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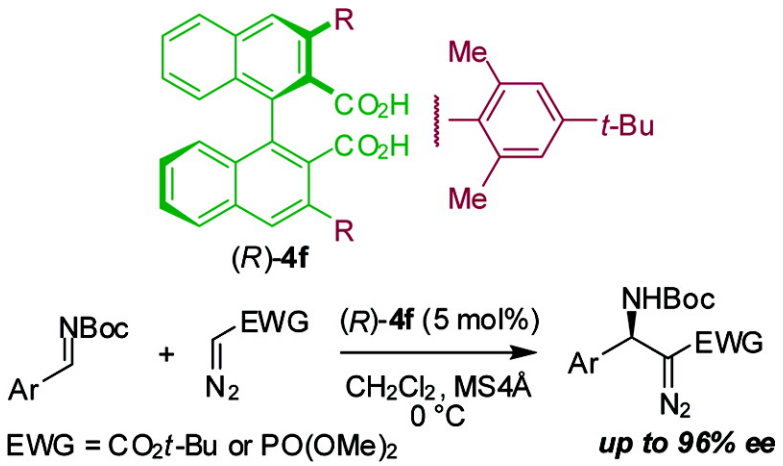
J. Am. Chem. Soc., **2007**, 129 (33), 10054-10055• DOI: 10.1021/ja0713375 • Publication Date (Web): 27 July 2007



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Design of Axially Chiral Dicarboxylic Acid for Asymmetric Mannich Reaction of Arylaldehyde *N*-Boc Imines and Diazo Compounds

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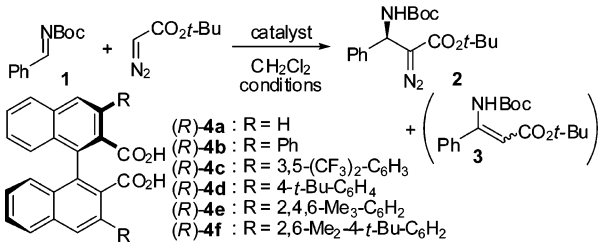
The state-of-the-art asymmetric hydrogen-bonding catalysis mainly relies on the use of thiourea, diol, and phosphoric acid as hydrogen-bonding donors.[1,2] Despite the fact that the key feature of these catalyses is the choice of a catalyst with appropriate acidity, the important class of moderate Brønsted acids, carboxylic acids, has rarely been employed in these catalyses.[3] This is quite surprising because carboxylic acids are often utilized as one of the most promising acid catalysts in various organic transformations.[4] We assumed that the poor reactivity of the carboxylic acid and the difficulty in building an effective chiral recognition site around the carboxylic acid might be the main reasons for this deficiency. In an effort to address this issue, we prepared chiral dicarboxylic acid catalysts, which consist of two carboxylic acids and an axially chiral binaphthyl moiety, and applied them to highly enantioselective Mannich reaction of *N*-Boc imines and diazo compounds.

Asymmetric addition of diazoacetate to imines[5−7] was selected as a starting point of the research in conjunction with our interest in the use of diazoacetate in organic synthesis (Table 1).[8] The initial attempt with benzaldehyde *N*-Boc imine **1** and *tert*-butyl diazoacetate under the influence of 2-naphthoic acid was not fruitful and provided only a trace amount of the desired compound *rac*-**2** (entry 1). To enhance the reactivity, a second carboxylic acid was introduced into the catalyst since such a dual activation by two acidic components in one catalyst is a commonly utilized approach both in Lewis acid and hydrogen-bonding catalysis.[1,9] Gratifyingly, the reaction catalyzed by *rac*-1,1′-binaphthyl-2,2′-dicarboxylic acid **4a** was found to be promising, providing *rac*-**2** in 41% yield (entry 2). As a comparison, the reaction catalyzed by 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (abbreviated as BNDHP in Table 1) was examined,[6] which was revealed to furnish not only *rac*-**2** but a considerable amount of side products, tentatively assigned as *E*/*Z* isomers of the ene carbamates **3** (entry 3).[10] These observations clearly indicated the necessity to use the catalyst with the appropriate acidity in hydrogen-bonding catalysis.

Capitalizing on the axially chiral nature of **4a**, the reaction was then conducted in the presence of optically pure (*R*)-**4a**.[11] However, no appreciable asymmetric induction was observed (Table 1, entry 4). At this point, we turned our attention to the introduction of aryl groups at the 3,3′-position of (*R*)-**4a** in consideration of our recent report on the synthesis of 3,3′-diaryl-1,1′-binaphthyl-2,2′-dicarboxylic acid esters (Scheme 1).[12−14]

