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Physical Organic Study of Structure–Activity–Enantioselectivity Relationships in Asymmetric Bifunctional Thiourea Catalysis: Hints for the Design of New Organocatalysts

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Hydrogen-bonding catalysis, which is ubiquitous in nature, has become a prominent organocatalytic motif that enables a broad range of transformations.[1] Among a variety of hydrogen-bonding organocatalysts explored so far, chiral thioureas have received special attention owing to their bidentate N–H hydrogen-bonding ability for versatile bi- or multifunctional catalysis as in the cases such as the Jacobsen catalyst,[2] Takemoto catalyst,[3] the cinchona-type catalysts,[4] and so on.[5] Although intensive research efforts have been devoted to studying the mechanism of bifunctional thiourea catalysis by using either experimental or computational approaches,[1,6] the in-depth knowledge is still substantially lacking and the use, therefore, for new catalyst designs remains elusive and warrants further exploration. In this regard, few studies have been performed on systematic examination of the structure–activity–stereoselectivity relationship, particularly from the point view of electronic effects on this type of catalysis.[7]

Physical organic parameters have long been used as powerful tools towards understanding reaction mechanisms and to serve as guidelines for the development of novel reactions as well as for the design of new catalysts. Recently, Mayr and co-workers reported the quantitative measure of nucleophilicities for a series of amines to interpret their organocatalytic behaviors, elegantly illustrating the power of physical organic parameters in guiding modern asymmetric catalysis.[8] However, the classical physical organic parameters of chiral thiourea catalysts, such as pK_a values, which are essential for evaluating their hydrogen-bonding capability, are still missing. Although electronic tuning has been practiced in some of the catalyst designs on a qualitative basis,[1a] the quantitative connections between electronic effects (pK_a values) and stereoselectivity, which would be helpful guidance for designing new catalysts, have been largely overlooked. In a single case, a linear free energy relationship (LFER) was observed between catalyst acidity and enantioselectivity in hydrogen-bonding catalyzed Diels–Alder reactions of Rawal's diene.[9] However, the direct indicator of the intrinsic hydrogen-bond-donating ability, that is, the absolute acidity scale (pK_a) of the catalysts, was not applied for the correlation. Herein, we report the first pK_a scales for chiral thiourea catalysts and their correlations with the corresponding parameters of the bifunctional catalysis. The experimentally determined pK_a values not only make direct comparisons of thioureas with either conjugated or nonconjugated substitutes possible, but also allow prediction of possible behaviors of analogous organocatalysts with varied skeletons.

With Takemoto's catalyst as a prototype, three different classes of thiourea–tertiary amine conjugates that represents the currently most widely applied skeletons, namely, cyclohexadiamine (Takemoto and Jacobsen catalysts), cinchona, and amino acid,[10] were chosen in this study. Accordingly, twenty chiral thiourea–tertiary amine compounds were synthesized and electronic variations were easily introduced in the thiourea moieties with either substituted aryl groups or alkyl groups (Table 1). The pK_a values were determined in DMSO by using the well-established overlapping indicator method.[11] As shown in Table 1, the chiral thioureas **1**, **2**,

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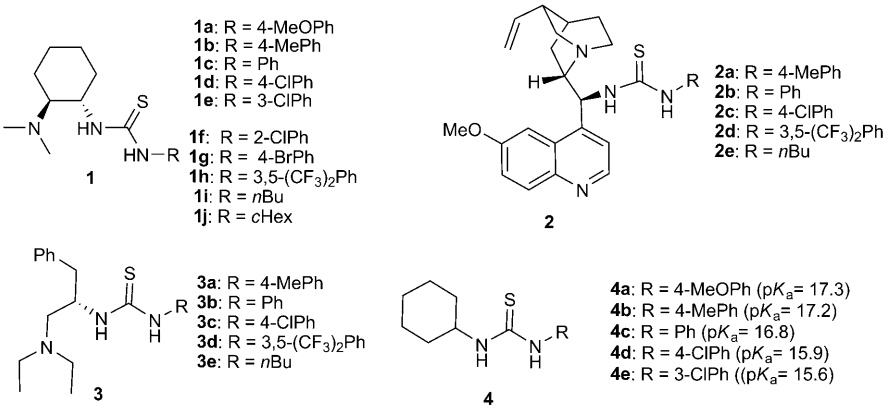
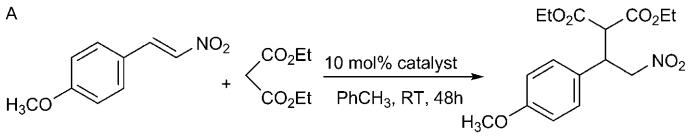


Table 1. The pK_a values of thiourea–tertiary amines and their catalytic results in the Michael addition of diethyl malonate to nitrostyrene (A).[a]



