 3, 4). Inspiringly, **L1**-$Sc(OTf)_3$ complex catalyzed the reaction smoothly, giving the desired allylic amine in 77% yield with 82% *ee* (Table 1, entry 5).

Table 1. Asymmetric three-component allylation of aldimines under indicated conditions.[a]



Entry	Metal	Ligand	Yield [%][b]	*ee* [%][c]
1	$Zr(OiPr)_4$	**L1**	NR	–
2	$Pd(OAc)_2$	**L1**	NR	–
3	$Cu(OTf)_2$	**L1**	81	0
4	$In(OTf)_3$	**L1**	98	1
5	$Sc(OTf)_3$	**L1**	77	82
6	$Sc(OTf)_3$	**L2**	82	80
7	$Sc(OTf)_3$	**L3**	81	93
8	$Sc(OTf)_3$	**L4**	85	56
9	$Sc(OTf)_3$	**L5**	83	53
10	$Sc(OTf)_3$	**L6**	90	50
11	$Sc(OTf)_3$	**L7**	89	38
12	$Sc(OTf)_3$	**L8**	87	17
13[d]	$Sc(OTf)_3$	**L9**	63	0
14[e]	$Sc(OTf)_3$	**L3**	81	95
15[f]	$Sc(OTf)_3$	**L3**	76	95
16[g]	$Sc(OTf)_3$	**L3**	83	80

[a] Unless specific indication, all reactions were carried out with 10 mol% **L**/metal complex (1:1) catalyst, 2-aminophenol (0.1 mmol), benzaldehyde (0.105 mmol), 4 Å molecular sieves (15 mg), allyltributyltin (0.15 mmol) and $CHCl_3$ (1.0 mL) under Ar atmosphere at 25 °C. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Reaction time was 40 h. [e] 1.5 mL $CHCl_3$ was used. [f] Benzaldehyde was added after the addition of allyltributyltin. [g] Pure aldimine prepared beforehand was used as substrate.

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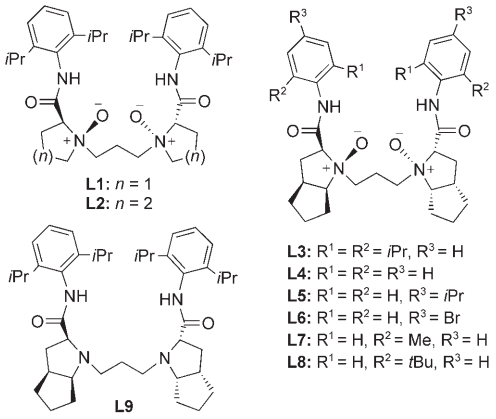
Supporting information for this article is available on the WWW under http://www.chemistry.org or from the author.

Modular and tuneable *N*,*N*′-dioxide ligands, easily synthesized from readily accessible chiral amino acids and amines, facilitated the catalyst structure optimization. Both the chiral backbone and steric effects of the amide portion of ligands played important roles on enantioselectivity towards this reaction. L-ramipril acid-oriented *N*,*N*′-dioxide **L3** was superior to L-proline-derived and (*S*)-pipecolic acid-based *N*,*N*′-dioxides (Table 1, entry 7 vs 5, 6). The enantioselectivity was also closely dependent on the steric effects of the aromatic amide portion. Simple aniline derivative **L4** provided

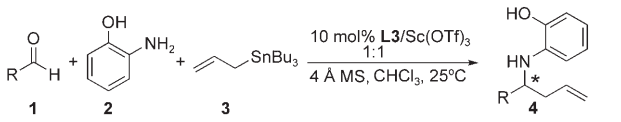


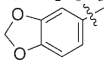
56% *ee* (Table 1, entry 8). Ligands regardless of steric and electronic substitution on *para*-position of aniline had not too much effects on enantioselectivity (Table 1, entries 9, 10 vs 8). Mono-*ortho*-substituted aniline derivatives greatly decreased the *ee* values (Table 1, entries 11, 12 vs 8). While the bulkier 2,6-diisopropyl aniline derived *N*,*N*′-dioxide **L3** dramatically increased enantioselectivity to 93% *ee* (Table 1, entry 7). With mother amide **L9** as ligand, only racemic product was obtained (Table 1, entry 13), which demonstrated that the existence of the *N*-oxide portion was essential for the enantioselectivity.

