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Linking Conformational Flexibility and Kinetics: Catalytic 1,4-Type Friedel–Crafts Reactions of Phenols Utilizing 1,3-Diamine-Tethered Guanidine/Bisthiourea Organocatalysts

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Abstract: Herein, we present details of our conformationally flexible, 1,3-diamine-tethered guanidine/bisthiourea organocatalysts for chemo-, regio-, and enantioselective 1,4-type Friedel–Crafts reactions of phenols. These organocatalysts show a unique stereo-discrimination governed by the differential activation entropy ($\Delta\Delta S^{\ddagger}$), rather than by the differential activation enthalpy ($\Delta\Delta H^{\ddagger}$). Extensive kinetic analyses using Eyring plots for a series of guanidine/bisthiourea organocatalysts revealed the key structural motif in the catalysts associated with a large magnitude of differential activation entropy ($\Delta\Delta S^{\ddagger}$). A plausible guanidine–thiourea cooperative mechanism for the enantioselective Friedel–Crafts reaction is proposed.

Keywords: asymmetric synthesis · entropy · Friedel–Crafts reaction · organocatalysis · phenols

Introduction

In enzyme-catalyzed reactions, precise regulation of the enzyme structure is essential to control the various specificities (e.g., substrate and stereochemical specificities) commonly observed in these processes.[1] The cooperativity of weak hydrogen-bonding interactions[2] in a polypeptide allows the flexible control of the transition-state architecture required to achieve the target reaction.[3] Enthalpy and entropy both play significant roles in governing the conformational changes that occur in the enzyme and the substrate.[4] Inspired by the well defined, but diverse ways in which enzymes function, enormous effort has been devoted to the exploration of new chiral hydrogen-bond donors that could serve as asymmetric catalysts.[5–7] However, very few effective asymmetric hydrogen-bond-donor catalysts with conformationally flexible scaffolds have been found.[8–11] The difficulty in employing acyclic organic molecules as asymmetric organocatalysts may arise mainly from free bond rotation.[12] The small barrier to rotation about single bonds connecting two sp^3 carbon atoms often results in rapid and reversible generation of an infinite number of conformers.[13] This is one of the reasons why most organocatalysts reported to date have a conformationally rigid chiral backbone (e.g., proline, cinchona alkaloids, cyclohexanediamines, and 1,1′-bi-2,2′-naphthyl scaffolds) that participates in a structurally rigid transition state.[5,6] In contrast, our group has shown that conformationally flexible organocatalysts **1** are effective for the construction of a variety of chiral environments for asymmetric organocatalysis,[14] facilitating several classes of catalytic asymmetric 1,2-additions, including nitroaldol,[9,14b–e] nitro-Mannich,[14g] Mannich,[14h,k] and Friedel–Crafts (FC) reaction of phenols.[14j] The high stereoselectivities are attributed to chemoselective dual activation of both the nucleophile and electrophile reacting partners in asymmetric space.[14,15] Herein, we describe our mechanistic stud-

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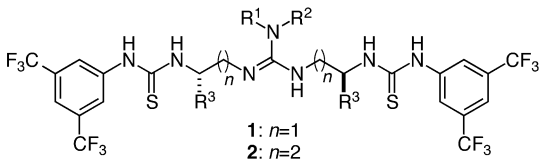
ies on the chemo-, regio-, and enantioselective FC reaction of phenols[16–18] catalyzed by the 1,3-diamine-tethered guanidine/bisthiourea organocatalysts **2**.[19–21]



The chiral phenol unit is a ubiquitous structural motif in biologically active natural products,[22] as well as chiral ligands.[23] Considering the high acidity of phenolic acid ($pK_a = 9.95$ in H_2O), C-alkylation through phenolic enolates, which can be generated from phenols under basic conditions, is potentially one of the most straightforward strategies for the preparation of chiral phenols. However, phenolic enolates currently have limited utility in organic synthesis; this is likely to be because they suffer from ligand exchange in metal-based catalysis.[24] Although several bifunctional organocatalyst-based approaches have recently been reported, direct and catalytic asymmetric 1,4-type FC reactions of phenols remain underdeveloped owing to problems rooted in reaction selectivities (chemo- and regio-) and reactivities.[25–28] With regards to selectivity, a major challenge is to obtain mono-*ortho*-alkylated adducts without second-*ortho* or O-alkylation to give difunctionalized products.[25,26] Lowering the reaction temperature is a common method to avoid overreaction, but this often causes a decrease in the reaction rate.[25] In this context, we have recently reported the development of 1,3-diamine-tethered guanidine/bisthiourea organocatalyst **2a**, which permitted enantioselective 1,4-type FC reactions of phenols (Figure 1).[14j] A unique feature is that stereo-discrimination under optimized conditions is governed by the differential activation entropy

