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Authors: Xin Li, Chen Yang, Jie Wang, Yang Liu, Xiang Ni, and JinPei Cheng

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Catalytic Behavior Study of Bifunctional Hydrogen-Bonding Catalysts Guided by Free Energy Relationship Analyses of Steric Parameters

Chen Yang,^{†,[a]} Jie Wang,^{†,[a]} Yang Liu,^[a] Xiang Ni,^[a] Xin Li,^{*,[a, b]} and Jin-Pei Cheng^[a,b]

Abstract: Free energy relationship (FER) studies to correlate steric parameters against enantiocatalytic performance of bifunctional tertiary-amine hydrogen-bonding type catalysts, including (*S*, *S*)-cyclohexane-1, 2-diamine derived thioureas, *Cinchona* alkaloid derived thioureas and (*S*, *S*)-cyclohexane-1, 2-diamine derived squaramides, for Michael reactions revealed that the Michael reactions are much favored by catalysts with less bulky *N*-substituents. The observed FERs are independent of chiral scaffold and hydrogen-bond donors, deepening the understanding of current bifunctional hydrogen-bonding catalysts. Moreover, DFT calculations were performed to interpret the observed high reactivities of thioureas with less bulky substituents. Especially, the computations demonstrated the advantage of benzyl thiourea catalyst, in which extra CH- π interaction of hydrogen bond between catalyst and substrate should be the key point.

Introduction

Quantitative descriptions of the interrelationships between structure and reactivity are the central issue of physical organic chemistry.^[1] Among the numerous principles established in past, now the most frequently used is still the (linear) free energy relationship (FER) analysis method, which has also proved its value for better understanding of asymmetric reactions.^[2]

In principle, establishing a correlation between the catalyst property and enantioselectivity depends on whether or not the difference in the two transition states (TSs) free energies of the enantiodetermining step in a specific reaction is primarily determined by the structural features of the catalyst (Figure 1), which are reflected by various parameters of molecules, such as Hammett constants,^[3] Charton values,^[4] pK_as,^[5] and so on. Hence, the goal to achieve useful relationships may be realized by manipulating the mathematical function $\Delta \Delta G^{\neq} = F(M_1, \cdots, M_n, \cdots, M_n)$, in which M_i represents the relevant parameter of the

- [a] C. Yang,⁺ J. Wang,⁺ Y. Liu, Dr. X. Ni, Prof. Dr. X. Li, Prof. Dr. J.-P. Cheng State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin 300071 (P. R. China). E-mail: xin_li@nankai.edu.cn
- [b] Prof. Dr. X. Li, Prof. Dr. J.-P. Cheng Collaborative Innovation Center of Chemical Science and Engineering, Tianjin 300071 (P. R. China).
- [+] These authors contributed equally to this work.

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Figure 1. Relationship between catalyst structure and enantiocatalytic performance in asymmetric reactions.

catalyst molecule. In fact, the seminal work of Jacobsen et al., who applied the linear FER as a probe to diagnose the performance of catalyst in asymmetric epoxidations of *cis*alkenes,¹⁶¹ much stimulated the research endeavors in this regard. On this basis, prediction of new chemical transformations has also started to emerge recently (Figure 2).^[2, 7-9] In this context, Sigman and co-workers have made remarkable contributions in finding correlations between the



Figure 2. Overview of probing asymmetric reactions by virtue of physical organic parameters.

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outcomes of asymmetric reactions and the two-, three-, or multiple dimensional models by employing a set of steric, electronic, and molecular vibrational parameters.^[2,7] Increased research attention in this area is also reflected by a number of recent investigations.^[8] However, cases focused on organocatalysis are still limited.^[7d,e,j, 8c,e-g,o]

It is well realized that the hydrogen-bonding interaction, due to its universal existence in nature, has become a prominent mode in exploring organocatalysis for useful transformations.^[10] Intensive efforts have been made on elucidating mechanisms in this connection by using either experimental or computational approaches. However, investigations to link the stereoselectivity of reaction with the performance of the catalysts remain elusive till present, and due to its great potential in guiding the design of new catalysts, it warrants immediate explorations.^[8e-h,o] Especially, given the fact that 3,5-bis(trifluoromethyl)phenyl, 3,5-bis(trifluoromethyl)benzyl, fluorinated ethyl as well as benzyl and methyl groups come forth in lots of privileged bifunctional hydrogen-bonding catalysts (Figure 3), the reason behind these phenomena need more rational explanations.



Figure 3. Representative tertiary-amine (thio)ureas/squaramide catalysts.

