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Enantioselective Three-Component Kabachnik−Fields Reaction Catalyzed by Chiral Scandium(III)−*N,N′*-Dioxide Complexes

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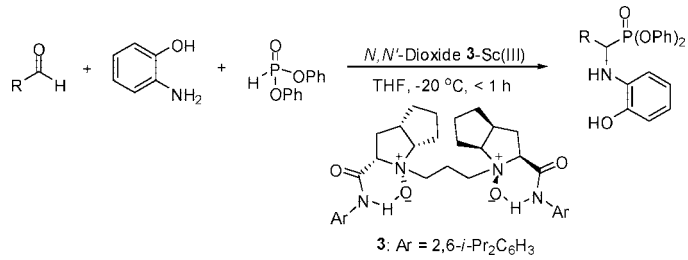
ABSTRACT



The *N,N′*-dioxide−Sc(III) complex has been applied in the three-component Kabachnik−Fields reaction of aldehydes, 2-aminophenol, and diphenyl phosphite, giving the corresponding α-amino phosphonates in good yields with high enantioselectivities (up to 87% ee). The direct Kabachnik−Fields reaction proceeded with extremely high reactivity under mild reaction conditions and could be used for large-scale synthesis of the α-amino phosphonates.

As mimics of α-amino acids,[1] chiral α-amino phosphonates exhibit intriguing biological activities and have found widespread use as antibacterial[2] and anti-HIV agents,[3] as well as protease inhibitors.[4,5] Thus their synthesis has attracted great attentions.[6] To the best of our knowledge, the asymmetric hydrophosphonylation of imines provides one of the most efficient methods for the preparation of chiral α-amino phosphonates.[7] The Shibasaki group reported the first enantioselective hydrophosphonylation of imine using various heterobimetallic complexes.[8] Subsequently, organocatalysts such as chiral thiourea derivatives,[9] chiral binol-derived phosphoric acid,[10] and cinchona alkaloids[11] were successfully applied in the reaction. Chiral aluminum(III)

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(1) Smith, A. B., III; Yager, K. M.; Taylor, C. M. *J. Am. Chem. Soc.* **1995**, *117*, 10879.

(2) (a) Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Holmes, S. W.; Lambert, R. W.; Nisbet, L. J.; Ringrose, P. S. *Nature* **1978**, *272*, 56. (b) Atherton, F. R.; Hassall, C. H.; Lambert, R. W. *J. Med. Chem.* **1986**, *29*, 29.

(3) Alonso, E.; Alonso, E.; Solis, A.; del Pozo, C. *Synlett* **2000**, 698.

(4) Hirschmann, R.; Smith, A. B., III; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengeler, P. A.; Benkovic, S. J. *Science* **1994**, *265*, 234.

(5) (a) Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989**, *32*, 1652. (b) Ding, J.; Fraser, M. E.; Meyer, J. H.; Bartlett, P. A.; James, M. N. G. *J. Am. Chem. Soc.* **1998**, *120*, 4610. (c) Smith, W. W.; Bartlett, P. A. *J. Am. Chem. Soc.* **1998**, *120*, 4622, and references therein. (d) Bird, J.; De Mello, R. C.; Harper, G. P.; Hunter, D. J.; Karran, E. H.; Markwell, R. E.; Miles-Williams, A. J.; Rahman, S. S.; Ward, R. W. *J. Med. Chem.* **1994**, *37*, 158.

(6) For reviews on noncatalytic variants, see: (a) Dhawan, B.; Redmore, D. *Phosphorus Sulfur* **1987**, *32*, 119. (b) Kukhar, V. P.; Soloshonok, V. A.; Solodenko, V. A. *Phosphorus Sulfur Silicon Relat. Elem.* **1994**, *92*, 239. (c) Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **1998**, *9*, 1279. For recent examples of auxiliary-controlled asymmetric hydrophosphonylations, see: (d) Davis, F. A.; Lee, S.; Yan, H.; Titus, D. D. *Org. Lett.* **2001**, *3*, 1757.