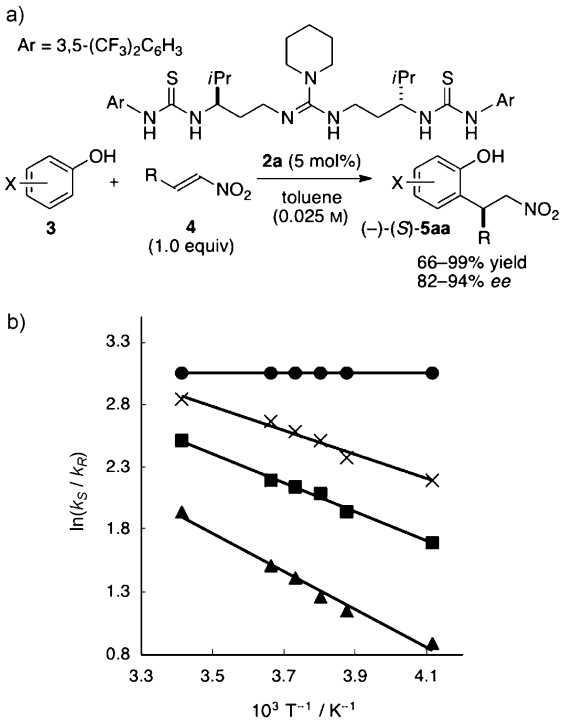


Figure 1. a) Catalytic enantioselective FC reaction of **3** with **4** utilizing **2a** under optimized conditions. b) Eyring plots of the **2a**-catalyzed FC reaction of sesamol (**3a**) with β-nitrostyrene (**4a**) at various concentrations: 0.025 (●), 0.05 (×), 0.1 (■), and 0.2 M (▲).[14j]

($\Delta\Delta S^{\ddagger} = 25.4\ J\,mol^{-1}K^{-1}$), rather than by the differential activation enthalpy ($\Delta\Delta H^{\ddagger} \approx 0\ kJ\,mol^{-1}$), thereby attaining maximum enantioselectivities without strict temperature control. Herein, we describe details of kinetic studies utilizing Eyring plots with a variety of guanidine/bisthiourea organocatalyst variants. A possible catalytic cycle in **2**-catalyzed 1,4-type FC reactions, including a chemoselective dual activation transition state is also discussed.

Abstract in Japanese:

最近、我々は、1,3-ジアミンをキラルスペーサーとして有する鎖状グアニジン/チオウレア触媒を用いるフェノール類の1,4-付加型フリーデル-クラフツ反応を報告している。本研究では、構造的に柔軟な鎖状有機触媒が触媒する立体選択性の制御機構について知見を得ることを目的に、メカニズム解析を行った。まず、活性化パラメーターを算出するために本触媒反応における Eyring プロットを解析した結果、最適条件下では、活性化エントロピー項 ($T\Delta\Delta S^{\ddagger}$)により立体選択性が制御されることが明らかとなった。触媒と生成物との不斉収率の間には良好な直線関係が得られ、また本触媒反応にはグアニジン官能基とチオウレア官能基が必須であった。これらの結果から、本触媒反応では、単一分子のキラル触媒により、二重活性化を介して立体選択性が制御されることが示された。