Herein, we evaluated three types of chiral bifunctional catalysts, including (S, S)-cyclohexane-1,2-diamine derived thioureas, *Cinchona* alkaloid derived thioureas and (S, S)-cyclohexane-1,2-diamine derived squaramides to reveal the effect of substituent group adhere to N-H hydrogen bonds on the Michael reaction enantioselectivities.

Results and Discussion

Among the hydrogen-bonding organocatalyst family,^[10] many bifunctional chiral (thio)ureas, such as Jacobsen catalysts,^[11] Takemoto catalyst,^[12] *cinchona*-type catalyst^[13] and BINOL derived catalyst,^[14] have been explored to achieve various asymmetric transformations.^[15] Subsequently, Rawal^[16a-e] found that squaramides can also serve as excellent hydrogen-bonding catalysts.^[16] If we look back to inspect the process of the catalyst's designing and/or optimization, one will find electronictuning strategy is widely used and proved to be very effective. Since the proton-donating ability is associated with hydrogenbond strengthening, the acidities (pK_as) of catalysts, which trend is generally consistent with the electronic effect, have been extensively studied.^[8h,17,18] Indeed, we observed a linear FER correlation between products' enantioselectivities and cataysts' pK_{as} in the Michael addition of diethyl malonate to nitrostyrene with catalyzed by three type meta- and/or para-substituted aromatic tertiary-amine thioureas.^[8h] However, We also noticed that alkyl substituted thioureas did not follow the correlation in that case. In 2014, Pápai and Soós[16f] found benzyl diaminocyclohexane-based squaramide catalyst without electronic perturbation can also lead to excellent enantioinduction in the reaction of acetylacetone and nitrostyrene.[19] Very recently, in the Michael addition of 3-substituted benzofuranones to alkyl 2phthalimidoacrylates, our group found that the methyl thiourea catalyst with the smallest alkyl substituent can induce as high stereoselectivities as 3,5-bis(trifluoromethyl)benzyl thiourea did.[80] These new findings remind us to revisit the role of steric hindrance properties of the bifunctional thioureas/squaramides in the stereocontrol for the mode Michael addition.

Table 1. Profiles of thioureas catalyzed model reaction.[a]

Ph NO	² + EtC	0₂C CO₂Et . 2a		S EtO ₂ ¢ t Pł	C CO ₂ Et NO ₂ 3a	
Cat	р <i>К</i> а ^[b]	k _{initial} min ^{-1[c]}	Yield(%) ^[d]	e.r. ^[e]	∆∆G [≠] (er) ^[f]	
4a (H)	-	4.12E-5	13	89.2:10.8	1.25	
4b (Me)	20.5	9.07E-4	78	86.0:14.0	1.07	
4c (Et)	21.0	8.63E-4	76	84.8:15.2	1.02	
4d (<i>i</i> Pr)	21.6	1.03E-3	88	82.7:17.3	0.93	
4e (Bn)	20.2	1.57E-3	91	88.7:11.3	1.22	
4f (<i>c</i> Hex)	20.5 ^[g]	8.95E-4	72	80.6:19.4	0.84	
4g (Ph)	17.0 ^[g]	1.15E-4	50	85.3:14.7	1.04	
4h (<i>t</i> Bu)	21.4	8.91E-5	41	72.4:27.6	0.57	
4i (Et ₃ C)	21.2	1.56E-4	41	67.1:32.9	0.42	
4j (CHPh ₂)	-	1.45E-3	90	83.6:16.4	0.96	

[a] The reaction was conducted with **1a** (0.1 mmol), **2a** (0.15 mmol) and 20 mol% catalyst in 0.4 mL toluene at room temperature for 48h. [b] pK_a values of catalysts were determined in DMSO via UV spectrophotometric titrations.^[20] [c] Isolated yield. [d] Initial rates were determined in C₆D₆ according to ref. 8h. [e] Determined by HPLC analysis. [f] $\Delta\Delta G^{\pm}$ =RTIn(e.r.), R= 0.001986 kcal/K/mol, T=298.15K. [g] Taken from ref. 8h.