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complexes based on salalen and tethered bis(8-quinolinato) ligands have also proved effective for the hydrophosphonylation of aldimine.[12,13] Despite these achieved works as well as the merit of in situ formation of imine, the direct catalytic asymmetric three-component Kabachnik−Fields reaction was scarcely investigated.[12,14] Only the List group reported such a reaction with great success using a phosphoric acid as the catalyst.[14] However, this research was focused on the Kabachnik−Fields reaction of α-branched aldehydes, and a long reaction time (168 h) was necessary to achieve high yield of product. Thus, searching for a new catalyst system that could achieve high reactivity and enantioselectivity for the Kabachnik−Fields reaction is still challenging and interesting. As part of our interest and ongoing programs on the asymmetric synthesis of biologically active functionalized phosphonates,[15] we describe herein a highly efficient asymmetric three-component Kabachnik−Fields reaction using chiral *N*,*N*′-dioxide−Sc(III) complex as the catalyst, providing α-amino phosphonates in high ee and yields within 1 h.

In the previous studies, the chiral *N*,*N*′-dioxide−Sc(III) complexes have exhibited an excellent ability for the activation of various electrophiles and showed strong asymmetry-inducing capability for many reactions.[16,17] As for the reaction of a bidentate substrate, chiral scandium(III) complexes were generally thought to coordinate in a bidentate manner, leading to high reactivity and excellent enantioselectivity.[18] In light of these successes, we envisioned that such a catalyst might be effective for the three-component Kabachnik−Fields reaction of aldehydes, 2-aminophenol, and diphenyl phosphite.

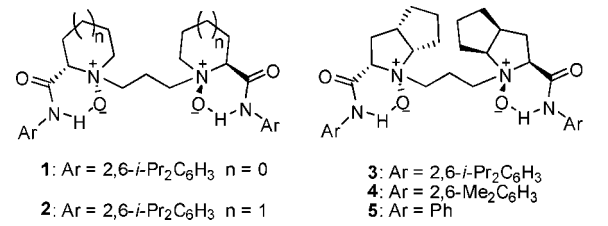


Figure 1. *N*,*N*′-Dioxide ligands evaluated.

Indeed, the direct asymmetric three-component Kabachnik−Fields reaction proceeded smoothly in the presence of *N*,*N*′-dioxide−Sc(III) complex (the molar ratio of ligand/$Sc(OTf)_3$ was 2:1) in THF.[19] To obtain the most effective ligand structure, various *N*,*N*′-dioxides were complexed in situ with $Sc(OTf)_3$ to catalyze the reaction. As shown in Table 1, the chiral backbone of the *N*,*N*′-dioxides had significant impact on the enantioselectivity of the reaction. L-Ramiprol acid derived *N*,*N*′-dioxide **3** was superior to **1** (derived from L-proline) and **2** (derived from L-pipecolic acid). Furthermore, the steric effect of the amide moiety played a crucial role on the asymmetric induction of the Kabachnik−Fields reaction. Decreasing the steric hindrance of the amide moiety led to dramatic reduction in the enantioselectivity (Table 1, entries 3−5). Racemic product was obtained when aniline-derived *N*,*N*′-dioxide **5** was used as the chiral ligand. It is noteworthy that just changing the substituent of the amide moiety may result in opposite stereoinduction of the reaction (Table 1, entry 3 vs 4).

Lanthanides (Ln) have numerous similar properties such as Lewis acidity, multifunctionality, and high coordination capability, thus showing somewhat analogical actions in organic synthesis. Promoted by the great successes obtained in asymmetric reactions using chiral Ln complexes,[20] we carried out a systematic screen of Ln complexes in the

(7) For reviews on enantioselective catalytic hydrophosphonylations, see: (a) Gröger, H.; Hammer, B. *Chem. Eur. J.* **2000**, *6*, 943. (b) Ma, J. A. *Chem. Soc. Rev.* **2006**, *35*, 630. (c) Merino, P.; Marqués-López, E.; Herrera, R. P. *Adv. Synth. Catal.* **2008**, *350*, 1195. (d) Ordóñez, M.; Rojas-Cabrera, H.; Cativiela, C. *Tetrahedron* **2009**, *65*, 17.