Results and Discussion

Structure and Catalytic-Activity Relationship Studies

Utilizing 1,2-Diamine-Tethered Guanidine/Bisthiourea Organocatalysts

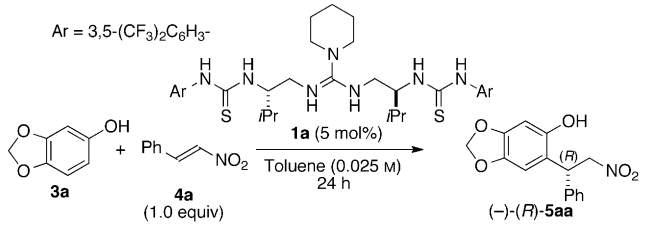
Differential activation parameters, including differential activation enthalpy ($\Delta\Delta H^{\ddagger}$) and entropy ($\Delta\Delta S^{\ddagger}$), are useful parameters for determining binding ability and degrees of randomness in studies of chiral recognition processes, rather than nominal activation parameters ($\Delta H^{\ddagger}_{nom}$ and $\Delta S^{\ddagger}_{nom}$).[30] For example, Jacobsen and co-workers used differential activation enthalpy ($\Delta\Delta H^{\ddagger}$) and differential activation entropy ($\Delta\Delta S^{\ddagger}$) to characterize the mechanism of conformationally constrained, thiourea-catalyzed, cationic polycyclizations.[31] In their catalytic system, the values of $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ were both negative, meaning that the stereo-discrimination in the catalytic reaction was controlled enthalpically. Based

CHEMISTRY
AN ASIAN JOURNAL

on the correlation of the degree of enantioselectivity and the increasing magnitude of $\Delta\Delta H^{\ddagger}$ with increasing size of polycyclic aromatic hydrocarbon on the catalyst, they proposed a cation–π activation mechanism, which served to broaden the scope of enantioselective counterion catalysis. In contrast, our findings[14j,k] have, for the first time, uncovered a situation where differential activation entropy ($\Delta\Delta S^{\ddagger}$) controls the outcome of asymmetric hydrogen-bond-donor catalysis.[32–34] As the entropy term is known to be tunable by selecting suitable reaction conditions,[14k,35] it is particularly important to gain insight into the structural origin of the catalytic action to attain a large magnitude of differential activation entropy ($\Delta\Delta S^{\ddagger}$). Therefore, we first carried out structure–activity relationship (SAR) studies on guanidine/bisthiourea organocatalysts.

The crucial role played by the 1,3-diamine spacer linking the two centers in **2a** is evident from the Eyring plots of the FC reaction of **3a** with **4a** catalyzed by **1a** with the corresponding 1,2-diamine spacer, at a substrate concentration of 0.025 M. As shown in Table 1, **1a** showed completely different catalytic activity from **2a**. 1,2-Diamine-tethered **1a** produced (*R*)-**5aa** as a major product, whereas 1,3-diamine-tethered catalyst **2a** predominantly gave (*S*)-**5aa**. Furthermore, the reactivity and enantioselectivity of **1a** are both drastically reduced in comparison with **2a**. These observations indicate that the selection of a suitable length of chiral spacer is critical to synergize the guanidine and thiourea functionalities in the catalyst and achieve drastic rate acceleration and effective stereocontrol. It is also important to note that the temperature-dependency profiles are different for the FC reactions catalyzed by **1a** and **2a**. In the case of **1a**, the enantioselectivity increased as the reaction temperature decreased, indicating that stereo-discrimination catalyzed by **1a** is controlled by differential enthalpy ($\Delta\Delta H^{\ddagger}$) with an unfavorable entropic contribution ($\Delta\Delta S^{\ddagger}$). Thus, we concluded that the 1,3-diamine spacer played a principal role in attaining entropy-controlled stereo-discrimination in the FC reaction catalyzed by **2a**.

Table 1. Temperature profile of the yield in **1a**-catalyzed 1,4-type FC reactions of **3a** with **4a**.



Entry	T [°C]	Yield [%][a]	*ee* [%][b]
1	−30	30	36
2	−10	43	35
3	0	51	31
4	20	69	27

[a] Yield of isolated product. [b] Determined by HPLC on a chiral stationary phase.

Substituent Effects on 1,3-Diamine-Tethered Guanidine/Bisthiourea Organocatalysts

Exploratory studies show that drastic enantioswitching can occur simply as a result of replacing the substituents (R^1 and R^2) on the guanidine moiety in **2**.[14j,36] These unique features of the present catalytic system, along with our wish to characterize the chiral recognition processes that take place in these asymmetric carbon–carbon bond-forming reactions, prompted us to conduct kinetic analyses using Eyring plots for selected 1,3-diamine-tethered catalysts **2**. According to the differential Eyring treatment,[31,37–39] the relative rates of formation of (*S*)-**5aa** in the reactions are expressed by Equation (1), in which $\Delta\Delta H^{\ddagger}$ represents the differential activation enthalpy and $\Delta\Delta S^{\ddagger}$ represents the differential activation entropy.