Firstly, nine (S, S)-cyclohexane-1,2-diamine based tertiaryamine thiourea catalysts (4a-4i) with different size substituents were evaluated in the model reaction (Table 1). The robust multifaceted Sterimol parameters (B1, B5, L) were chosen to perform the following correlative steric analyses.^[21] By performing a stepwise regression,^[22] the dependence of the enantioselectivity $(\Delta\Delta G^{\neq})$ on substituents was determined as $\Delta\Delta G^{\neq}$ = -0.49*B₁+0.04*B₅+1.7 with a confidence level of 95% (determined by an f-test, similarly hereinafter). As shown in Figure 4, a very good linear plot between predicted and experimentally measured $\Delta\Delta G$ $^{\scriptscriptstyle \neq}$ values indicated a strong positive correlation between substituents and catalytic enantioselective results. The negative coefficient of B1 reflects the present reaction requests a catalyst with a minimum width substituent to induce high enantioselectivity, while the width of substituent (B₅) impacts the enantioselectivity a little. This outcome is somewhat non-intuitive, because a general ligand and catalyst design practice is to use a component of larger size in order to achieve better stereoselective outcome.[7a, 8o] The nature of the correlation between steric parameters and observed enantioselectivities was also maintained for the Michael reaction of ortho-chloro nitrostvrene (Figure S1) and the reaction of dibenzoylmethane to alkyl nitrostyrene (Figure S2). The simplest catalyst 4a can induce highest enantioselectivity. but its poor solubility in apolar solvents precludes the practical application. Benzyl, followed by methyl, ethyl and phenyl, all exhibited good ability of stereoselective induction. The further electronical optimizations on phenyl and benzyl groups have led to the discovery of Takemoto catalyst^[12] and Li & Cheng catalyst^[80] respectively. The fluorinated ethyl catalyst has been successfully used in several asymmetric reactions.[23] Very recently, we also proved that methyl catalyst can induce excellent stereoselectivities in our recent report.[80] These findings indicated the power of FER analyses in understanding of catalytic behavior.



Figure 4. FER analysis of Cyclohexane-1, 2-diamine derived thioureas.

The determination of initial rates^[24] indicated that the steric effect had negative influence on the activity, albeit no linear correlation was observed. Interestingly, the reaction catalyzed by alkyl catalysts (e.g. **4b**, **4d**, **4e**) shared faster rates than that catalyzed by phenyl catalyst **4g**, especially the benzyl catalyst **4e** shared a most fast rate among studied catalyst (Table 1). It

should be noted that, the lower reaction rate of **4a** was attributed to its very low concentration in the reaction. Additionally, we also noticed there is no correlation between the catalyst acidities and the enantioselectivities, if the aryl and alkyl substituted catalysts were considered together (Figure S3). Less acidic alkyl catalysts, such as **4b**, **4c** and **4e** can induce good enantioselectivities as good as more acidic phenyl catalysts, indicating acidity may not be the key factor in control of catalytic performance for alkyl catalysts.

Table 2. DFT calculation results for catalysts 4b, 4e and 4g. ^[a]						
Cat.	TS	∆G [≠] (kcal/mol)	рі (%)	e.r. (calc.)	e.r. (exptl.)	
4b (Me)	4b-B-S	18.2	92.5	93.2:6.8	86.0:14.0	
	4b-B-R	19.8	6.8			
	4b-A-S	21.2	0.7			
	4b-A-R	26.2	0.0			
4e (Bn)	4e-B-S ₁	16.4	90.2	92.6:7.4	88.7:11.3	
	4e-B-S ₂	18.6	2.3			
	4e-B-R ₁	17.9	7.3			
	4e-B-R ₂	20.5	0.1			
	4e-A-S ₁	22.6	0.0			
	4e-A-S ₂	20.7	0.1			
	4e-A-R1	24.4	0.0			
	4e-A-R ₂	24.3	0.0			
4g (Ph)	4g-B-S	19.3	73.9	89.0:11.0 8		
	4g-B-R	20.4	11.0		05 2.14 7	
	4g-A-S	20.2	15.1		00.3.14.7	
	4g-A-R	27.1	0.0			

[a] Active energies of transition states are calculated according to solution-phase (Toluene) Gibbs free energies: $\Delta G^{*}=G_{Ts}-G_{acet/ideatone^{-}}G_{nitrostyrene^{-}}G_{cat}$. The distribution of product is calculated using Maxwell-Boltzmann statistics: p=100*exp(- $\Delta G_{i}^{*}/RT)/\Sigma(exp(-\Delta G_{i}^{*}/RT))$, where ΔG_{i}^{*} represents the activation energy of corresponding transition state.