The direct allylation of aldimine with three-component method exhibited clearly superiority also in the enantioselectivity. The addition sequence of benzaldehyde and allyltributyltin had no effect on *ee* (Table 1, entry 15 vs 14), while with prepared pure aldimine as substrate, the enantioselectivity was decreased to 80% *ee* (Table 1, entry 16). Optimization of other conditions (see Supporting Information) showed that 1.5 mL $CHCl_3$, 10 mol% catalyst with the ratio of ligand to metal 1:1 in the presence of 4 Å molecular sieves at 25 °C were optimal.

Under the optimal conditions, a variety of aldehydes were investigated and the corresponding products were provided in good yields with excellent enantioselectivities, as shown in Table 2. Neither the electronic property of the substitution at the aromatic ring, nor the steric hindrance had obvious influence on the enantioselectivity and up to 97% *ee* could be obtained (Table 2, entries 1–20). In addition, condensed-ring aromatic aldehydes (1- and 2-naphthaldehyde) were also found to be suitable substrates, giving the desired products with 90% and 96% *ee*, respectively (Table 2, entries 21, 22). It was noteworthy that excellent enantioselectivities could be attained with 3- and 4-pyridinecarboxaldehyde (Table 2, entries 23, 24, up to 96% *ee*). Thiophene-2-carbaldehyde also gave the desired product in 71% yield with 87% *ee* (Table 2, entry 25). Cinnamaldehyde provided 71% *ee* (Table 2, entry 26).[15]

Table 2. Substrate scope for the catalytic asymmetric three-component allylation of aldimines.[a]



Entry	R	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ph	**4a**	10	81	95
2	2-MeC_6H_4	**4b**	24	76	95
3	3-MeC_6H_4	**4c**	24	80	93
4	4-MeC_6H_4	**4d**	24	74	92
5	2-$NO_2C_6H_4$	**4e**	18	88	96
6	3-$NO_2C_6H_4$	**4f**	18	85	95
7	4-$NO_2C_6H_4$	**4g**	18	84	97 (*S*)[d]
8	3,4-$Cl_2C_6H_3$	**4h**	16	85	96
9	2,4-$Cl_2C_6H_3$	**4i**	16	81	97
10		**4j**	18	72	90
11	3-$MeOC_6H_4$	**4k**	18	80	95
12	3-$PhOC_6H_4$	**4L**	20	89	93
13	4-PhC_6H_4	**4m**	20	76	95
14	2-ClC_6H_4	**4n**	18	85	97
15	3-ClC_6H_4	**4o**	18	79	95
16	4-ClC_6H_4	**4p**	18	73	97
17	3-BrC_6H_4	**4q**	18	81	90
18	4-BrC_6H_4	**4r**	18	81	97
19	4-CNC_6H_4	**4s**	18	78	96
20	4-FC_6H_4	**4t**	18	75	96
21	1-naphthyl	**4u**	18	82	90
22	2-naphthyl	**4v**	18	75	96
23	3-pyridyl	**4w**	30	81	96
24	4-pyridyl	**4x**	30	79	96
25	2-thienyl	**4y**	20	71	87
26	(*E*)-PhCH=CH	**4z**	20	67	71

[a] All reactions were carried out with 10 mol% **L3**/metal complex (1:1) catalyst, 2–aminophenol (0.1 mmol), aldehyde (0.105 mmol), allyltributyltin (0.15 mmol), 4 Å molecular sieves (15 mg) and $CHCl_3$ (1.5 mL) under Ar at 25 °C. [b] Isolated yield. [c] Determined by HPLC analysis. [d] The absolute configuration of the major product was determined by comparison with the reported value of optical rotation, see ref. [4d,e].

In summary, we have developed the catalytic asymmetric three-component allylation of aldimines, in which readily accessible and tuneable C_2-symmetric *N*,*N*′-dioxide–Sc^{III} complex catalysts were successfully utilized. A wide range of homoallylic amines were obtained with high enantioselectivities (up to 97% *ee*) and good yields under mild conditions. The operational simplicity, practicability, and mild reaction conditions render it an attractive approach for the asymmetric reactions. Further investigations to clarify the mechanism of the reaction are currently underway.

Experimental Section

Typical experimental procedure: The mixture of ligand **L3** (7.0 mg, 0.01 mmol), $Sc(OTf)_3$ (4.9 mg, 0.01 mmol), 2-aminophenol (11 mg, 0.1 mmol), aldehyde (0.105 mmol) and 4 Å molecular sieves (15 mg) in $CHCl_3$ (1.5 mL) was stirred in a test tube under Ar atmosphere at room temperature for 1 h. Then allyltributyltin (47 μL, 0.15 mmol) was added, and the reaction mixture was stirred until 2-aminophenol was consumed. The residue was purified by flash chromatography to afford the desired product.