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

In accordance with Equation (1), plots of the natural logarithm of the relative rate of formation of (*S*)-**5aa** versus reciprocal temperature were fitted to straight lines with good correlation coefficients (Figure 2).[40] These observations confirm that a single mechanism is operating in the catalytic process over the temperature range explored.[38d] An important feature is that **2b–g** display broadly similar temperature and concentration profiles in the FC reaction of **3a** with **4a**. At less than a threshold concentration, positive values of $\Delta\Delta H^{\ddagger}_{S-R}$ and $\Delta\Delta S^{\ddagger}_{S-R}$ are obtained from the negative slopes and positive y intercept of the plots, respectively. Thus, differential activation entropy ($\Delta\Delta S^{\ddagger}_{S-R}$) contributes to lowering the value of $\Delta\Delta G^{\ddagger}_{S-R}$ ($=\Delta\Delta H^{\ddagger}_{S-R} - T\Delta\Delta S^{\ddagger}_{S-R}$), with an unfavorable enthalpic contribution ($\Delta\Delta H^{\ddagger}_{S-R}$). Notably, when **2b** and **2c** were used as catalysts, the major enantiomer produced switched from (*R*)- to (*S*)-**5aa** at the equipodal temperature (T_0), and thereafter the *S* selectivity continued to increase as the temperature further increased.[40] Enantioswitching in the FC reaction when using 1,3-diamine-tethered guanidine/bisthiourea is a consequence of the occurrence of the equipodal temperature (T_0) in the temperature range with negative slopes in the Eyring plots.[41] It is also important to note that stereo-discrimination catalyzed by **2a** (maximum enantiomeric excess (*ee*) of (*S*)-**5aa**: 91% *ee*)[14j] and **2g** (Figure 2f, maximum *ee* of (*S*)-**5aa**: 91% *ee*) is governed by only $\Delta\Delta S^{\ddagger}_{S-R}$ at 0.025 M substrate concentration. In the case of catalysts **2e** (Figure 2d, maximum *ee* of (*S*)-**5aa**: 80% *ee*) and **2f** (Figure 2e, maximum *ee* of (*S*)-**5aa**: 80% *ee*), a decrease in the substrate concentration to 0.01 M is effective to increase the magnitude of $\Delta\Delta S^{\ddagger}_{S-R}$ for stereo-discrimination and $\Delta\Delta H^{\ddagger}_{S-R}$ approaches zero. Although further studies to probe the relationship between kinetics and molecular mechanism are required, these results suggest that both the six-membered ring containing the guanidine moiety and the α-branched substituent on the chiral spacer in **2** are crucial for attaining the maximum magnitude of differential activation entropy ($\Delta\Delta S^{\ddagger}_{S-R}$) in the stereo-determining processes in the FC reaction of **3a** with **4a**.