(8) (a) Sasai, H.; Arai, S.; Tahara, Y.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 6656. (b) Gröger, H.; Saida, Y.; Arai, S.; Martens, J.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 9291. (c) Gröger, H.; Saida, Y.; Sasai, H.; Yamaguchi, K.; Martens, J.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 3089. (d) Schlemminger, I.; Saida, Y.; Gröger, H.; Maison, W.; Durot, N.; Sasai, H.; Shibasaki, M.; Martens, J. *J. Org. Chem.* **2000**, *65*, 4818.

(9) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102.

(10) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583.

(11) (a) Pettersen, D.; Marcolini, M.; Bernardi, L.; Fini, F.; Herrera, R. P.; Sgarzani, V.; Ricci, A. *J. Org. Chem.* **2006**, *71*, 6269. (b) Nakamura, S.; Nakashima, H.; Yamamura, A.; Shibata, N.; Toru, T. *Adv. Synth. Catal.* **2008**, *350*, 1209.

(12) For a one-pot in situ sequence, see: Saito, B.; Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, *129*, 1978.

(13) Abell, J. P.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 10521.

(14) Cheng, X.; Goddard, R.; Buth, G.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 5079.

(15) (a) Huang, J. L.; Wang, J.; Cheng, X. H.; Wen, Y. H.; Liu, X. H.; Feng, X. M. *Adv. Synth. Catal.* **2008**, *350*, 287. (b) Zhou, X.; Liu, X. H.; Yang, X.; Shang, D. J.; Xin, J. G.; Feng, X. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 392. (c) Gou, S. H.; Zhou, X.; Wang, J.; Liu, X. H.; Feng, X. M. *Tetrahedron* **2008**, *64*, 2864. (d) Liu, J.; Yang, Z. G.; Wang, Z.; Wang, F.; Chen, X. H.; Liu, X. H.; Feng, X. M.; Su, Z. S.; Hu, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 5654. (e) Cheng, X. H.; Wang, J.; Zhu, Y.; Shang, D. J.; Gao, B.; Liu, X. H.; Feng, X. M.; Su, Z. S.; Hu, C. W. *Chem. Eur. J.* **2008**, *14*, 10896. (f) Wang, F.; Liu, X. H.; Cui, X.; Xiong, Y.; Zhou, X.; Feng, X. M. *Chem. Eur. J.* **2009**, *15*, 589.

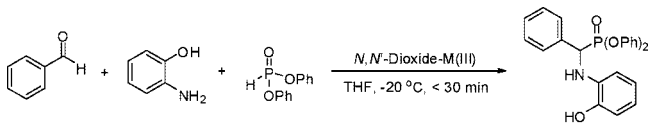
(16) For reviews of chiral *N*-oxides, see: (a) Chelucci, G.; Murineddu, G.; Pinna, G. A. *Tetrahedron: Asymmetry* **2004**, *15*, 1373. (b) Malkov, A. V.; Kŏcovský, P. *Eur. J. Org. Chem.* **2007**, 29, and references therein.

(17) For examples of enantioselective reactions catalyzed by *N*,*N*′-dioxide-scandium(III) complexes, see: (a) Shang, D. J.; Xin, J. G.; Liu, Y. L.; Zhou, X.; Liu, X. H.; Feng, X. M. *J. Org. Chem.* **2008**, *73*, 630. (b) Li, X.; Liu, X. H.; Fu, Y. Z.; Wang, L. J.; Zhou, L.; Feng, X. M. *Chem. Eur. J.* **2008**, *14*, 4796. (c) Kokubo, M.; Ogawa, C.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6909. Chiral *N*,*N*′-dioxide−Sc(III) complexes also exhibited excellent asymmetric activating abilities for other carbonyl compounds and bidentate substrates. For selected examples of asymmetric reactions catalyzed by chiral scandium complexes based on other chiral ligands, see: (d) Kobayashi, S.; Araki, M.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3758. (e) Ishikawa, S.; Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 12236. (f) Mai, E.; Schneider, C. *Chem. Eur. J.* **2007**, *13*, 2729. (g) Nojiri, A.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 5630, and reference therein.