Subsequently, DFT calculations^[25-28]were performed to rationalize the difference of rates between alkyl and aryl substituents as well as to figure out the reason why benzyl catalyst shared a most fast rate and highest enantioselectivity (Table 2, Figure 5-7). Two popular dual activation paths have been proposed in the Michael addition reaction of diethyl malonate to nitrostyrene.[16f, 26] Path A involves the activation of the nucleophile and electrophile by tertiary amine and thiourea, respectively. In Path B, the protonated amine interacts with the electrophile, while the thiourea stabilizes the deprotonated nucleophile. Taking 4b, 4e and 4g as model catalysts, corresponding transition states of the model reaction (Figure 5-7 were calculated according to the above mentioned two activation models. The calculated results were outlined in Table 2. It was found that path B may be the most possible reaction route for catalyst 4b, 4e and 4g. However, path A cannot be excluded in the case of 4g, which shares a 15% portion.^[26] The calculated stereoselectivities reproduced the experimental observations very well, indicating the calculations are applicable for the current system (Table 2). The active energies of TSs for 4b, 4e and 4g leading to main product were predicted as 18.2, 16.4 and and 19.3 kcal/mol respectively, which agreed well with the

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determined rates for **4b** (9.07E-4), **4e** (1.57E-3) and **4g** (1.15E-4). Compared to phenyl catalyst, the model reaction catalyzed by alkyl catalysts possesses a lower energetic barrier, which should be responsible for the fast reaction rates.



Figure 5. Relative energies and optimized transition-state geometries in the model reaction catalyzed by 4b (units: kcal/mol).

We then turned our attention to make sense of the peculiar action of catalyst 4e, which showed both the fastest reaction rate and the highest enantiomeric ratio. The key feature of benzyl group can be reflected by its flexibility^[29] and aromatic ring, which should be the origin of the observed good performance. Thus, two typical conformation of benzyl group in TSs were calculated (Figure 6). In the two typical transition states leading to major (S) enantiomer, TS 4e-B-S1 is predicted to be more stable than TS 4e-B-S₂ by 2.2 kcal/mol (Figure 6). Similarly, in the transition states leading to minor (R) enantiomer, TS 4e-B-R1 is predicted to be more stable than TS 4e-B-R₂ by 2.6 kcal/mol. These data suggested extra interactions between benzyl group and substrate stabilized corresponding transition states. The following noncovalent interaction analysis $^{[\,30\,]}$ of TS 4e-B-S1 confirmed the existence of extra CH- π and CH-O interactions^[31] (Figure 6 and 8a). It can be deduced that $CH-\pi$ interactions $(C68-H73-\pi \& C61-H78-\pi, see TS 4e-B-S_1 in Figure 6)$ between benzyl catalyst and electrophile contributed more in the stabilization of the transition state than CH-O interaction between benzylic hydrogen and nucleophile. As a result, the active energy further lowered down to 16.4 kcal/mol. The mentioned CH- π interactions can be clearly seen from the representation of transition state in Van der Waals radii form (Figure 8b). In fact, Houk and Schafmeister et al. have observed that the CH- π interaction can boost reaction rate in an aldol reaction, where reactions catalyzed by N-Bn proline derivative reacted faster than that catalyzed by N-Et derivative.^[32] Due to the different strength of CH-π hydrogen bond in transition states,



Figure 6. Transition-state geometries in the model reaction catalyzed by 4e and their relative energies (units: kcal/mol).

the energy of *R* transition state (4e-B-R₁) is 1.5 kcal/mol higher than the *S* transition state. This calculation is in good agreement with the observed e.r. value of 88.7:11.3 (Table 1). The peculiar performance of **4e** in the Michael reaction of dibenzoylmethane to alkyl nitrostyrene (Figure S2) can also be attributed to the existence of CH- π hydrogen bond between benzylic aromatic ring and vinylic hydrogen in nitrostyrene (Figure S4).^[33] To

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further validate theadvantage of CH- π interaction, we decided to test a "new" catalyst according to the steric analysis. The CHPh₂ substituted thiourea **4j** should show a better performance than the *i*Pr substituted catalyst **4d** for existence of CH- π interaction, although **4j** possesses a slightly bigger steric effect than **4d**. As expected, **4j** exhibited a better enantioselective inducement and a faster reaction rate (1.45E-3) than **4d**. This phenomenon reminds us a "butterfly" substituent like CHPh2 may be a better choice in some reactions. Indeed, a recent report from the Soós group achieved an asymmetric Robinson annulation reaction with a CHNaph2 derived bifunctional organocatalyst.^[34]



Figure 7. Relative energies and optimized transition-state geometries in the model reaction catalyzed by 4g (units: kcal/mol).