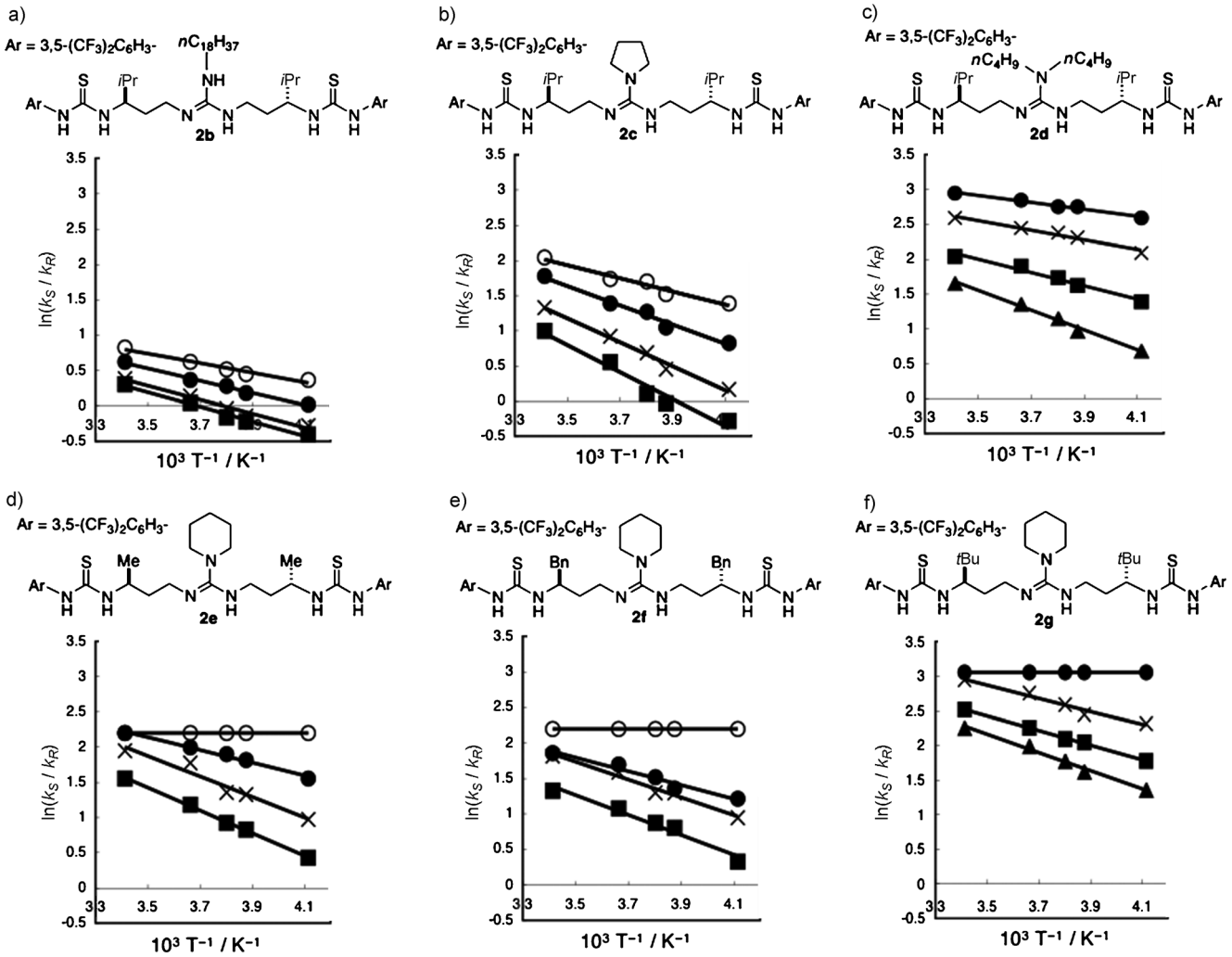
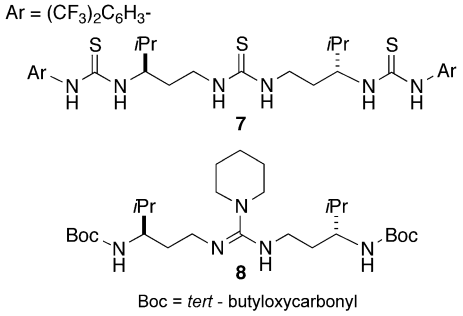


Figure 2. Temperature dependence of the enantioselectivity in the enantioselective FC reaction of **3a** with **4a** using various catalysts at various concentrations: 0.01 (○), 0.025 (●), 0.05 (×), 0.1 (■), and 0.2 M (▲). Bn = benzyl.

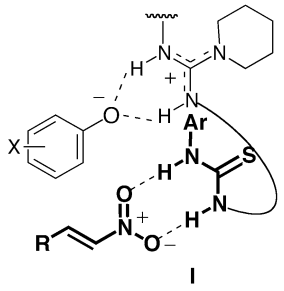
Mechanistic Studies

A key assumption in the rationalization of our catalytic system is that a chemoselective interaction of catalyst **2** and the substrate in the transition state occurs to control the *ortho*- and enantioselective 1,4-addition of **3** with **4**. As illustrated in the proposed ternary complex (Scheme 1), we anticipate that the electron-deficient thiourea moiety might activate **4** through bidentate coordination to the nitro group in **4**, and the guanidinium cation would effectively orient the phenol enolate.[14,42]

To confirm crucial contributions of the guanidine and thiourea functional groups, we initially examined the FC reaction of **3a** with **4a** using variant catalysts **7** and **8**.