(18) For some selected reports in which the chiral scandium complexes chelated with bidentate substrate, see: (a) Yang, D.; Yang, M.; Zhu, N. Y. *Org. Lett.* **2003**, *5*, 3749. (b) Evans, D. A.; Wu, J. *J. Am. Chem. Soc.* **2005**, *127*, 8006. (c) Evans, D. A.; Aye, Y. *J. Am. Chem. Soc.* **2006**, *128*, 11034. (d) Evans, D. A.; Fandrick, K. R.; Song, H.-J.; Scheidt, K. A.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029, and reference therein.

(19) (a) The *N*,*N*′-dioxide−Sc(III) complexes (molar ratio of ligand/$Sc(OTf)_3$ was 2:1 and 1:1) were both effective for the asymmetric activation of 2-aminophenol masked aldimine in the previous works. Thus the molar ratio of ligand/$Sc(OTf)_3$ was first investigated, and *N*,*N*′-dioxide−Sc(III) complex (molar ratio of ligand/$Sc(OTf)_3$ was 2:1) was shown to be superior. (b) Aliphatic aldehydes were also investigated. The reactions proceeded smoothly to give the corresponding products with only moderate enantioselectivities (*n*-butyraldehyde, 63% yield, 41% ee; cyclohexanecarbaldehyde, 82% yield, 38% ee).

Table 1. Direct Catalytic Asymmetric Three-Component Kabachnik−Fields Reaction under the Indicated Conditions[a]



6a 7 8 9a

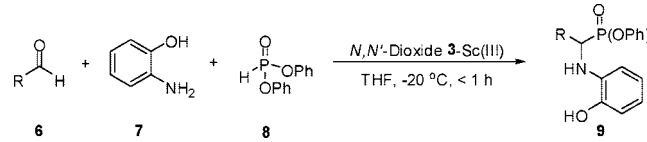
entry	ligand	metal	yield (%)[b]	ee (%)[c]
1	**1**	$Sc(OTf)_3$	87	25 (+)
2	**2**	$Sc(OTf)_3$	89	63 (+)
3	**3**	$Sc(OTf)_3$	86	84 (+)
4	**4**	$Sc(OTf)_3$	91	41 (−)
5	**5**	$Sc(OTf)_3$	83	0
6	**3**	$Y(OTf)_3$	49	45 (−)
7	**3**	$La(OTf)_3$	13	24 (−)
8	**3**	$Sm(OTf)_3$	17	30 (−)
9	**3**	$Yb(OTf)_3$	38	45 (−)

[a] Reactions were carried out with ligand (10 mol %), metal (5 mol %), **6a** (0.2 mmol), **7** (0.2 mmol), and **8** (0.2 mmol) in THF (1.0 mL) at −20 °C within 30 min. [b] Isolated yield. [c] Determined by HPLC using chiral AS-H column.

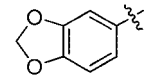
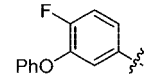
presence of the *N*,*N*′-dioxide ligand **3** (Table 1, entries 6−9). It was interesting that products with the opposite configuration were obtained using such catalysts. Furthermore, the activating and asymmetry-inducing capabilities of *N*,*N*′-dioxide **3**−Ln complexes showed a similar trend. The enantioselectivity of the reaction improved with increasing reactivity, which may ascribed to the different Lewis acidity of *N*,*N*′-dioxide **3**−Ln complexes. Unfortunately, no better result was obtained. Thus, the best result was obtained when the three-component Kabachnik−Fields reaction of aldehyde, 2-aminophenol, and diphenyl phosphite was performed in THF by using 5 mol % *N*,*N*′-dioxide **3**−Sc(III) complex (Table 1, entry 3).

