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Design of Structurally Rigid *trans*-Diamine-Based Tf-Amide Organocatalysts with a Dihydroanthracene Framework for Asymmetric Conjugate Additions of Heterosubstituted Aldehydes to Vinyl Sulfones

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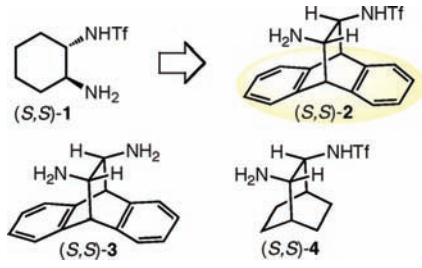
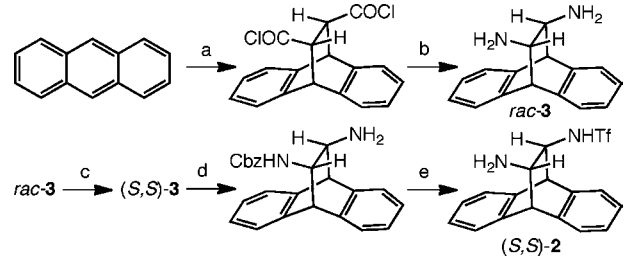
Abstract: Asymmetric conjugate addition of α-heterosubstituted aldehydes such as α-amido and α-alkoxy aldehydes to vinyl sulfone was effected under the influence of structurally rigid *trans*-diamine-based Tf-amido organocatalyst (*S,S*)-**2** with a dihydroanthracene framework to furnish α,α-dialkyl(amido)aldehydes and α,α-dialkyl-(alkoxy)aldehydes with high enantioselectivity. The chiral efficiency of the structurally unique catalyst (*S,S*)-**2** is apparent in comparison with (*S,S*)-**1** and (*S,S*)-**4** with similar functionality.

Asymmetric aminocatalysis has been recognized as one of the most fundamental, yet important reactions in the field of asymmetric organocatalysis.[1] In such asymmetric aminocatalysis, the use of chiral secondary amine catalysts including proline-derived ones has proven to be an extremely powerful approach.[1b] In recent years, primary amine catalysis using primary amino acids and chiral *trans*-1,2-cyclohexanediamine-derived organocatalysts (e.g., **1**) has emerged as a complementary tool for activating sterically demanding carbonyl substrates, because of its advantage over chiral secondary amine catalysis.[2,3] In this context, we are interested in designing a structurally rigid, chiral *trans*-1,2-cyclohexanediamine-derived organocatalyst of type **2** with a 9,10-dihydroanthracene subunit in order to shield one side of the catalyst more efficiently than catalysts **1** and **4** which have similar functionality. The chiral, bifunctional organocatalyst **2** would be highly effective for remotely controlled transformations like asymmetric conjugate additions. Here we wish to report the asymmetric conjugate addition of α-heterosubstituted aldehydes such as α-amido and α-alkoxy aldehydes under the influence of structurally unique organocatalyst **2** to create asymmetric quaternary carbon centers. This asymmetric transformation has broad substrate generality and provides general access to the asymmetric synthesis of structurally diverse α,α-dialkylamino aldehydes, since starting α-amido aldehydes are readily available from a wide variety of both natural and unnatural α-amino acids in addition to α-amino nitriles.[4]



The requisite catalyst (*S,S*)-**2** can be easily prepared by a Diels−Alder reaction of fumaryl chloride with anthracene and subsequent transformations as shown in Scheme 1.[5]

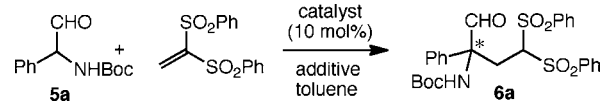
Scheme 1. Synthesis of Catalyst (*S,S*)-**2**[a]



[a] Reagents and conditions: (a) fumaryl chloride, toluene reflux; (b) (i) aq. NaN_3/toluene, 0 °C; (ii) toluene reflux, then conc. HCl; (iii) aq. NaOH (56% overall yield); (c) (i) (−)-mandelic acid, MeOH; (ii) aq. NaOH (36% yield, >99% ee); (d) (i) conc. HCl, (ii) Cbz-Cl, aq. NaOH, MeOH, 0 °C (83% yield); (e) Tf_2O, Et_3N, CH_2Cl_2, −78 °C; Pd/C, H_2, MeOH, room temp (93% yield).