The optimized catalyst **2a** promoted *ortho*-selective 1,4-type FC alkylation reactions of **3a** with **4a** to give the corresponding FC adduct in 97% yield with 91% *ee* (Table 2, entry 1). In contrast, no reaction occurred with **7**, in which the guanidine moiety of **2a** was replaced with a thiourea group (Table 2, entry 2). Compound **8**, in which the electron-deficient thiourea moieties in **2a** are replaced with Boc groups, promoted the FC reaction to afford **5aa** in 77% yield with 3% *ee*. The drastic decrease in the *ee* value clearly shows the importance of the thiourea moieties for stereodetermination in the FC reaction catalyzed by **2a**. In addition, when *O*-methylsesamol **9a** was used in place of sesamol **3a**, then **2a** displayed no catalytic activity. These observations suggest that generation of phenolic enolate catalyzed



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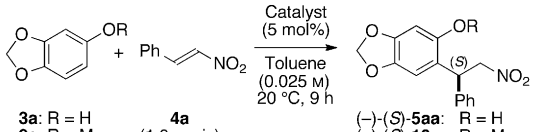
Scheme 1. Proposed ternary complex involved in the FC reaction of phenol enolate with **4** catalyzed by **2**.

Table 2. Catalytic asymmetric FC reaction of **3a** or **9a** with **4a**.



3a: R = H
9a: R = Me

4a (1.0 equiv)

(–)-(*S*)-**5aa**: R = H
(–)-(*S*)-**10aa**: R = Me

Entry	Catalyst	Nucleophile	Yield [%][a]	*ee* [%][b]
1	**2a**	**3a**: R = H	97	91
2	**7**	**3a**: R = H	n.r.	–
3	**8**	**3a**: R = H	77	3
4	**2a**	**9a**: R = Me	n.r.	–

[a] Yield of isolated product. [b] Determined by HPLC on a chiral stationary phase. [c] n.r. = no reaction.

by the guanidine base is critical for the enhancement in the FC reactions of phenols. This is complementary to the situation in the Brønsted acid catalyzed FC reaction of arenes.[43] Because the *ee* values in FC alkylation of **3a** with **4a** catalyzed by **2a** are independent of the percentage conversion, stereo-discrimination appears to be kinetically governed by cooperative activation of the substrates by thioureas and guanidine base in **2a**.

We next investigated the relationship between the *ee* value of the catalyst and *ee* value of FC product **5aa** to gain insight into the assembly state of the catalyst,[44] because assembly states generally play a key role in constructing the ordered conformation of acyclic molecules.[45] Indeed, mechanistic studies and the observation of nonlinear effects established the importance of catalyst assembly in catalytic asymmetric nitroaldol reactions utilizing **1**·HCl with a lipophilic long alkyl chain on the guanidinium moiety.[14d] In sharp contrast, linear relationships between the *ee* values of **2a** and adduct **5aa** were obtained for reactions at substrate concentrations of both 0.1 and 0.025 M (Figure 3). These results suggest that the enantioselectivity in the FC reaction in toluene catalyzed by **2a** is governed by the inherent structures of the monomeric chiral catalyst **2a** without generation of complex dimers or oligomers,[46] regardless of substrate concentration.

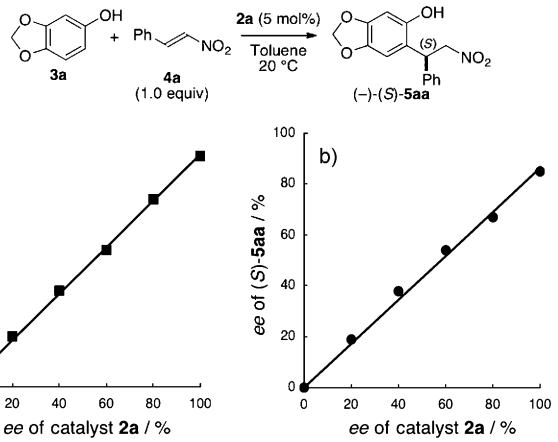
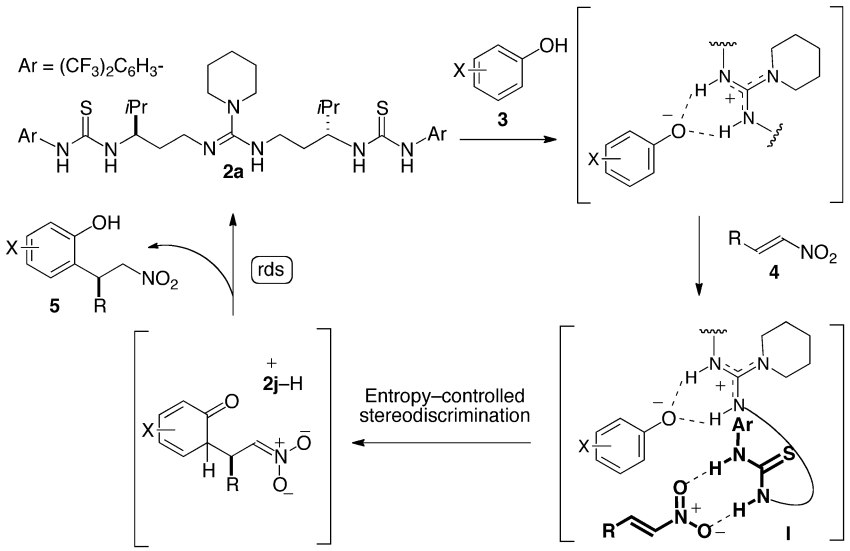