Catalyst	pK_a[b]	$k_{initial}$ [min^{-1}][c]	R/S[d]
1a	17.6	2.36×10^{-5}	7.5
1b	17.5	2.49×10^{-5}	7.9
1c	17.0	3.06×10^{-5}	8.9
1d	16.1	5.78×10^{-5}	10.6
1e	15.7	6.74×10^{-5}	11.8
1f	15.2	2.89×10^{-5}	6.4
1g	16.0	5.95×10^{-5}	11.0
1h	13.8	3.90×10^{-4}	20.7
1i	21.1	1.60×10^{-4}	7.8
1j	20.5	5.69×10^{-5}	5.8
2a	16.2	5.62×10^{-5}	7.3
2b	15.8	8.13×10^{-5}	7.8
2c	15.2	1.58×10^{-5}	8.7
2d	13.2	5.42×10^{-5}	16.2
2e	19.5	6.57×10^{-5}	6.5
3a	16.9	6.13×10^{-5}	7.8
3b	16.3	9.75×10^{-5}	8.9
3c	15.5	1.61×10^{-5}	9.9
3d	13.3	8.95×10^{-5}	20.3
3e	19.9	1.75×10^{-5}	8.0

[a] The reaction was carried out on a 0.1 mmol scale in toluene (200 μL) at room temperature and the molar ratio of diethyl malonate/nitroolefin was 2:1. [b] Determined by using overlapping indicator methods in DMSO with the uncertainty of ±0.1. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis.

and **3** have pK_a values greater than 13.2, indicating that they are generally less acidic than AcOH (pK_a=12.3 in DMSO).[12] From further comparison of the pK_a values of catalysts **1** with other thioureas, the pK_a values of which were known, we found that the acidities of the studied Takemoto's catalysts are a little weaker than $(PhNH)_2C{=}S$ (pK_a=13.4 in DMSO),[12] and much stronger than $(NH_2)_2C{=}S$ (pK_a=21.1 in DMSO).[12] As expected, the pK_a values of aryl thioureas were found to correlate linearly with the corresponding Hammet σ constant (see the Supporting Information). Notably, it has been determined in our studies that the dimethyl amino group generally decreases the overall acidity of thioureas **1** by 0.1–0.3 pK_a relative to the parent catalyst **4**. This observation indicates that the experimentally determined pK_a values give an overall evaluation of the intrinsic acidity of bifunctional thioureas by taking into consideration of the impact of the tertiary amine group.

The Michael addition reaction[13] of diethyl malonate to nitrostyrene was selected as our initial test reaction (Table 1). The same reaction has been frequently used as a testing ground for new catalyst development.[3,10] To probe the electronic effects on catalysis, thioureas **1**, **2**, and **3** were subjected to the model reaction, and the corresponding enantioselectivity and initial rate were determined (Table 1).

Inspection of the data in Table 1 reveals that, in general, more acidic catalysts give faster reaction times and better enantioselectivities. To verify the observed trend, plots of the experimentally determined pK_a values versus the logarithm of the initial rate and enantiomeric ratio, respectively, were constructed. Excellent LFERs were observed for both initial reaction rates and enantioselectivity for all three sets of reactions catalyzed by thiourea catalysts **1**, **2**, and **3** with *meta*- and/or *para*-substituted aromatic groups (Figure 1). These results represent, to the best of our knowledge, the first reported LFERs in asymmetric bifunctional catalysis. In addition, the LFER slopes were found to be nearly constant for all three types of bifunctional thiourea-catalyzed reactions, both in terms of the pK_a–log(k) correlations (Figure 1a) and the pK_a–log(R/S) correlations (Figure 1b), with a slope of -0.31 ± 0.01 for the former and slope -0.11 ± 0.01 for the latter. Despite the considerable differences in the skeletons and in the tertiary amino moieties, the obtained parallel LFERs suggest that the working mechanism, that is, the general pattern of forming the transition state in the reaction coordinate, should remain quite similar for all of these catalysts. The LFER, which is independent of the specific thiourea catalysts employed, should thus reflect the intrinsic electronic properties of the reactions under investigation.

