

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

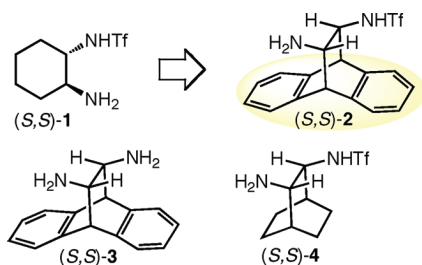
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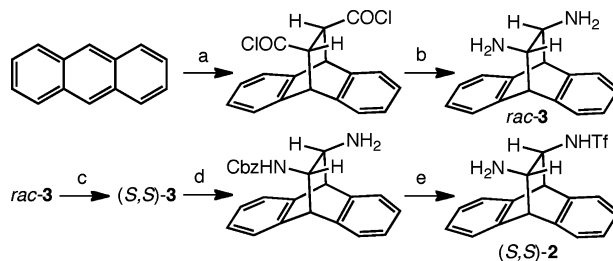
Abstract: Asymmetric conjugate addition of α -heterosubstituted aldehydes such as α -amido and α -alkoxy aldehydes to vinyl sulfone was effected under the influence of structurally rigid *trans*-diamine-based Tf-amido organocatalyst (*S,S*)-**2** with a dihydroanthracene framework to furnish α,α -dialkyl(amido)aldehydes 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. NaN₃/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) Tf₂O, Et₃N, CH₂Cl₂, –78 °C; Pd/C, H₂, MeOH, room temp (93% yield).

Attempted asymmetric conjugate addition of *N*-Boc α -aminophenylacetaldehyde **5a**⁶ to 1,1-bis(benzenesulfonyl)-ethylene⁷ 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	(<i>S,S</i>)- 2	none	24	90	86
2	(<i>S,S</i>)- 2	HCl	3	96	91
3	(<i>S,S</i>)- 3	HCl	24	98	71
4	(<i>S,S</i>)- 3	HCl ^d	24	84	60
5	(<i>S,S</i>)- 4	HCl	2	72	1
6	(<i>S,S</i>)- 1	HCl	24	58	0
7	(<i>S,S</i>)- 2	CF ₃ CO ₂ H	3	99	89
8	(<i>S,S</i>)- 2	TfOH	12	90	92
9	(<i>S,S</i>)- 2	PhCO ₂ H	24	94	79
10	(<i>S,S</i>)- 2	4-(NO ₂)C ₆ H ₄ CO ₂ H	36	86	76
11	(<i>S,S</i>)- 2	3-(NO ₂)C ₆ H ₄ CO ₂ H	12	99	75
12	(<i>S,S</i>)- 2	2-(NO ₂)C ₆ H ₄ CO ₂ H	10	96	79
13	(<i>S,S</i>)- 2	2,6-(NO ₂) ₂ C ₆ H ₃ CO ₂ H	0.5	98	93
14	(<i>S,S</i>)- 2	2-(OH)C ₆ H ₄ CO ₂ H	20	96	75
15	(<i>S,S</i>)- 2	2,6-(OH) ₂ C ₆ H ₃ CO ₂ H	0.5	99	93
16 ^e	(<i>S,S</i>)- 2	2,6-(OH) ₂ C ₆ H ₃ CO ₂ H	12	98	95
17	(<i>S,S</i>)- 2	2,6-(CH ₃) ₂ C ₆ H ₃ CO ₂ H	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.

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).

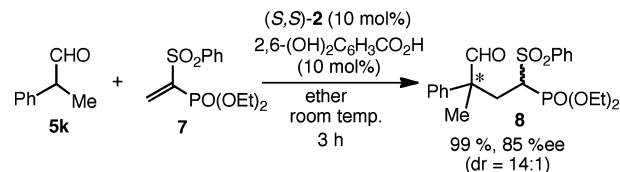
With the optimized conditions in hand, we investigated the scope of this asymmetric conjugate addition using α -heterosubstituted aldehydes and vinyl sulfone as shown in Table 2. As for the α -amino-substituted aldehydes **5a–e** possessing the different substituent pattern of aromatic groups, *m*- and *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 (<i>m</i> -MeO-C ₆ H ₄ , NHBoc)	10	98	95
3	5c (<i>p</i> -MeO-C ₆ H ₄ , NHBoc)	10	98	94
4	5d (<i>p</i> -Cl-C ₆ H ₄ , NHBoc)	25	90	94
5 ^e	5e (α -Np, NHBoc)	24	99	91
6	5f (<i>t</i> -Bu, NHBoc)	48	94	94
7	5g (<i>i</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, ArCO₂[−] 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.

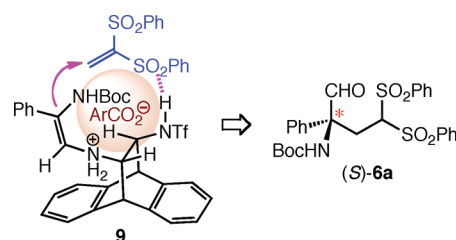


Figure 1. A possible transition state structure.

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>.

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