Figure 3. Relationships between *ee* values of **2a** and (*S*)-**5aa** for substrate concentrations of a) 0.1 and b) 0.025 M.

In order to obtain further information on the catalytic cycle, initial rate kinetic studies at −30 °C were performed at 0.025 M substrate concentration.[47] The rate dependencies of each reaction component are shown in Figure 4. First-order dependency was observed for the catalyst (Figure 4a), whereas the reaction rate had zeroth-order dependency for sesamol (**3a**, Figure 4b) and β-nitrostyrene (**4a**, Figure 4c). The initial kinetics indicate that the rate-determining step is dissociation of the complex of protonated **2a** and nitronate.



Scheme 2. Proposed catalytic cycle in FC reaction of **3** with **4** catalyzed by **2a**.

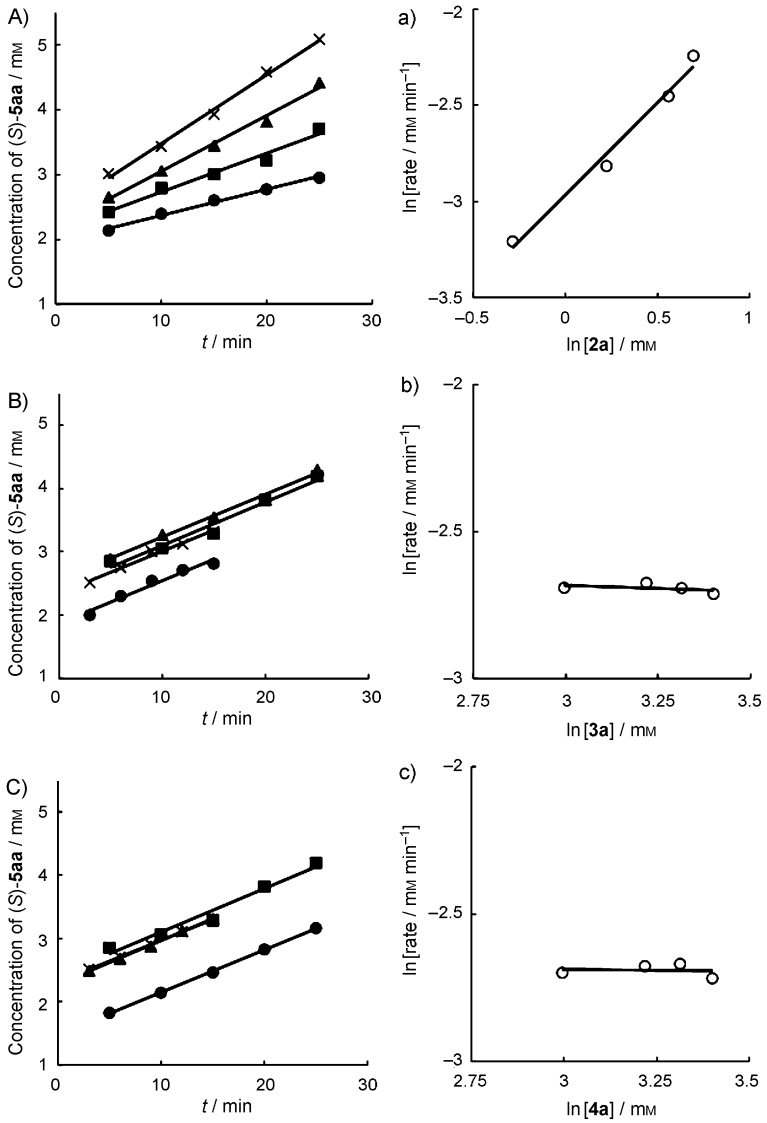


Figure 4. A) Reaction profiles of the FC reaction for **2a** at concentrations of 0.75 (●), 1.25 (■), 1.75 (▲), and 2.0 mM (×). B) Reaction profiles of the FC reaction for **3a** at concentrations of 20 (●), 25 (■), 27.5 (▲), and 30 mM (×). C) Reaction profiles of the FC reaction for **4a** at concentrations of 20 (●), 25 (■), 27.5 (▲), and 30 mM (×). a) Rate dependency on **2a**. $y=0.963x-2.97$ ($R^2=0.983$) b) Rate dependency on **3a**. $y=-0.0423x-2.56$ c) Rate dependency on **4a**. $y=-0.00926x-2.66$

On the basis of the series of mechanistic studies described above, we propose a catalytic cycle for the 1,4-type FC reaction catalyzed by **2a** (Scheme 2). The SAR studies with respect to catalytic active sites, summarized in Table 2, suggest crucial roles of both guanidine and thiourea moieties in **2a**. Thus, we assumed that the guanidine base deprotonated **3** and the electron-deficient thiourea moieties might have activated **4** through bidentate coordination to the nitro group, thus forming the reactive ternary complex **I**, in which the stereoselectivity of the FC reaction should be controlled. Kinetic studies performed by using Eyring plots suggested that the dynamic motion of conformationally flexible **2a** in response to formation of the ternary complex **I** leads to extensive desolvation of toluene from the catalyst, resulting in effective stereocontrol simply due to the differential activation entropy ($\Delta\Delta S^{\neq}$).[48] Finally, proton transfer between the guanidinium **2a**-H and nitronate intermediate produces **5** and regenerates the catalyst. Further investigations to broaden the utility of the conformationally flexible guanidine/bisthiourea organocatalysts **2** based on these mechanistic studies are ongoing.

