Synthetic Methods

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Solvent-Dependent Enantiodivergent Mannich-Type Reaction: Utilizing a Conformationally Flexible Guanidine/Bisthiourea Organocatalyst**

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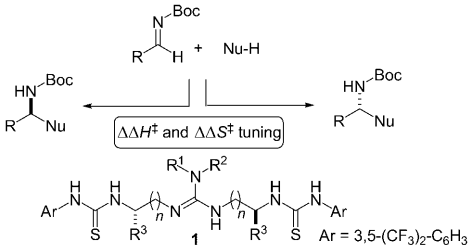
Hydrogen bonding promoted asymmetric catalysis has rapidly grown over the past decade.[1] Most organocatalysts probed to date have conformationally rigid chiral backbones that participate in structurally rigid transition states.[2] In contrast, recent findings from our group have shown that conformationally flexible guanidine/bisthiourea organocatalysts **1**[3–7] display unique stereodiscrimination processes that are governed by differential activation entropy ($\Delta\Delta S^{\ddagger} = 25.4\ J\,mol^{-1}\,K^{-1}$) rather than differential activation enthalpy ($\Delta\Delta H^{\ddagger} = \sim 0\ kJ\,mol^{-1}$) in *ortho*- and enantioselective 1,4-type Friedel–Crafts alkylations of sesamol.[8] A new perspective described herein concerns the possibility of bringing about dynamic control of the stereochemical outcomes in the organocatalytic system by tuning the enthalpy and entropy related external factors (e.g., reaction solvents, the substrate concentration, and pressure).[9] The development of the solvent-dependent enantiodivergent Mannich-type reaction of *N*-aldimines with malonates that enable selective synthesis of either enantiomer by employing a single enantiomer of a chiral catalyst is presented (Scheme 1). The *S* adducts are selectively formed with 87–94% *ee* in reactions run in *m*-xylene, whereas *R* adducts predominate (80–89% *ee*) in reactions carried out in acetonitrile. High catalytic efficiencies are also observed as exemplified by the catalyst turnover frequencies (TOF) under optimized reaction conditions; the TOF for the *S*-selective reaction is 66 h^{-1}, and 25 h^{-1} for the *R*-selective reaction.



Scheme 1. A design concept for organocatalytic enantiodivergent reaction by utilizing **1**. Boc = *tert*-butyloxycarbonyl.

Enantiodivergent syntheses utilizing a single chiral catalyst is one of the most straightforward approaches for selective formation of both enantiomers of a product.[10] From the time of the disclosure by Mosher and co-workers in 1972[11] on the asymmetric reduction of unsymmetric ketones with stoichiometric chiral alkoxyalminiumhydrides, several metal-based methodologies for enantiodivergent catalysis, in which the central metal and reaction conditions were tuned, have been studied.[10–12] In these systems, individual metal properties, such as Lewis acidity, oxophilicity, azophilicity, and atomic radius, have been exploited for the formation of a variety monomeric and oligomeric catalytic active species.[10] In contrast, enantiodivergent reactions promoted by organocatalysts have been less often reported.[13,14] In addition, for most cases the enantiodivergent organocatalytic reactions described to date require the use of high catalyst loadings (ca. 10 mol%) to attain high conversions (>90%) and maximum selectivity.[13,14] To broaden the organocatalytic enantiodivergent catalysis, the development of a basic strategy that can be applied to a variety of catalytic stereodivergent reactions is desirable.

Efforts directed at exploring a strategy for using a chiral organocatalyst in to controlled enantioswitching by tuning both the enthalpy and entropy related external factors, first focused on the development of the catalytic Mannich-type reaction of *N*-Boc aldimines **2** with malonates **3**.[15,16] We envisioned that since these reactions are irreversible, enantiodifferentiation of the Mannich adducts might be achieved with the use of a single organocatalyst in which the relative conformation with respect to the guanidinium and thiourea functional groups might be altered by changing the reaction conditions. If successful, the enantiodifferentiation of the Mannich adducts by a single organocatalyst might be possible. In previously developed catalytic asymmetric Mannich-type reactions of aromatic α-amido sulfones, stoichiometric amounts of Cs_2CO_3 were used as an external base for in situ preparation of the *N*-aldimine acceptors **2** in the presence of 10 mol% of the catalyst **1**·HCl.[17] To evaluate the occurrence of using a chiral catalyst in a controlled way so as to reverse enantioselectivity, it was important to avoid achiral-base-

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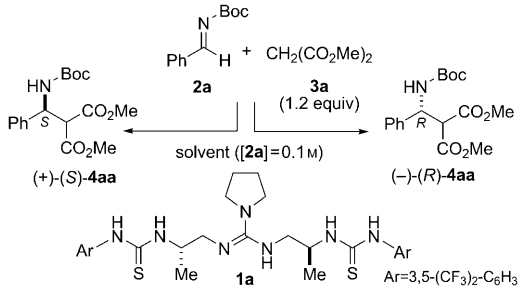
mediated racemic pathways. Therefore, an alternative protocol for the Mannich-type reaction of *N*-Boc imines **2** was developed in which the catalyst **1** is formed by reaction of **1**·HCl with a base.