Attempted asymmetric conjugate addition of *N*-Boc α-aminophenylacetaldehyde **5a**[6] to 1,1-bis(benzenesulfonyl)-ethylene[7] in toluene in the presence of catalyst (*S,S*)-**2** gave rise to conjugate adduct **6a** in 90% yield with 86% ee (entry 1 in Table 1). Use of HCl as

Table 1. Screening of Reaction Conditions for Asymmetric Conjugate Addition of Heterosubstituted Aldehydes[a]



entry	catalyst	additive	time (h)	% yield[b]	% ee[c]
1	(*S,S*)-**2**	none	24	90	86
2	(*S,S*)-**2**	HCl	3	96	91
3	(*S,S*)-**3**	HCl	24	98	71
4	(*S,S*)-**3**	HCl[d]	24	84	60
5	(*S,S*)-**4**	HCl	2	72	1
6	(*S,S*)-**1**	HCl	24	58	0
7	(*S,S*)-**2**	CF_3CO_2H	3	99	89
8	(*S,S*)-**2**	TfOH	12	90	92
9	(*S,S*)-**2**	$PhCO_2H$	24	94	79
10	(*S,S*)-**2**	4-$(NO_2)C_6H_4CO_2H$	36	86	76
11	(*S,S*)-**2**	3-$(NO_2)C_6H_4CO_2H$	12	99	75
12	(*S,S*)-**2**	2-$(NO_2)C_6H_4CO_2H$	10	96	79
13	(*S,S*)-**2**	2,6-$(NO_2)_2C_6H_3CO_2H$	0.5	98	93
14	(*S,S*)-**2**	2-$(OH)C_6H_4CO_2H$	20	96	75
15	(*S,S*)-**2**	2,6-$(OH)_2C_6H_3CO_2H$	0.5	99	93
16[e]	(*S,S*)-**2**	2,6-$(OH)_2C_6H_3CO_2H$	12	98	95
17	(*S,S*)-**2**	2,6-$(CH_3)_2C_6H_3CO_2H$	60	82	71

[a] Unless otherwise specified, asymmetric conjugate addition of heterosubstituted aldehydes and 1,1-bis(benzenesulfonyl)ethylene in the presence of 10 mol % of catalyst (*S,S*)-**1**−**4** and 10 mol % of additive in toluene at room temperature under the given conditions. [b] Isolated yield. [c] Enantiopurity of conjugate adducts was determined by HPLC analysis using a chiral column with hexane−isopropyl alcohol as solvent (see Supporting Information). [d] 20 mol % of additive. [e] At −20 °C.

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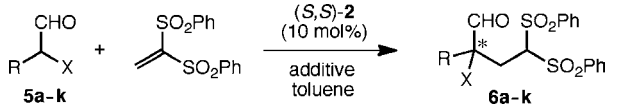
an additive enhanced both reactivity and selectivity (entry 2). However, diamine hydrochloride, (*S*,*S*)-**3**•HCl, and (*S*,*S*)-**3**•$(HCl)_2$ lowered the enantioselectivity (entries 3−4). Notably, amino Tf-amide catalysts of type (*S*,*S*)-**1** and (*S*,*S*)-**4** totally lost the enantioselection (entries 5−6). Additional optimizations with regard to additives led to the reaction conditions using 2,6-dinitro- and 2,6-dihydroxybenzoic acid as additives (entries 7−17), and by using these additives, conjugate adduct **6a** was obtained with a short reaction time with 93% ee (entries 13 and 15). Further, 95% ee was achieved by lowering the reaction temperature (entry 16).

With the optimized conditions in hand, we investigated the scope of this asymmetric conjugate addition using α-heterosubstituted aldehydes and vinyl sulfone as shown in Table 2. As for the α-amino-substituted aldehydes **5a**−**e** possessing the different substituent pattern of aromatic groups, *m*- and *p*-electron-donating substituents, as well as the fused ring and the electron-withdrawing group, were all tolerated, providing the corresponding conjugated adducts **6a**−**e** with uniformly high selectivity (entries 1−5). In the case of α-amino-substituted aliphatic aldehydes **5f**−**g** having *sec*- and *tert*-alkyl groups, the reaction provided the conjugated adducts **6f**−**g** consistently with 94% ee (entries 6 and 7). Whereas the reaction with benzyl-substituted aldehyde **5h** resulted in moderately high enantioselectivity (entry 8), use of methyl-substituted analogue **5i** furnished the conjugate adduct **6i** with 81% ee (entry 9). In general, the conjugate addition of α-amino-α-alkyl-substituted aldehydes **5f**−**i** proceeded slowly at −20 °C and required room temperature (entries 6−9).[8] Other substituted aldehydes such as α-oxy and α-methyl aldehydes **5j**−**k**[7b] were also employable with high enantioselectivities (entries 10−12).