Conclusion

We have carried out a series of mechanistic studies on the chemo-, regio-, and enantioselective FC reaction of phenols catalyzed by 1,3-diamine-tethered-guanidine/bisthiourea organocatalysts. Extensive kinetic studies performed by using Eyring plots identified that both the six-membered ring containing the guanidine moiety and the α-branched substituent on the chiral spacer in **2** play a pivotal role for attaining the maximum magnitude of differential activation entropy ($\Delta\Delta S^{\neq}_{S-R}$) in the stereo-determining processes in the FC reaction of **3a** with **4a**. Evidence for the proposed guanidine/thiourea cooperative reaction mechanism and for the importance of the 1,3-diamine chiral spacer in **2a** was obtained by means of experiments with structural variants of the catalyst. We believe our findings provide basic information that will be broadly useful in the design of conformationally flexible architectures and will extend the utility of asymmetric organocatalysts.

Experimental Section

Nitroolefin **4a** (14.9 mg, 0.100 mmol) was added to a mixture of **2a** (4.3 mg, 0.005 mmol) and **3a** (13.8 mg, 0.100 mmol) in toluene (4.0 mL) at 20 °C. After stirring for 9 h at 20 °C, the reaction was quenched with a saturated aqueous solution of NH_4Cl. The resulting mixture was diluted with EtOAc and poured into water. The aqueous layer was extracted with EtOAc (×3) and the combined organic layer was washed with brine and then dried over $MgSO_4$. After removing solvents under reduced pressure, the residue was purified by flash column chromatography (*n*-hexane/EtOAc = 15:1 to 5:1) to afford (−)-(*S*)-**5aa** (27.8 mg, 97% yield) and **2a**·HCl (4.5 mg, 99% recovery). The *ee* value of (−)-(*S*)-**5aa**

(91% *ee*) was determined by means of chiral HPLC analysis (Chiral AD-H, 0.46 cm (ϕ) × 25 cm (L), *n*-hexane/2-propanol = 90:10, 1.0 mL min^{-1}, major 39.4 min, minor 30.4 min).

Acknowledgements

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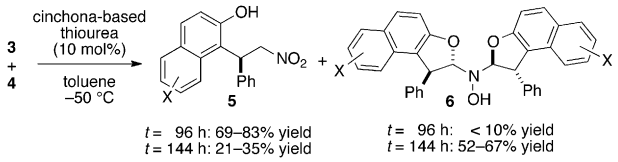

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