Synthetic Methods

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Entropy-Controlled Catalytic Asymmetric 1,4-Type Friedel–Crafts Reaction of Phenols Using Conformationally Flexible Guanidine/Bisthiourea Organocatalyst**

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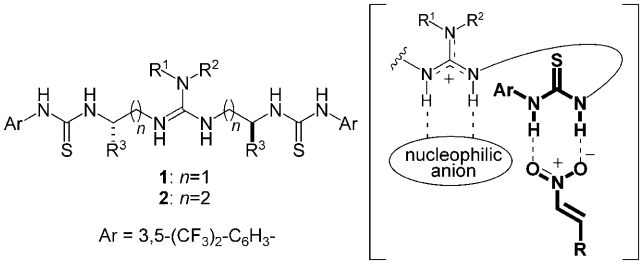
One of the most important aspects of protein function is the motion that occurs in response to substrate binding.[1] In the dynamics of enzyme catalysis, multiple weak hydrogen-bonding interactions[2] in the polypeptide that are controlled by interrelated enthalpy and entropy changes play a significant role in governing the conformational changes that take place.[3] In contrast, the development of asymmetric organocatalysts has rarely focused on hydrogen-bond donors[4–8] that have conformationally flexible scaffolds[9–11] as a likely consequence of difficulties in controlling the conformation of acyclic skeletons.[12] However, recently our research group has successfully demonstrated the utility of conformationally flexible guanidine/bisthiourea organocatalysts **1** for organocatalytic carbon–carbon bond-forming reactions.[9] Herein, we describe studies that have led to the development of new acyclic C_3-linked guanidine/bisthiourea organocatalysts **2**. Analysis of these processes shows that the catalytic effect resides in a trade off between enthalpies and entropies of activation and reveals the existence of dramatic concentration effects. This investigation has uncovered a unique catalytic stereodiscrimination process controlled only by differences in the activation entropies.

The primary aim of this study was to extend our newly developed organocatalytic system to asymmetric 1,4-additions reactions of nitroolefins.[13] A plausible interaction mode for the catalytic reactions of nitroolefins with nucleophilic anions is shown in Scheme 1. In the reactive complex involving an acyclic guanidine/bisthiourea organocatalyst, the thiourea moiety can interact with the nitro group in the acceptor and ionic interactions with the guanidinium cation can orient a nucleophilic anion.[14] We envisaged that a long chiral spacer between the two centers in the catalyst would be required for the promotion of the 1,4-addition reactions that take advantage of these synergistic proximity effects.



Scheme 1. The structures of **1** and **2**, and working model for 1,4-additions with nitroolefins.

In the current study, we initially selected catalytic asymmetric Friedel–Crafts (FC) reactions[15,16] of phenol derivatives.[17–19] Although a variety of electron-rich aromatic compounds such as indoles, pyrroles, and furans have been successfully utilized as nucleophiles in 1,4-addition processes,[15,16] asymmetric reactions of phenol derivatives have been rarely studied. The difficulty in employing phenol derivatives in these processes could be a result of two intrinsic factors that are related to the fact that phenoxide anions generated in situ 1) often promote ligand exchange with metal catalysts,[17] and 2) can participate in reactions that take place with low levels of chemo- and regioselectivity. In 2007, Chen and co-workers developed the first 1,4-type of FC reaction of naphthols with nitroolefins that utilize cinchona-based thiourea catalysts. These processes give *ortho*-selective FC products with 85–95% *ee*.[18a] However, the undesired dimeric furans that are formed in these reactions cannot be easily separated from the target chiral phenols. Following this early study, most catalytic reactions of phenols were designed to prepare pyrans[18b,c] and chromanes[18d] through C-alkylation/O-cyclization cascade processes. Thus, to broaden the utility of this process in the preparation of chiral phenols, alternative approaches have been explored to repress the inherent cascade pathway.[18e]

To evaluate the catalytic activities of newly designed C_3-tethered guanidine/bisthiourea catalysts,[20] initial studies were conducted using sesamol (**3a**) and nitroalkene **4a** (1.0 equiv) as substrates.[18e] As the results displayed in Table 1 show, **2** effectively promotes nucleophilic addition at the C6 position of **3a** to selectively afford the corresponding

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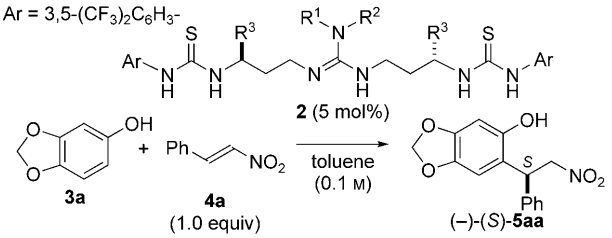
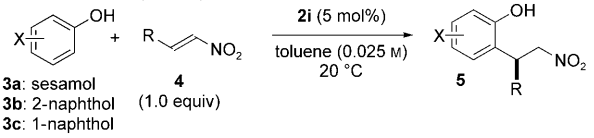
Table 1: Catalyst screening and optimization studies.