Deviation from the LFERs was observed for *ortho* substituents (i.e., **1f**) and for aliphatic ones such as **1i**, **1j**, **2e**, and **3e**. This observation is not totally unexpected because *ortho* and alkyl substituents normally exhibit quite distinctive behaviors owing to steric effects. Consequently, it has been a standard practice to exclude *ortho* and adjacent alkyl substituents from single-parameter LFER analysis.[14] Also note that the performance of **1f** (pK_a=15.2) lies far below that of *meta*- or *para*-substituted aromatic thioureas, whereas the alkyl-substituted thioureas (pK_a values=19.5–21.1),

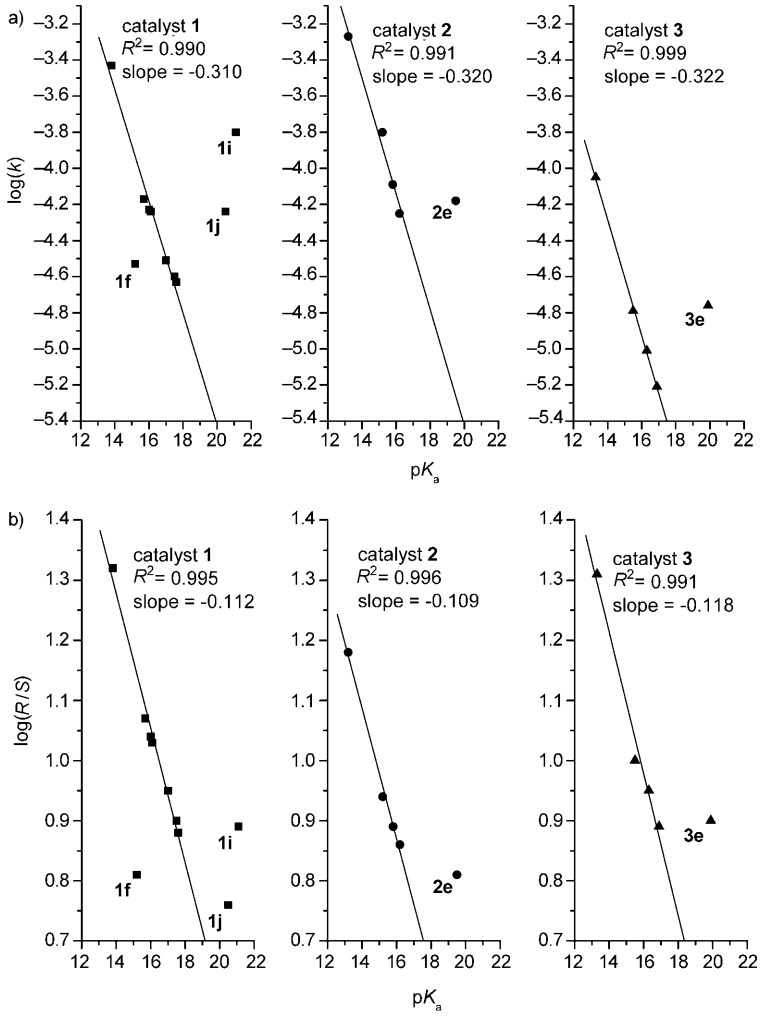


Figure 1. Correlations of pK_a values with reaction rate (a) and enantioselectivity (b) in the Michael addition of diethyl malonate to nitrostyrene (model A).

which are less acidic than their aromatic counterparts, demonstrated even higher activity and better enantioselectivity (Table 1, also see Figure 1). Similar phenomena were observed with three different catalysts in the model reaction A.

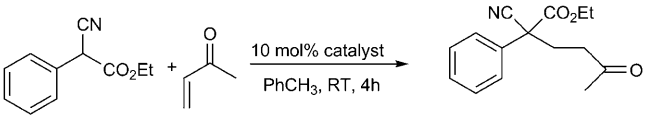
To verify the LFERs further and to prove their general applications, two other different Michael addition reactions[15,4a] were also investigated by using catalyst **1a**–**1j** (Table 2, reaction B and C). The reactions were selected because these structurally varied reaction partners often demonstrate quite distinctive hydrogen-binding modes. Again, excellent LFERs both in terms of the activity and stereoselectivity were obtained for reactions B and C (see Figure 2 and Figure 3, respectively).[16] In both cases, the correlations of *meta* and/or *para*-substituted aromatic thioureas obeyed the LFERs, whereas those of *ortho*-substituted aromatic thioureas such as **1f** and aliphatic thioureas such as **1i** and **1j** deviated from the lines. Their catalytic behaviors were shown to be highly consistent with those observed in reaction A. In all of these cases, negative slopes were obtained in the LFERs, suggesting a general trend, that is, the more acidic catalyst leads to faster reaction times and better enantioselectivities, for the bifunctional catalysis under investigation.