After evaluation of some aryl groups, use of 3,3′-dimesityl dicarboxylic acid (*R*)-**4e** was found to be encouraging, providing **2** in 38% yield with 69% ee (entry 8). The enantiomeric excess could be improved by performing the reaction at 0 °C (entry 9). Further experiments proved the effectiveness of 3,3′-bis(2,6-Me_2-4-*t*-Bu-C_6H_2) dicarboxylic acid (*R*)-**4f** and molecular sieves 4 Å (entries 10, 11). Under this condition, the reaction could be carried out with 5 mol % of (*R*)-**4f** at 0 °C, leading to the adduct **2** in 81% yield with 95% ee (entry 11). We speculate that 2,6-dimethyl groups contribute to rigidify the flexible aryl−aryl bond axis, and the 4-*tert*-butyl group may impart the axial chirality of the binaphthyl moiety to the substrate (entries 7, 8). Molecular sieves 4 Å would prevent the imine hydrolysis.[15]

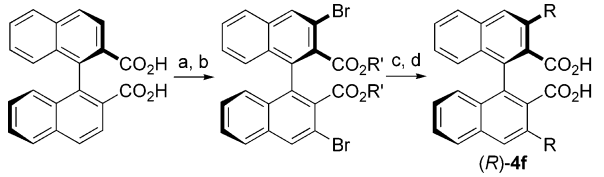
Table 1. Asymmetric Mannich Reaction of Benzaldehyde *N*-Boc Imine and *tert*-Butyl Diazoacetate[a]



entry	catalyst (mol %)	conditions (°C, h)	yield (%)[b]	ee (%)[c]
1	2-NpCO_2H (20)	rt, 40	3	
2	*rac*-**4a** (10)	rt, 40	41	
3	*rac*-BNDHP (10)	rt, 0.5	17 (22)[e]	
4	(*R*)-**4a** (10)	rt, 20	33	0
5	(*R*)-**4b** (10)	rt, 6	33	29
6	(*R*)-**4c** (10)	rt, 20	25	17
7	(*R*)-**4d** (10)	rt, 20	35	49
8	(*R*)-**4e** (10)	rt, 16	38	69
9	(*R*)-**4e** (5)	0, 15	39	74
10	(*R*)-**4f** (5)	0, 38	38	95
11[d]	(*R*)-**4e** (5) + MS4Å	0, 20	81	95

[a] Reactions were performed with benzaldehyde *N*-Boc imine (0.10 mmol) and *tert*-butyl diazoacetate (0.12 mmol) in the presence of a dicarboxylic acid in CH_2Cl_2 (1 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] With MS 4 Å (100 mg). [e] Isolated yield of **3**.

Scheme 1. Preparation of the Dicarboxylic Acid (*R*)-**4f**[a]



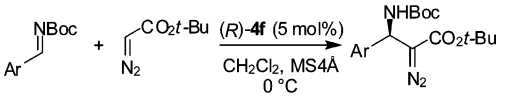
(R' = CH_2CH_2TMS) (R = 2,6-Me_2-4-*t*-Bu-C_6H_2)

[a] Conditions: (a) (i) $SOCl_2$; (ii) $TMSCH_2CH_2OH$, pyridine, THF, 97%; (b) (i) $Mg(TMP)_2$, THF; (ii) Br_2, THF, 44%; (c) 2,6-Me_2-4-*t*-Bu-$C_6H_2B(OH)_2$, $Pd(OAc)_2$, 2-(2′,6′-dimethoxybiphenyl)dicyclohexylphosphine, K_3PO_4, toluene, 62%; (d) TBAF, THF, 74%.

With the optimized condition in hand, the scope of the Mannich reaction with various arylaldehyde *N*-Boc imines was surveyed as shown in Table 2. High enantiomeric excess was observed regardless of the substituent pattern at the aryl group, although the reaction rate dropped significantly when the *o*-tolyl imine was utilized (entries 1−5). The reaction was general for both electron-rich and electron-poor substrates, furnishing the corresponding products in excellent ee (entries 6−9). In the case of imine bearing a heteroaromatic group, slight decrease of the enantiomeric excess was observed (entry 10).

10.1021/ja0713375 CCC: $37.00

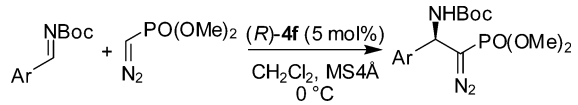
Table 2. Asymmetric Mannich Reaction of Arylaldehyde *N*-Boc Imines and *tert*-Butyl Diazoacetate[a]



entry	Ar	time (h)	yield (%)[b]	ee (%)[c]
1	Ph	24	80	95 (*R*)[d]
2	*o*-tolyl	72	53	90
3	*m*-tolyl	20	74	92
4	*p*-tolyl	18	79	95
5	2-Np	17	77	94
6	*p*-FC_6H_4	20	83	95
7	*p*-ClC_6H_4	26	89	96
8	*p*-$NO_2C_6H_4$	72	38	95
9	*p*-$MeOC_6H_4$	20	72	95
10	2-furyl	5	84	85

[a] Reactions were performed with arylaldehyde *N*-Boc imine (0.10 mmol) and *tert*-butyl diazoacetate (0.15 mmol) in the presence of (*R*)-**4f** (0.005 mmol) and MS 4 Å (100 mg) in CH_2Cl_2 (1 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] See Supporting Information.