Entry	Cat.	R^1	R^2	R^3	T [°C]	t [h]	Yield [%][a]	*ee* [%][b]	Config[c]
1	**2a**	$C_{18}H_{37}$	H	Me	−10	12	55	22	*R*
2	**2b**	$C_{18}H_{37}$	H	Bn	−10	12	69	22	*R*
3	**2c**	$C_{18}H_{37}$	H	*i*Pr	−10	12	66	8	*R*
4	**2d**	-$(CH_2)_4$-		Me	−10	12	35	21	*R*
5	**2e**	-$(CH_2)_4$-		Bn	−10	12	62	15	*R*
6	**2f**	-$(CH_2)_4$-		*i*Pr	−10	12	71	2	*R*
7	**2g**	-$(CH_2)_5$-		Me	−10	12	88	43	*S*
8	**2h**	-$(CH_2)_5$-		Bn	−10	12	88	41	*S*
9	**2i**	-$(CH_2)_5$-		*i*Pr	−10	12	88	78	*S*
10	**2j**	-$(CH_2)_5$-		*i*Bu	−10	12	82	50	*S*
11	**2i**	-$(CH_2)_5$-		*i*Pr	0	12	95	80	*S*
12	**2i**	-$(CH_2)_5$-		*i*Pr	20	2	96	85	*S*
13[d]	**2i**	-$(CH_2)_5$-		*i*Pr	20	9	97	91	*S*
14[d]	**1i**	-$(CH_2)_5$-		*i*Pr	20	9	46	34	*R*

[a] Yield of the isolated product. [b] Determined by HPLC on a chiral stationary phase. [c] The absolute configuration of **5aa** was determined by using X-ray crystallographic analysis of a derivative. See the Supporting Information for details. [d] The reaction was carried out in toluene at a concentration of 0.025 M. Bn = benzyl.

Table 2: Asymmetric FC reaction with various phenol derivatives **3** and nitroolefins **4** catalyzed by **2i**.



Entry	**3**	**4**: R	Product **5**	t [h]	Yield [%][a]	*ee* [%][b]
1	**3a**	**4b**: 4Cl-C_6H_4	**5ab**	12	99	90
2	**3a**	**4c**: 4-$MeOC_6H_4$	**5ac**	12	91	87
3	**3a**	**4d**: 2-naphthyl	**5ad**	12	99	94
4	**3a**	**4e**: 2-thienyl	**5ae**	9	98	90
5	**3a**	**4f**: 2-furyl	**5af**	12	99	88
6[c,d]	**3a**	**4g**: *c*-C_6H_{11}-	**5ag**	48	84[e]	91
7[f]	**3a**	**4h**: $CH_3(CH_2)_5$-	**5ah**	24	66[e]	90
8[f]	**3a**	**4i**: $Ph(CH_2)_2$-	**5ai**	24	88[e]	89
9	**3b**	**4a**: Ph	**5ba**[g]	12	95[e]	88
10	**3b**	**4d**: 2-naphthyl	**5bd**	12	84	84
11	**3b**	**4e**: 2-thienyl	**5be**[g]	12	99	84
12[h]	**3b**	**4j**: $CH_3(CH_2)_2$-	**5bj**[g]	24	90[e]	93
13[f]	**3c**	**4a**: Ph	**5ca**	24	77	82
14	**3c**	**4b**: 4-ClC_6H_4	**5cb**[g]	24	78	83

[a] Yield of the isolated product. [b] Determined by HPLC on a chiral stationary phase. [c] The reaction was carried out in toluene at a concentration of 0.1 M. [d] 1.5 equivalents of **3a** was used. [e] Yield based on ^{1}H NMR spectroscopy. [f] 2.0 equivalents of **3** was used. [g] The absolute configuration of **5** was determined by comparison of the $[\alpha]_D$ values with those reported earlier.[18a] [h] 10 mol% of **2i** was used.