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Keywords: aldimines · allylation · amines · asymmetric catalysis

[1] a) K. C. Nicolaou, H. J. Mitchell, F. L. van Delft, F. Rübsam, R. M. Rodríguez, *Angew. Chem.* **1998**, *110*, 1972–1974; *Angew. Chem. Int. Ed.* **1998**, *37*, 1871–1874; b) D. L. Wright, J. P. Schulte II, M. A. Page, *Org. Lett.* **2000**, *2*, 1847–1850; c) W. Q. Xie, B. Zou, D. Q. Pei, D. W. Ma, *Org. Lett.* **2005**, *7*, 2775–2777.

[2] For examples of imine allylation with chiral substrates, see: a) G. R. Cook, B. C. Maity, R. Karbo, *Org. Lett.* **2004**, *6*, 1741–1743; b) H. Miyabe, Y. Yamaoka, T. Naito, Y. Takemoto, *J. Org. Chem.* **2004**, *69*, 1415–1418; c) T. Vilaivan, C. Winotapan, V. Banphavichit, T. Shinada, Y. Ohfune, *J. Org. Chem.* **2005**, *70*, 3464–3471; d) G. K. Friestad, C. S. Korapala, H. Ding, *J. Org. Chem.* **2006**, *71*, 281–289.

[3] For examples of allylation of imine with chiral reagents, see: a) R. Berger, K. Duff, J. L. Leighton, *J. Am. Chem. Soc.* **2004**, *126*, 5686–5687; b) P. V. Ramachandran, T. E. Burghardt, *Chem. Eur. J.* **2005**, *11*, 4387–4395; c) J. D. Huber, J. L. Leighton, *J. Am. Chem. Soc.* **2007**, *129*, 14552–14553; d) P. M. A. Rabbat, S. C. Valdes, J. L. Leighton, *Org. Lett.* **2006**, *8*, 6119–6121; e) M. Nakamura, A. Hirai, E. Nakamura, *J. Am. Chem. Soc.* **1996**, *118*, 8489–8490; f) N. R. Perl, J. L. Leighton, *Org. Lett.* **2007**, *9*, 3699–3701; g) T. R. Wu, J. M. Chong, *J. Am. Chem. Soc.* **2006**, *128*, 9646–9647.

[4] For examples of imine allylation with stoichiometric chiral catalysts, see: a) F. G. Flores, L. S. F. Michel, E. Juaristi, *Tetrahedron Lett.* **2006**, *47*, 8235–8238; b) C. Ogawa, M. Sugiura, S. Kobayashi, *Angew. Chem.* **2004**, *116*, 6653–6655; *Angew. Chem. Int. Ed.* **2004**, *43*, 6491–6493; c) S. Kobayashi, C. Ogawa, H. Konishi, M. Sugiura, *J. Am. Chem. Soc.* **2003**, *125*, 6610–6611; d) S. B. Jagtap, S. B. Tsogoeva, *Chem. Commun.* **2006**, 4747–4749; e) C. Baudequin, D. Chaturvedi, S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 2623–2629.

[5] a) A. E. Taggi, A. M. Hafez, T. Lectka, *Acc. Chem. Res.* **2003**, *36*, 10–19; b) H. Nakamura, K. Nakamura, Y. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 4242–4243; c) R. A. Fernandes, Y. Yamamoto, *J. Org. Chem.* **2004**, *69*, 735–738; d) R. A. Fernandes, A. Stimac, Y. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 14133–14139; e) D. Ferraris, T. Dudding, B. Young, W. J. Drury, T. Lectka, *J. Org. Chem.* **1999**, *64*, 2168–2169; f) D. Ferraris, B. Young, C. Cox, T. Dudding, W. J. Drury, L. Ryzhkov, A. E. Taggi, T. Lectka, *J. Am. Chem. Soc.* **2002**, *124*, 67–77; g) X. M. Fang, M. Johannsen, S. L. Yao, N. Gathergood, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **1999**, *64*, 4844–4849; h) H. Kiyohara, Y. Nakamura, R. Matsubara, S. Kobayashi, *Angew. Chem.* **2006**, *118*, 1645–1647; *Angew. Chem. Int. Ed.* **2006**, *45*, 1615–1617; i) R. Wada, T. Shibuguchi, S. Makino, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 7687–7691; j) T. Hamada, K. Manabe, S. Kobayashi, *Angew. Chem.* **2003**, *115*, 4057–4060; *Angew. Chem. Int. Ed.* **2003**, *42*, 3927–3930; k) H. Ding, G. K. Friestad, *Synthesis* **2004**, 2216; l) T. Itoh, M. Miyazaki, H. Fukuoka, K. Nagata, A. Ohsawa, *Org. Lett.* **2006**, *8*, 1295–1297; m) M. Fujita, T. Nagano, U. Schneider, T. Hamada, C. Ogawa, S. Kobayashi, *J. Am. Chem. Soc.* **2008**, *130*, 2914–2915.