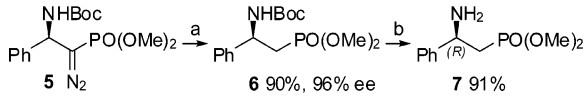
Table 3. Asymmetric Mannich Reaction of Arylaldehyde *N*-Boc Imines and Dimethyl Diazomethylphosphonate[a]



entry	Ar	time (h)	yield (%)[b]	ee (%)[c]
1	Ph	85	68	96
2	*p*-tolyl	68	68	96
3	*p*-FC_6H_4	52	85	96
4	*p*-ClC_6H_4	68	81	96
5	*p*-$MeOC_6H_4$	50	40	95
6	2-furyl	46	89	92

[a] Reactions were performed with arylaldehyde *N*-Boc imine (0.10 mmol) and dimethyl diazomethylphosphonate (0.15 mmol) in the presence of (*R*)-**4f** (0.005 mmol) and MS 4 Å (100 mg) in CH_2Cl_2 (1 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis.

Scheme 2. Derivatization of the Mannich Adduct[a]



[a] Conditions: (a) Pd/C, H_2 (balloon), MeOH; (b) CH_2Cl_2/TFA (10:1).

Our synthetic methodology was further exploited in the hitherto unknown catalytic asymmetric Mannich reaction of *N*-Boc imines and dimethyl diazomethylphosphonate (Table 3), as a means of creating optically enriched β-aminophosphonate derivatives.[16,17] The identical reaction condition as described above was employed to give the various α-diazo-β-aminophosphonates in a highly enantioselective manner.

To demonstrate the synthetic utility and to establish the absolute configuration,[18] the adduct **5** was subjected to the catalytic hydrogenation condition and deprotection. Consequently, dimethyl β-phenyl-β-aminophosphonate **7** was obtained in good yield without an erosion in the enantiomeric excess (Scheme 2).

In summary, we have developed asymmetric Mannich reactions of diazo compounds catalyzed by a novel axially chiral dicarboxylic acid. Further research to expand the utility of chiral dicarboxylic acids in asymmetric catalysis is currently underway in our laboratory.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental details and characterization data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews, see: (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (b) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062. (c) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (d) Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758. (e) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (f) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (g) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909.

(2) For some leading works, see: (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (b) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279. (c) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964. (d) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094. (e) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (f) Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5846. (g) Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336. (h) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (i) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418. (j) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (k) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583. (l) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070. (m) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756. (n) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (o) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804. (p) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292. (q) Rueping, M.; Sugiono, E.; Azap. C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781. (r) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2097. (s) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626.

(3) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080.

(4) *Handbook of Reagents for Organic Synthesis: Acidic and Basic Reagents*; Reich, H. J., Rigby, J. A., Eds.; John Wiley & Sons: New York, 1999.

(5) For a review, see: Zhao, Y.; Wang, J. *Synlett* **2005**, 2886.

(6) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, *127*, 9360.

(7) (a) Zhao, Y.; Ma, Z.; Zhang, X.; Zou, Y.; Jin, X.; Wang, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5977. (b) Zhao, Y.; Jiang, N.; Chen, S.; Peng, C.; Zhang, X.; Zou, Y.; Zhang, S.; Wang, J. *Tetrahedron* **2005**, *61*, 6546.

(8) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2174.

(9) (a) Hanawa, H.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 1708. (b) Hanawa, H.; Uraguchi, D.; Konishi, S.; Hashimoto, T.; Maruoka, K. *Chem.—Eur. J.* **2003**, *9*, 4405. (c) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 11926. (d) Ooi, T.; Takahashi, M.; Yamada, M.; Tayama, E.; Omoto, K.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 1150.

(10) In contrast to *N*-Boc imines, the reaction of *N*-acyl imines catalyzed by this type of phosphoric acid catalysts provided the adduct cleanly; see ref 6.

(11) Seki, M.; Yamada, S.; Kuroda, T.; Imashiro, R.; Shimizu, T. *Synthesis* **2000**, 1677.

(12) Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Org. Chem.* **2003**, *68*, 4576.

(13) For Suzuki−Miyaura coupling to synthesize hindered biaryls, see: Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

(14) For details, see Supporting Information.

(15) BNDHP-catalyzed reaction re-evaluated in the presence of MS 4 Å improved the total yield of the products (56%) with the same ratio of **2** and **3**.

(16) Juaristi, E., Soloshonok, V., Eds. *Enantioselective Synthesis of β-Amino Acid*, 2nd ed.; John Wiley and Sons: Hoboken, NJ, 2005.

(17) For the base-catalyzed Mannich reaction of *N*-Ts imines and dimethyl diazomethylphosphonate, see: Zhao, Y.; Jiang, N. Wang, J. *Tetrahedron Lett.* **2003**, *44*, 8339.

(18) Xu, C.; Yuan, C. *Eur. J. Org. Chem.* **2004**, 4410.

JA0713375