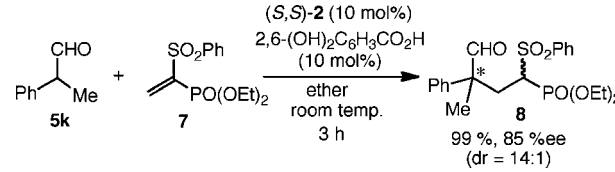
Table 2. Asymmetric Conjugate Addition of Heterosubstituted Aldehydes Catalyzed by (*S*,*S*)-**2**[a]



entry	substrate **5** (R,X)	time (h)	% yield[b]	% ee[c]
1[d]	**5a** (Ph, NHBoc)	12	98	95
2	**5b** (*m*-MeO-C_6H_4, NHBoc)	10	98	95
3	**5c** (*p*-MeO-C_6H_4, NHBoc)	10	98	94
4	**5d** (*p*-Cl-C_6H_4, NHBoc)	25	90	94
5[e]	**5e** (α-Np, NHBoc)	24	99	91
6	**5f** (*t*-Bu, NHBoc)	48	94	94
7	**5g** (*i*-Pr, NHBoc)	7	95	94
8	**5h** ($PhCH_2$, NHBoc)	5	90	86
9	**5i** (Me, NHBoc)	3	99	81
10[d]	**5j** (Ph, OMe)	36	99	92
11[d,f]	**5j** (Ph, OMe)	16	93	93
12[d]	**5k** (Ph, Me)	24	96	93

[a] Unless otherwise specified, asymmetric conjugate addition of heterosubstituted aldehydes and 1,1-bis(benzenesulfonyl)ethylene in the presence of 10 mol % of catalyst (*S*,*S*)-**2** and 10 mol % of 2,6-dihydroxybenzoic acid in toluene at room temperature under the given conditions. [b] Isolated yield. [c] Enantiopurity of conjugate adducts was determined by HPLC analysis using a chiral column with hexane−isopropyl alcohol as solvent (see Supporting Information). [d] At −20 °C. [e] At 0 °C. [f] Use of 2,6-dinitrobenzoic acid.

In addition to 1,1-bis(benzenesulfonyl)ethylene, α-benzenesulfonylvinylphosphate **7** can be also utilized as a conjugate acceptor in the asymmetric conjugate addition of α-substituted aldehyde **5k** to furnish the desired adduct **8** with high diastereo- and enantioselectivities.



The absolute stereochemistry of the conjugate adduct **6a** was unambiguously determined to be *S* by conversion to the known (*S*)-2-amino-2-phenyl-1-butanol as shown in the Supporting Information.[9] Based on the absolute configuration of (*S*)-**6a**, a possible transition state model has been proposed as shown in Figure 1 to account for the observed absolute configuration of conjugate adduct **6a**. In the generation of *Z*-enamine derived from *N*-Boc α-aminophenylacetaldehyde **5a** and the catalyst (*S*,*S*)-**2** under the experimental conditions, the *Z*-enamine **9** would be stabilized by the hydrogen bonding between the ammonium hydrogen and *N*-Boc group. Here, $ArCO_2^-$ as an additive would effectively shield the backside of **9**. Then, 1,1-bis(benzenesulfonyl)ethylene might approach from the upper side via additional hydrogen bonding of a sulfonyl group with the Tf-amide hydrogen, leading to conjugate adduct **6a** with the observed *S* configuration.

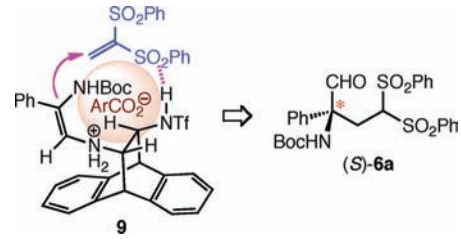


Figure 1. A possible transition state structure.

In summary, we have succeeded in the asymmetric conjugate addition of heterosubstituted aldehydes such as α-amido and α-alkoxy aldehydes under the influence of structurally unique organocatalyst **2**. This strategy is, in principle, applicable to other catalytic systems, and further effort to this end is currently underway in our laboratory.

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

References

(1) Recent reviews on asymmetric aminocatalysis: (a) List, B. *Angew. Chem., Int. Ed* **2010**, *49*, 1730. (b) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (c) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (d) List, B. *Chem. Commun.* **2006**, 819. (e) List, B. *Synlett* **2001**, *11*, 1675.

(2) Reviews on asymmetric aminocatalysis by primary amino acids: (a) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, *14*, 1807. (b) Chen, Y.-C. *Synlett* **2008**, *13*, 1919. (c) Peng, F.; Shao, Z. *J. Mol. Catal. A* **2008**, *285*, 1.