Extensive screening[18] led to the identification of catalyst **1a**, which displays dramatic solvent-dependent enantiodivergence in the Mannich-type reaction of **2a** with **3a**.[18,19] For example, reactions in nonpolar solvents such as dichloromethane, toluene, chlorobenzene, and *m*-xylene led to the production of (+)-(*S*)-**4aa** (Table 1, entries 1–5). In contrast, when reactions were carried out in polar aprotic solvents, (−)-(*R*)-**4aa** was obtained as the major product (Table 1, entries 9–13). Among the polar aprotic solvents examined, nitriles gave the highest *R* selectivity (Table 1, entries 11–13). With suitable solvents for enantioswitching in hand, our efforts then focused on optimization of both the *S*- and *R*-selective reactions. In the course of this effort, significant temperature effects on **1a**-catalyzed enantiodivergent Mannich-type reactions were observed. Specifically, as the reaction temperature increased the *S* selectivity in *m*-xylene increased (Table 1, entry 5 versus entry 6), whereas a decrease in reaction temperature increased the *R* selectivity in reactions in acetonitrile (Table 1, entry 13 versus entry 14). High reaction rates for reactions catalyzed by **1a** were also noted. As shown in entries 7 and 15 in Table 1, guanidine/bisthiourea **1a** promotes rapid *S*-selective reactions that proceed to completion within 1.5 hours, and the *R*-selective reactions require 3 hours for completion. Moreover, catalyst loading can be reduced without any loss of enantioselectivity (Table 1, entry 8: TOF = 66 h^{-1} in *S*-selective reaction,and entry 16: 25 h^{-1} in *R*-selective reaction).

The scope and limitations of the enantiodivergent reactions were probed next (Table 2). The organocatalytic reactions promoted by **1a** in *m*-xylene or toluene consistently showed *S* selectivity (Table 2, entries 1–9). Fine tuning of the reaction conditions led to high *S* selectivity (87–97% *ee*) for reactions involving a range of aromatic *N*-Boc imines. The reactions of aromatic imines bearing *para*, *meta,* and *ortho* substituents gave products in 97–99% yield with *S* selectivity in the range of 91–93% *ee* (Table 2, entries 1–3). A longer reaction time is required for the reaction of imine **2f**, which contains an electron-donating group at the *para* position of the aromatic ring, nevertheless excellent enantioselectivity was observed (Table 2, entry 5). 2-Naphthyl-, 2-furyl- and 2-thienyl-substituted imines also afford products in yields of 97–99% with *ee* values of 89–97% (Table 2, entries 6–8). Although the benzyl malonate **3b** displays a lower reactivity

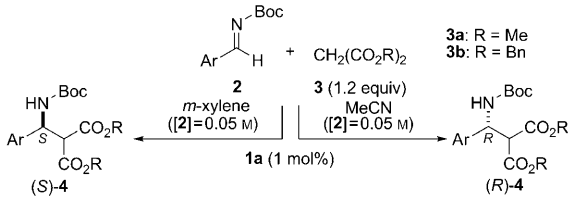
Table 1: Optimization studies on the **1a**-catalyzed enantiodivergent Mannich-type reactions of **2a** with **3a**.



Entry	Solvent	**1a** [mol%]	*T* [°C]	*t* [h]	Yield [%][a]	*ee* [%][b,c]
1	Et_2O	10	−10	24	96	+42
2	CH_2Cl_2	10	−10	24	99	+71
3	toluene	10	−10	24	97	+90
4	chlorobenzene	10	−10	24	98	+90
5	*m*-xylene	10	−10	24	95	+86
6	*m*-xylene	10	0	24	99	+92
7	*m*-xylene	10	0	1.5	99	+92
8	*m*-xylene	1	0	1.5	99	+92
9	THF	10	−10	24	97	−31
10	EtOAc	10	−10	24	96	−16
11	*i*PrCN	10	−10	24	99	−72
12	EtCN	10	−10	24	99	−76
13	MeCN	10	−10	24	98	−79
14	MeCN	10	−30	24	98	−88
15	MeCN	10	−30	3	99	−88
16	MeCN	1	−30	4	99	−88

[a] Yield of isolated product. [b] Determined by HPLC analysis using a chiral column. [c] The *ee* value of (*S*)-**4** is defined as plus and that of (*R*)-**4** as minus. The absolute stereochemistry of **4aa** was determined on the basis of its optical rotation.[16j]

Table 2: **1a**-Catalyzed enantiodivergent Mannich-type reactions with various aromatic *N*-Boc imines **2**.