[6] T. Gastner, H. Ishitani, R. Akiyama, S. Kobayashi, *Angew. Chem.* **2001**, *113*, 1949–1951; *Angew. Chem. Int. Ed.* **2001**, *40*, 1896–1898.

[7] a) R. Kargbo, Y. Takahashi, S. Bhor, G. R. Cook, G. C. Lloyd-Jones, I. R. Shepperson, *J. Am. Chem. Soc.* **2007**, *129*, 3846–3847; b) K. L. Tan, E. N. Jacobsen, *Angew. Chem.* **2007**, *119*, 1337–1339; *Angew. Chem. Int. Ed.* **2007**, *46*, 1315–1317.

[8] S. Lou, P. N. Moquist, S. E. Schaus, *J. Am. Chem. Soc.* **2007**, *129*, 15398–15404.

[9] For a review on catalytic asymmetric multicomponent reactions, see: a) J. Seayad, B. List, in *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienaymé), Wiley-VCH, Weinheim (Germany), **2005**; pp. 277–298; b) D. J. Ramóm, M. Yus, *Angew. Chem.* **2005**, *117*, 1628–1661; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602–1634.

[10] For three-component reaction about the formation of homoallylic amines, see: a) G. L. Li, G. Zhao, *Org. Lett.* **2006**, *8*, 633–636; b) M. Sugiura, K. Hirano, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 7182–7183; c) B. Choucair, H. Léon, M.-A. Miré, C. Lebreton, P. Mosset, *Org. Lett.* **2000**, *2*, 1851–1853; d) T-S. Jang, II. W. Ku, M. S. Jang, G. Keum, S. B. Kang, B. Y. Chung, Y. Kim, *Org. Lett.* **2006**, *8*, 195–198; e) D. J. Lipomi, J. S. Panek, *Org. Lett.* **2005**, *7*, 4701–4707; f) P. Wipf, C. Kendall, *Org. Lett.* **2001**, *3*, 2773–2776; g) H. C. Aspinall, J. S. Bissett, N. Greeves, D. Levin, *Tetrahedron Lett.* **2002**, *43*, 323–325; h) S. Kobayashi, T. Hamada, K. Manabe, *Synlett* **2001**, 1140–1142.

[11] For reviews on *N*-oxide in the asymmetric synthesis, see: a) A. V. Malkov, P. Kočovský, *Eur. J. Org. Chem.* **2007**, 29–36; b) S. E. Denmark, Y. Fan, *J. Am. Chem. Soc.* **2002**, *124*, 4233–4235; c) T. Shimada, A. Kina, T. Hayashi, *J. Org. Chem.* **2003**, *68*, 6329–6337; d) R. Hrdina, I. Valterová, J. Hodačová, I. Císařová, M. Kotora, *Adv. Synth. Catal.* **2007**, *349*, 822–826.

[12] a) M. Nakajima, Y. Sasaki, M. Shiro, S. Hashimato, *Tetrahedron: Asymmetry* **1997**, *8*, 341–344; b) M. Nakajima, M. Saito, M. Shiro, S. Hashimoto, *J. Am. Chem. Soc.* **1998**, *120*, 6419–6420; c) Y. H. Wen, X. Huang, J. L. Huang, Y. Xiong, B. Qin, X. M. Feng, *Synlett* **2005**, 2445–2448; d) J. L. Huang, X. H. Liu, Y. H. Wen, B. Qin, X. M. Feng, *J. Org. Chem.* **2007**, *72*, 204–208.

[13] a) X. Zhang, D. H. Chen, X. H. Liu, X. M. Feng, *J. Org. Chem.* **2007**, *72*, 5227–5233; b) K. Zheng, B. Qin, X. H. Liu, X. M. Feng, *J. Org. Chem.* **2007**, *72*, 8478–8483; c) D. J. Shang, J. G. Xin, Y. L. Liu, X. Zhou, X. H. Liu, X. M. Feng, *J. Org. Chem.* **2008**, *73*, 630–637.

[14] When the aldimine prepared from aniline or 2-methoxyaniline was used under the same reaction conditions, only trace products were obtained.

[15] 35 and 44% *ee* were obtained for isobutyraldehyde and 3-phenylpropanal, respectively.

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