Figure 8. (a) Local nonovalent interactions in TS 4e-B-S₁; (b) Representation of 4e-B-S₁ in Van der Waals radii.

We speculated the above mentioned FER relationship may be universal in similar tertiary-amine (thio)ureas/squaramide systems. Thus, two set of catalytic systems were next inspected (Table 3-4, Figure 9-10). For *Cinchona* alkaloid derived thioureas (**5a-5g**), the equation was determined as $\Delta\Delta G^{*} = 0.54^{*}B_{1}+0.079^{*}L+1.7$. The slope of the plot is 0.91 and the intercept is 0.067, which indicated the enantioselectivities correlated well with the substituents (Figure 9). Since the methyl, ethyl, benzyl and phenyl substituents are still optimal candidates, the relationship maintains the same form regardless of the alternation of chiral scaffold. Holding the (*S*, *S*)-cyclohexane-1,2-diamine scaffold still, the relationship are expected to be kindred when changing the hydrogen-bonding section from thioureas to squaramides. Thus, a set of squaramides (**6a-6f**) were evaluated (Table 4). It should be noted that 1,3-diphenylpropane-1,3-dione was used to replace diethyl malonate for the Michael addition of diethyl malonate to nitrostyrene catalyzed by **6** didn't work under our conditions. Meanwhile, 4 mol% catalysts were used for their poor solubility. The best-fit



[a] The reaction was conducted with **1a** (0.1 mmol), **2a** (0.15 mmol) and 20 mol% catalyst in 0.4 mL toluene at room temperature for 48h. [b] Isolated yield. [c] Determined by HPLC analysis. [d] $\Delta\Delta G^{\ddagger}$ =RTIn(e.r.), R= 0.001986 kcal/K/mol, T=298.15K.

equation was determined as $\Delta\Delta G^{\neq} = -0.72*B_1-0.19*L+3.2$. The plot of the predicted and experimentally measured $\Delta\Delta G^{\neq}$ values shows a good linear correlation with a slope of 0.93 and a y intercept of 0.077 (Figure 10). The correlation pointed out that methyl, ethyl and benzyl substituents are still optimal candidates Interestingly, phenyl was not a suitable substituent for the Michael addition studied here. It could be anticipated that electronic perturbation of benzyl rather than phenyl may further promote the enantioselectivity for this Michael reaction. This finding is in line with the results reported by the Rawal group, who firstly introduced 3,5-bis(trifluoromethyl)benzyl squaramide to organocatalysis in 2008.^[19] Though one could think that the methyl group is too small to affect the enantioselectivities, the good performance of methyl squaramide confirmed its value and may make itself applicable in some transformations in future.^[80]

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Figure 9. FER analysis of Cinchona alkaloid derived thioureas.

Overall, we observed kindred FERs in the three classic bifunctional hydrogen-bonding organocatalyst families, which confirmed the steric effects on enantioselectivities at least in Michael reactions. All FERs pointed out the Michael reactions catalyzed under catalysts with less hindrance substituents would be favorable. The observed FERs are independent of chiral scaffold and hydrogen-bond donors, toning up our of bifunctional understanding current tertiary-amine (thio)ureas/squaramides (Figure 3). The FER tactic may also lend us much help to design new catalysts.



Ph NO ₂ +			
1a Cat	2b Yield(%) ^[b]	e.r. ^[c]	ΔΔG [≠] (er) ^[d]
6a (Me)	48	92.4:7.6	1.476
6b (Et)	40	91.4:8.6	1.399
6c (<i>i</i> Pr)	46	89.0:11.0	1.240
6d (Bn)	62	89.9:10.1	1.296
6e (Ph)	54	77.7:23.3	0.738
6f (<i>t</i> Bu)	40	71.3:28.7	0.539

[a] The reaction was conducted with **1a** (0.1 mmol), **2a** (0.15 mmol) and 4 mol% catalyst in 0.4 mL toluene at room temperature for 48h. [b] Isolated yield. [c] Determined by HPLC analysis. [d] $\Delta\Delta G^{\pm}$ =RTIn(e.r.), R= 0.001986 kcal/K/mol, T=298.15K.



Figure 10. FER analysis of cyclohexane-1, 2-diamine derived squaramides.