Entry	**2:** Ar	Solvent	Product	*T* [°C]	*t* [h]	Yield [%][a]	*ee* [%][b,c]
1[d,h]	**2b**: 4-MeC_6H_4	*m*-xylene	**4ba**	0	1.5	99	+92
2[d]	**2c**: 3-MeC_6H_4	*m*-xylene	**4ca**	0	2	97	+91
3[d]	**2d**: 2-MeC_6H_4	*m*-xylene	**4da**	0	3	98	+93
4[d,h]	**2e**: 4-ClC_6H_4	*m*-xylene	**4ea**	0	2	99	+90
5	**2f**: 4-MeOC_6H_4	*m*-xylene	**4fa**	0	8	99	+97
6[d]	**2g**: 2-naphthyl	*m*-xylene	**4ga**	0	1.5	99	+94
7[d,e]	**2h**: 2-furyl	*m*-xylene	**4ha**	−10	1	97	+89
8[d,e]	**2i**: 2-thienyl	toluene	**4ia**	−10	1	98	+97
9[d,g]	**2a**: Ph	*m*-xylene	**4ab**	0	2	97	+87
10[d]	**2b**: 4-MeC_6H_4	MeCN	**4ba**	−40	18	98	−89
11[d]	**2c**: 3-MeC_6H_4	MeCN	**4ca**	−40	15	96	−89
12[d,f]	**2d**: 2-MeC_6H_4	MeCN	**4da**	−30	14	90	−80
13[d]	**2e**: 4-ClC_6H_4	MeCN	**4ea**	−40	6	99	−82
14	**2f**: 4-MeOC_6H_4	MeCN	**4fa**	−40	20	88	−84
15[d]	**2g**: 2-naphthyl	MeCN	**4ga**	−40	12	97	−80
16[d]	**2h**: 2-furyl	MeCN	**4ha**	−30	10	92	−84
17[d,f]	**2i**: 2-thienyl	MeCN	**4ia**	−40	12	97	−86
18[d,g]	**2a**: Ph	MeCN	**4ab**	−10	2	99	−82

[a] Yield of isolated product. [b] Determined by chiral HPLC analysis using a chiral column. [c] The *ee* value of (*S*)-**4** is defined as plus and that of (*R*)-**4** as minus. [d] The absolute stereochemistry of **4** was determined on the basis of its optical rotation.[16] [e] Used 2 mol% of **1a** [f] Used 3 mol% of **1a**. [g] Used 5 mol% of **1a**. [h] The reaction was carried out at 0.1 M with respect to **2**.

in the catalytic system, increasing the catalyst loading significantly enhances the reaction rate. In the presence of 5 mol% of **1a**, the Mannich-type reaction of **2a** with **3b** is completed in 2 hours and affords product in 97% yield with 87% *ee* (Table 2, entry 9). Importantly, when the reaction is carried out in acetonitrile reversal of the enantioselectivity is observed compared to that seen with *m*-xylene and toluene. The Mannich-type reactions in acetonitrile give the corresponding *R* products in 88–99% yield with 80–89% *ee* (Table 2, entries 10–18).

Considering that Gibbs free energy is defined as $\Delta\Delta G^{\ddagger} = \Delta\Delta H^{\ddagger} - T\Delta\Delta S^{\ddagger}$, the difference in temperature profiles between the *S*-selective reaction and *R*-selective reaction in the present organocatalytic system suggest that enthalpy-entropy compensation may contribute to the solvent-dependent enantioswitching. This speculation, along with the goal of characterizing the chiral recognition processes that take place in the bond-forming reaction,[21] led us to perform a kinetic analysis of the reaction using Eyring plots[9,22–24] to obtain the differential activation parameters.

In the differential Eyring treatment,[22] the relative rates of formation of (*S*)-(+)- and (*R*)-(−)-**4aa** in *S*-selective and *R*-selective reactions are expressed by Equations (1) and (2), respectively, where $\Delta\Delta S^{\ddagger}$ represents the differential activation entropy and $\Delta\Delta H^{\ddagger}$ represents the differential activation enthalpy.

$$\ln(k_S/k_R) = -\Delta\Delta H^{\ddagger}_{S\text{-}R}/RT + \Delta\Delta S^{\ddagger}_{S\text{-}R}/R \quad (1)$$

$$\ln(k_R/k_S) = -\Delta\Delta H^{\ddagger}_{R\text{-}S}/RT + \Delta\Delta S^{\ddagger}_{R\text{-}S}/R \quad (2)$$