FC product **5aa**. The results of extensive catalyst development studies suggested that both the six-membered ring containing the guanidine moiety and the α-branched substituent on the chiral spacer are crucial for the achievement of high levels of asymmetric induction (Table 1, entries 1–8 vs. entries 9 and 10). Among the catalysts probed, **2i** bearing an isopropyl moiety on the chiral spacer gave the best results in terms of both reactivity and enantioselectivity (Table 1, entry 9; 88% yield with 78% *ee*). Notably, we observed that the enantiomeric excess of **5aa** increased as the reaction temperature was increased, thus reaching an *ee* value of 85% at 20°C (Table 1, entries 11 and 12). Finally, tuning the solvent concentration led to the optimum processes in which **5aa** was produced with 91% *ee* (Table 1, entry 13). Thus, this investigation led to the development of a highly atom-economical protocol[21] for 1,4-type FC reactions of phenols and nitroalkenes. The importance of the length of the C_3 spacer on **2i** is evident from a comparison of reactions promoted by this catalyst versus its structural variant **1i** that bears a C_2 spacer (Table 1, entry 13: 97% yield, 91% *ee* vs. entry 14: 46% yield, 34% *ee*).

The catalyst **2i** developed in the exploratory studies was applied to reactions of various phenol derivatives **3** and nitroolefins **4** (Table 2). Nitroolefins having aromatic groups (Table 2, entries 1–5) as well as aliphatic substituents (Table 2, entries 6–8) participated in the catalytic process, and afforded the corresponding Friedel–Crafts products with 87–94% *ee*. For the less reactive nitroalkene **4g** that bears a bulky aliphatic substituent at the β position, a higher concentration (0.1M) was required for good conversions (Table 2, entry 6). 2-Naphthol (Table 2, entries 9–12) and 1-naphthol (Table 2, entries 13 and 14) also reacted and gave the corresponding FC adducts **5** in 77–99% yield with 82–93% *ee*.[18a]

Subsequent kinetic analysis based on an Eyring Equation [see Eq. (1)][22] revealed the effects of differential activation enthalpies ($\Delta\Delta H^{\ddagger}_{S-R} = \Delta H^{\ddagger}_{S} - \Delta H^{\ddagger}_{R}$) and activation entropies ($\Delta\Delta S^{\ddagger}_{S-R} = \Delta S^{\ddagger}_{S} - \Delta S^{\ddagger}_{R}$)[23–26] on the enantioselective FC reactions catalyzed by **2i**.

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

First, in accord with Equation (1), plots of natural logarithms of the relative rates of formation of (*S*)-**5aa** and (*R*)-**5aa**, that is, $\ln(k_S/k_R) = \ln[(100 + \%\ ee)/(100 - \%\ ee)]$ versus the reciprocal of the temperature for each reactant

concentration gave straight lines with good correlation coefficients (Figure 1).[26] These results document that a single reaction mechanism of catalysis is followed in the temperature range at each concentration.[23e]

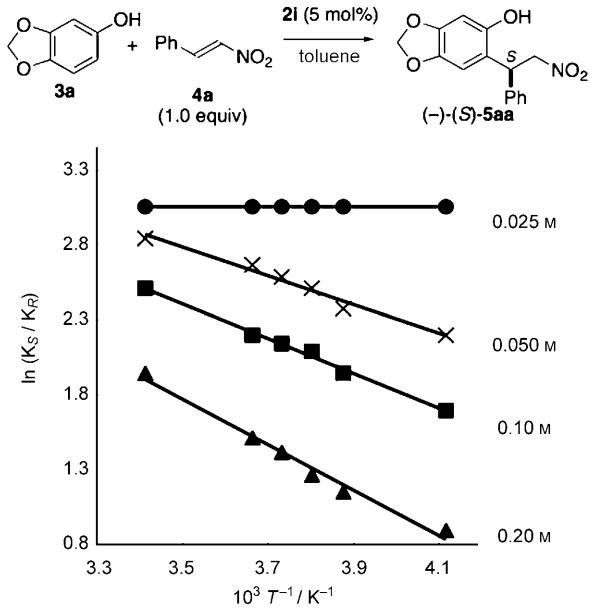


Figure 1. Temperature dependence of the enantioselectivity in the **2i**-catalyzed enantioselective FC reaction of **3a** with **4a** at various concentrations; 0.025 M (circle), 0.05 M (cross), 0.1 M (square), and 0.2 M (triangle). See the Supporting Information for details.