Under the optimized reaction conditions, the substrate scope of the Kabachnik−Fields reaction was investigated, and the cooresponding α-amino phosphonates were obtained in good yields with high enantioslectivities. It is noteworthy that the reaction showed extremely high reactivity and was completed within 1 h. As shown in Table 2, the electronic properties of the substituent on the aromatic ring had no obvious effect on the enantioselectivity of the reaction. Moreover, the multisubstituted aromatic aldehyde, which was rarely investigated previously, underwent the reaction smoothly and gave the corresponding product with 87% ee (Table 2, entry 13). The condensed ring aldehyde also proved to be an excellent substrate with respect to enantioselectivity and yield of the reaction (Table 2, entry 6).[19b]

Table 2. Substrate Scope for the Direct Catalytic Asymmetric Three-Component Kabachnik−Fields Reaction[a]



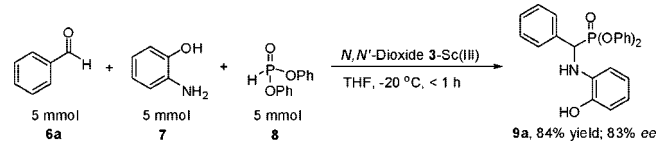
6 7 8 9

entry	R	product	yield (%)[b]	ee (%)[c]
1	Ph	**9a**	86	84
2	4-$NO_2C_6H_4$	**9b**	76	84
3	4-FC_6H_4	**9c**	90	84
4	4-MeC_6H_4	**9d**	89	83
5	3-MeC_6H_4	**9e**	96	84
6	2-naphthyl	**9f**	88	81
7	3-$NO_2C_6H_4$	**9g**	79	87
8	4-$MeOC_6H_4$	**9h**	75	80
9	4-ClC_6H_4	**9i**	94	86
10	3-$MeOC_6H_4$	**9j**	73	83
11	4-$C_6H_5C_6H_4$	**9k**	88	83
12		**9l**	93	81
13		**9m**	79	87

[a] Unless otherwise noted, reactions were carried out with *N*,*N*′-dioxide **3** (10 mol %), $Sc(OTf)_3$ (5 mol %), **6** (0.2 mmol), **7** (0.2 mmol), and **8** (0.2 mmol) in THF (1.0 mL) at −20 °C within 1 h. [b] Isolated yield. [c] Determined by HPLC using commercial chiral columns.

To test the synthetic potential of the present approach, a large-scale synthesis of the chiral α-amino phosphonates was performed. As shown in Scheme 1, by treatment of 5 mmol of starting materials under the optimal reaction conditions, the desired product was produced without loss of reactivity or enantioselectivity.

Scheme 1. Scaled-Up Version of the Kabachnik−Fields Reaction



5 mmol 6a 5 mmol 7 5 mmol 8

In conclusion, we have demonstrated the highly enantioselective three-component Kabachnik−Fields reaction of aldehydes, 2-aminophenol, and diphenyl phosphite using chiral *N*,*N*′-dioxide−Sc(III) complex as the catalyst. The reaction was performed with extremely high reactivity and produced α-amino phosphonates with high yield and high enantioselectivies within 1 h. Moreover, the present catalytic approach provided a potential for large-scale synthesis of

(20) For reviews of lanthanide complexes in asymmetric reactions, see: (a) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 1236. (b) Aspinall, H. C. *Chem. Rev.* **2002**, *102*, 1807. (c) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. (d) Inanaga, J.; Furuno, H.; Hayano, T. *Chem. Rev.* **2002**, *102*, 2211. (e) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227. (f) Mikami, K.; Terada, M.; Matsuzawa, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3554. (g) For *N*,*N*′-dioxide−La complex catalyzed reaction, see: Yang, X.; Zhou, X.; Lin, L. L.; Chang, L.; Liu, X. H.; Feng, X. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7079.

chiral α-amino phosphonates. Further studies of the reaction mechanism are in progress.

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Supporting Information Available: Experimental procedures and spectral and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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