In accord with Equations (1) and (2), plots of natural logarithms of the relative rates of formation of (*S*)-(+)- and (*R*)-(−)-**4aa** versus reciprocal temperatures were fitted to straight lines with good correlation coefficients (Figure 1). These observations confirm that a single mechanism is operable in the catalytic process occurring in each solvent in the temperature range explored.[23d]

As seen by inspecting the data in Table 3, both enthalpy ($\Delta\Delta H^{\ddagger}$) and entropy ($\Delta\Delta S^{\ddagger}$) compensation govern the stereodetermining step of solvent-dependent organocatalytic reactions promoted by **1a**. Positive values of $\Delta\Delta H^{\ddagger}_{S\text{-}R}$ and $\Delta\Delta S^{\ddagger}_{S\text{-}R}$ in *S*-selective reactions run in nonpolar solvent systems are obtained (Table 3, entries 1–4). In these cases, differential activation entropies ($\Delta\Delta S^{\ddagger}_{S\text{-}R}$) contribute to lowering the $\Delta\Delta G^{\ddagger}_{S\text{-}R}$ of reactions having unfavorable enthalpic contributions. In contrast, negative values of $\Delta\Delta H^{\ddagger}_{R\text{-}S}$ and $\Delta\Delta S^{\ddagger}_{R\text{-}S}$ control the stereodiscrimination processes in *R*-selective reactions in aprotic polar solvents (Table 3, entries 5–8), in which the $\Delta\Delta H^{\ddagger}_{R\text{-}S}$ term has a major influence on lowering the $\Delta\Delta G^{\ddagger}_{R\text{-}S}$ in the *R*-selective reactions. Thus, the observed solvent-dependent stereodiscrimination in **1a**-catalyzed Mannich-type reaction resides in compensating differences in the enthalpies and entropies of activation.[25] Additional efforts designed to probe the link between kinetics and molecular mechanism are underway.[26]

Table 3: Differential activation parameters.

Entry	Solvent	$\Delta\Delta H^{\ddagger}$ [kJ mol^{-1}]	$\Delta\Delta S^{\ddagger}$ [J mol^{-1} K^{-1}]
1	toluene	+15.1	+82.3
2	*m*-xylene	+19.9	+99.6
3	chlorobenzene	+9.99	+59.6
4	CH_2Cl_2	+16.8	+79.7
5	EtOAc	−24.0	−87.3
6	THF	−29.4	−106
7	EtCN	−19.4	−57.2
8	MeCN	−14.6	−37.2

In conclusion, we have developed an enantiodivergent catalytic Mannich-type reaction by utilizing conformationally flexible organocatalysts. The simple methodology has a broad aromatic *N*-Boc imine substrate scope and it enables selective access to both enantiomers of the Mannich adducts using a single chiral organocatalyst. Kinetic analyses uncovered that the origin of solvent-dependent stereodiscrimination is controlled by the enthalpy-entropy compensation. The stereoselectivities of *S*-selective Mannich-type reactions in nonpolar solvents are governed by the differences in the entropies of activation ($\Delta\Delta S^{\ddagger}_{S\text{-}R}$), whereas the stereodiscrimination processes of *R*-selective reactions are governed by differences in the enthalpies of activation ($\Delta\Delta H^{\ddagger}_{R\text{-}S}$). We believe that these findings will serve as a foundation for the design of new stereoswitchable asymmetric organocatalytic processes. Additional efforts to apply the concepts described above to other classes of asymmetric transformations, including diastereoswitching and organocascade processes, are underway.

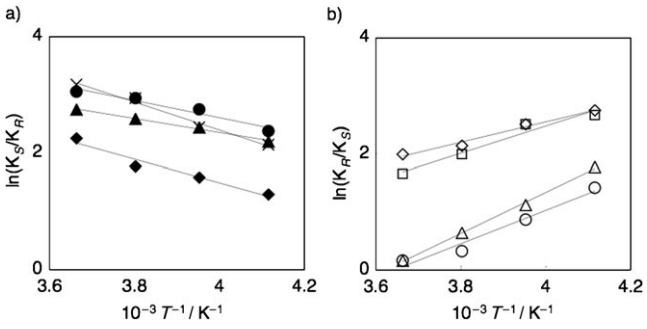


Figure 1. Eyring plots of ln[(100+% *ee*)/(100−% *ee*)] vs. 1/*T* for **1a**-catalyzed Mannich-type reactions in various solvents. a) *S*-Selective reactions in toluene (closed circle; $R^2 = 0.949$), *m*-xylene (cross; $R^2 = 0.983$), chlorobenzene (closed triangle; $R^2 = 0.992$), and CH_2Cl_2 (closed diamond; $R^2 = 0.956$). b) *R*-Selective reactions in EtOAc (open circle; $R^2 = 0.967$), THF (open triangle; $R^2 = 0.998$), EtCN (open square; $R^2 = 0.955$), and MeCN (open diamond; $R^2 = 0.981$).

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