As seen by inspecting the data in Table 3, with the present catalytic system, differential activation parameters were found to depend on the concentration of the reaction mixture. Both the $\Delta\Delta H^{\ddagger}_{S-R}$ and $\Delta\Delta S^{\ddagger}_{S-R}$ values are reduced as the reactant concentration is decreased. Cooperative contributions of the positive values of $\Delta\Delta H^{\ddagger}_{S-R}$ and $\Delta\Delta S^{\ddagger}_{S-R}$ (Table 3, entries 1–3) explain the unusual temperature profile observed (Table 1, entries 10–12). Specifically, when the concentration decreases to 0.025 M in the FC reaction catalyzed by **2i**, $\Delta\Delta H^{\ddagger}_{S-R}$ approaches zero, and $\Delta\Delta S^{\ddagger}_{S-R}$ becomes responsible for the stereodiscrimination (Table 3, entry 4). These results contrast with those seen in general organocatalytic systems that employ conformationally rigid organocatalysts, where stereoselectivities are dominated by enthalpy differences.[23] It is important to note that entropy-controlled asymmetric catalysis has not been reported previously.[27] An advantage of the entropy-controlled catalytic systems is that they do not need high levels of temperature control to attain maximum stereoselectivities. In addition, the entropy term can be tuned by altering the reaction conditions—an important component in the design of switchable functions of organocatalysts.[23b]

As the plots in Figure 2 show, the $\Delta\Delta H^{\ddagger}_{S-R}$ and $\Delta\Delta S^{\ddagger}_{S-R}$ values for the reaction of **3a** with **4a** promoted by **2i** are reasonably well-fitted to a straight line with a good correlation coefficient ($R^2 = 0.979$). A unique feature of the enthalpy–entropy compensation line is the positive value of the intercept ($\Delta\Delta S^{\ddagger}_{0} = 26.6\ \mathrm{J\,mol^{-1}\,K^{-1}}$). These results suggest that the stereodetermining step in the present process is associated in part with differences in solvent orientation about the catalyst.[28] We speculate that a decrease in the concentrations of substrates in the catalytic enantioselective FC reaction catalyzed by the C_3-tethered guanidine/bisthiourea catalyst **2i** results in destruction of the structure of toluene around the catalyst and leads to an increase in the magnitude of the differential activation entropy in the stereodetermining process. Further studies designed to probe the link between thermodynamics and molecular mechanism are underway.

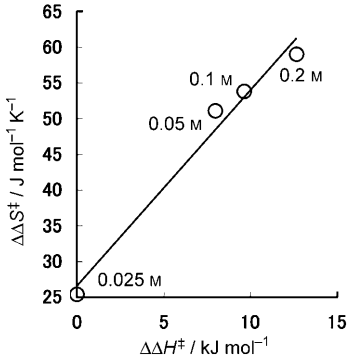


Figure 2. Enthalpy–entropy plots for the Friedel–Crafts reaction of **3a** with **4a** catalyzed by **2i**.

In summary, the studies described above have resulted in the development of a new strategy for asymmetric organocatalysis that involves the use of conformationally flexible organocatalysts. The developed chiral C_3-linked guanidine/bisthiourea **2i** was found to promote *ortho*-selective 1,4-type FC alkylation reactions of phenols with nitroalkenes that take place with 82–94% *ee*. The availability of acyclic scaffolds that can be used as asymmetric organocatalysts may broaden the concepts involved in catalyst design. Kinetic studies by using Eyring plots provide evidence that differences in the activation entropies play a principal role in the stereodiscrimination seen in FC reactions catalyzed by **2i**. The ability to attain maximum enantioselectivities over a wide reaction temperature range leads to operationally simple organocatalytic systems that do not require fine-tuning of the reaction temperature. Further efforts to apply the entropy-controlled organocatalytic system to other classes of asymmetric transformations, including enantio-switching, regio-switching, and organo-cascade processes are ongoing.

Table 3: Differential activation parameters for the FC reaction of **3a** with **4a** catalyzed by **2i** at various concentrations of the substrates.

Entry	Concentration [M]	$\Delta\Delta H^{\ddagger}$ [kJ mol^{-1}]	$\Delta\Delta S^{\ddagger}$ [J mol^{-1} K^{-1}]
1	0.2	12.6	59.0
2	0.1	9.65	53.8
3	0.05	7.97	51.1
4	0.025	≈0	25.4

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[26] See the Supporting Information for details.

[27] For an example of an entropy-controlled supramolecular complexation, see; a) M. V. Rekharsky, T. Mori, C. Yang, Y. H. Ko, N. Selvapalam, H. Kim, D. Sobransingh, A. E. Kaifer, S. Liu, L. Isaacs, W. Chen, S. Moghaddam, M. K. Gilson, K. Kim, Y. Inoue, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 20737; for an entropy-controlled micellization, see; b) S. K. Mehta, K. K. Bhasin, R. Chauhan, S. Dham, *Colloids Surf. A* **2005**, *255*, 153.

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