Conclusions

In summary, we have conducted FER analyses of enantiomeric ratios against the steric parameters for three type bifunctional tertiary-amine thioureas/squaramides, including (S, S)cyclohexane-1, 2-diamine derived thioureas, Cinchona alkaloid derived thioureas and (S, S)-cyclohexane-1, 2-diamine derived squaramides, in Michael reactions. Kindred FERs revealed that tertiary-amine hydrogen-bonding catalysts bearing an Nsubstituent of smaller size should be promising catalyst candidates, which are applicable for further electronic modulations. DFT calculations were performed to investigate high reactivity of alkyl thioureas as well as the peculiar performance of a benzyl catalyst. The CH- π interaction was proposed to interpret the high reactivity of benzyl catalyst. Nevertheless, a complete mechanistic picture that accounts for the observed correlation between steric parameters and enantioselectivities is yet to emerge. More calculations are underway in our laboratory.

Experimental Section

Catalysts **4b-4j** were synthesized according to our previous report.^[8o] **Synthesis of 4a**.^[35] Benzoyl isothiocyanate (6.0 mmol) was dissolved in CH₂Cl₂ (10 mL) and cooled to 0 °C. (*S*, *S*)-*N*,*N*-dimethylcyclohexane-1,2diamine (6.6 mmol) was added dropwise. The resulting mixture was warmed to room temperature and stirred for 2h. Then, the mixture was washed with water (5 mL), dried over Na₂SO₄. Concentration under vaccum gave the *N*-((1*S*,*2S*)-2-(dimethylamino)cyclohexyl)benzamide as a white solid in 83% yield. The obtained compound was dissolved in ethanol (10 mL). Then aqueous potassium carbonate (0.76 g) was added The mixture was stirred at reflux temperature for 4h. When the reaction is completed, the mixture was concentrated to a small volume and filtrated. The product was washed with petroleum ether and dried in vacuo to give **4a** as a white solid (0.3 g).

General Procedure A for Synthesis of Catalysts 5.^[13a] 9-amino quinidine (2.0 mmol) and corresponding isocyanate (2.1 mmol) were stirred overnight in 5.0 ml dry CH_2Cl_2 under argon atmosphere. Then the reaction mixture was concentrated in vacuo. The residue was subjected to column chromatography on silica gel to afford the desired catalysts 5.

General Procedure B for Synthesis of Catalysts 6.^[16a] Substituted amine (2.1 mmol) was added to a CH_2Cl_2 solution of dimethylsquatate (2.0 mmol) under argon atmosphere. The mixture was stirred for 24h. Then it was filtered and the filtrate was washed with 1M HCI. The organic layer was dried, filtered and concentrated to afford a mono-aminosubstituted squarate. The obtained squarate (1.0 mmol) was dissolved in 10mL MeOH under argon atmosphere. Then (*S*, *S*)-*N*,*N*dimethylcyclohexane-1,2-diamine (1.1 mmol) was added. After it was stirred for 24h, the mixture was filtered. The precipitate was washed with cold MeOH for three times to afford squaramide **6**.

General procedure for Michael addition reactions. Nitrostyrene 1 (0.1 mmol) and diethyl malonate 2 (0.15 mmol) were stirred in 0.4 ml toluene at room temperature in the presence of 20 mol % catalyst for 48h. The reaction mixture was directly subjected to column chromatography on silica gel (EtOAc: Petroleum ether 1:10) to afford the desired products **3**.

Computational methods. The structures of all species were calculated with the GAUSSIAN 09 packages at M06-2X/6-31+G(d) level. The solution phase free energy calculations (in toluene) were performed with SMD model at the B97D/6-311++G(d,p) level. For consideration of simplicity and saving time, diethyl malonate was replaced by acetylacetone in all calculations. The nature of the stationary points was confirmed by frequency calculations at the M06-2X/6-31+G(d) level. Transition states were confirmed by frequency calculations to have only one imaginary frequency using the same level of theory. Structures were generated using CYLview, ³⁶ Multiwfn, ³⁷ VMD ³⁸ and Pov-Ray ³⁹ packages. All the bond lengths are in angstroms (Å).

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Keywords: bifunctional hydrogen-bonding catalysis • free energy relationship • density functional calculations • steric analyses

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Free energy relationship studies to correlate steric parameters against enantiocatalytic performance of bifunctional tertiary-amine hydrogenbonding type catalysts, including (*S*, *S*)-cyclohexane-1, 2-diamine derived thioureas, *Cinchona* alkaloid derived thioureas and (*S*, *S*)-cyclohexane-1, 2-diamine derived squaramides, for Michael reactions revealed that the Michael reactions are much favored by catalysts with less bulky *N*substituents.



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Catalytic Behavior Study of Bifunctional Hydrogen-Bonding Catalysts Guided by Free Energy Relationship Analyses of Steric Parameters

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