(3) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161. See also: (a) Uehara, H.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2009**, *48*, 9848. (b) Zhang, X.-J.; Liu, S.-P.; Li, X.-M.; Yan, M.; Chan, A. S. C. *Chem. Commun.* **2009**, 833. (c) Luo, S.; Xu, H.; Chen, L.; Cheng, J.-P. *Org. Lett.* **2008**, *10*, 1775. (d) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. (e) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366. (f) Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964.

(4) Recent reviews on α,α-dialkylated amino acids: (a) Tanaka, M. *Chem. Pharm. Bull.* **2007**, *55*, 349. (b) Vogt, H.; Braese, S. *Org. Biomol. Chem.* **2007**, *5*, 406. (c) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, *24*, 5127. (d) Ohfune, Y.; Shinada, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1115.

Previous examples of chiral α,α-dialkylamino aldehyde synthesis: (a) Baumann, T.; Baechle, M.; Hartmann, C.; Braese, S. *Eur. J. Org. Chem.* **2008**, *13*, 2207. (b) Baumann, T.; Vogt, H.; Braese, S. *Eur. J. Org. Chem.* **2007**, *2*, 266. (c) Kim, S.-G.; Park, T.-H. *Tetrahedron Lett.* **2006**, *47*, 9067. (d) Guo, H.-M.; Cheng, L.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Chem. Commun.* **2006**, 429. (e) Suri, J. T.; Steiner, D. D.; Barbas, C. F., III. *Org. Lett.* **2005**, *7*, 3885. (f) Chowdari, N. S.; Barbas, C. F., III. *Org. Lett.* **2005**, *7*, 867. (g) Vogt, H.; Vanderheiden, S.; Braese, S. *Chem. Commun.* **2003**, 2448. (h) Wenglowsky, S.; Hegedus, L. S. *J. Am. Chem. Soc.* **1998**, *120*, 12468. (i) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1995**, *117*, 7379.

(5) For preparation of (*S*,*S*)-**3**, see: (a) Fox, M. E.; Gerlach, A.; Lennon, I. C.; Meek, G.; Praquin, C. *Synthesis* **2005**, *19*, 3196. (b) Allenmark, S.; Skogsberg, U.; Thunberg, L. *Tetrahedron: Asymmetry* **2000**, *11*, 3527.

(6) Preparation of α-amino-substituted aldehydes **5a**−**i**: (a) Alfaro, R.; Yuste, F.; Ortiz, B.; Sanchez-Obregon, R.; Garcia Ruano, J. L. *Tetrahedron* **2009**, *65*, 357. (b) Dondoni, A.; Perrone, D.; Semola, T. *Synthesis* **1995**, *2*, 181. α-Methoxyphenylacetaldehyde **5f**: (c) Trost, B. M.; Ball, Z. T.; Laemmerhold, K. M. *J. Am. Chem. Soc.* **2005**, *127*, 1002.

(7) Use of 1,1-bis(benzenesulfonyl)ethylene for the generation of quaternary carbon centers: (a) Alba, A.-N. R.; Companyo, X.; Valero, G.; Moyano, A.; Rios, R. *Chem.*—*Eur. J.* **2010**, *16*, 5354. (b) Zhu, Q.; Lu, Y. *Chem. Commun.* **2010**, 2235. (c) Liu, T.-Y.; Long, J.; Li, B.-J.; Jiang, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Org. Biomol. Chem* **2006**, *4*, 2097. For other examples of Michael addition of aldehydes to vinyl sulfones, see: (d) Quintard, A.; Belot, S.; Marchal, E.; Alexakis, A. *Eur. J. Org. Chem.* **2010**, *5*, 927. (e) Quintard, A.; Alexakis, A. *Chem.*—*Eur. J.* **2009**, *15*, 11109. (f) Sulzer-Mosse, S.; Alexakis, A.; Mareda, J.; Bollot, G.; Bernardinelli, G.; Filinchuk, Y. *Chem.*—*Eur. J.* **2009**, *15*, 3204. (g) Landa, A.; Maestro, M.; Masdeu, C.; Puente, A.; Vera, S.; Oiarbide, M.; Palomo, C. *Chem.*—*Eur. J.* **2009**, *15*, 1562. (h) Zhu, Q.; Lu, Y. *Org. Lett.* **2008**, *10*, 4803. (i) Mosse, S.; Alexakis, A. *Org. Lett.* **2005**, *7*, 4361.

(8) Asymmetric conjugate addition of **5i** at −20 °C for 72 h gave **6i** in 98% yield with 80% ee.

(9) Leuser, H.; Perrone, S.; Liron, F.; Kneisel, F. F.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 4627.

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