As previously proposed,[2–4,6] the mechanism for bifunctional thiourea catalysis should involve a ternary complex in the transition state wherein simultaneous activation of the two reactants through multiple hydrogen bonding occurs prior to the C–C bond formation. The current studies indicate that a single spot electronic tuning may considerably impact the overall hydrogen-bonding affinity and geometry,[17] leading to significantly varied catalytic outcomes. In addition, the proven LFERs in different reactions with different catalysts suggest that LFERs would be prevalent in bifunctional thiourea catalysis, and consequently, highly conserved bifunctional catalytic modes are likely involved with different thioureas catalysts.[3b,6,9]

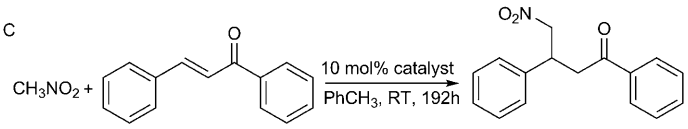
The current results also provide a basis for the development of new bifunctional catalysts through electronic tuning of a single functional group. In this regard, both the LEFRs and their deviations provide useful information for catalyst design. As shown in Figures 1–3, aromatic thioureas may not be favorable structural moieties for bifunctional catalysts, a result ascribed at least partially to the unfavorable steric effect. In this regard, the alkyl groups turned out to be favorable structural features for the present bifunctional catalysis that has not yet been identified.[18] Therefore, alkyl thiourea would serve as a good starting point for the evolution of new catalysts. In our preliminary efforts, simple electronic tuning of the alkyl side chain of **1i** led to a significantly improved catalyst, trifluoroethyl thiourea **5** (pK_a = 16.9) with $k_{initial} = 1.84 \times 10^{-4}\ min^{-1}$ and $R/S = 19.0$ (Scheme 1) for model reaction A, a result comparable to the current best catalyst **1h** (Scheme 1, see the Supporting Information for other examples). Improvements on the enantioselectivity for reaction B and C have also been observed with catalyst **5** over its parent catalyst **1i** (Table 2, Figures 2 and 3). Furthermore, the potentials of the obtained alkyl-substituted thiourea **5** could be demonstrated in a quaternary–tertiary C–C-bond-forming Michael addition reaction, wherein the

Table 2. Evaluation of thiourea–tertiary amine catalysts **1** in other Michael addition reactions. Method B: Ethyl α-phenyl cyanoacetate to methyl vinyl ketone.[a] Method C: CH_3NO_2 to chalcone.[b]

B



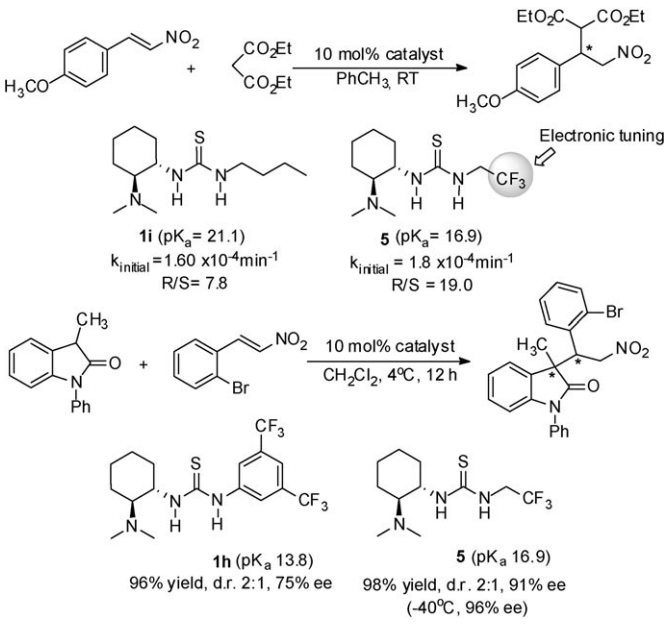
C



Catalyst	$k_{initial}$ (B) [min^{-1}][c]	*R*/*S* (B) [d]	$k_{initial}$ (C) [min^{-1}][c]	*R*/*S* (C)[d]
1a	0.055	1.57	7.24×10^{-6}	5.58
1b	0.060	1.63	7.41×10^{-6}	5.94
1c	0.065	1.65	8.32×10^{-6}	8.09
1d	0.079	1.80	9.55×10^{-6}	9.87
1e	0.093	1.97	1.02×10^{-5}	11.50
1f	0.073	1.73	7.24×10^{-6}	7.85
1g	0.090	1.84	9.77×10^{-6}	10.37
1h	0.145	2.46	1.41×10^{-5}	19.00
1i	0.122	1.75	1.23×10^{-5}	9.00
1j	0.103	1.51	8.91×10^{-6}	7.06
5	0.096	2.39	9.77×10^{-6}	12.33

[a] The reaction was carried out on a 0.1 mmol scale in toluene (200 μL) at room temperature and the molar ratio of ethyl α-phenyl cyanoacetate to methyl vinyl ketone was 1:2. [b] The reaction was carried out on a 0.1 mmol scale in toluene (200 μL) at room temperature and the molar ratio of CH_3NO_2 and chalcone was 3:1. [c] Determined by ^1H NMR spectroscopy. [d] Determined by HPLC analysis.

aromatic thioureas might not be favorable catalysts owing to the steric effect. Indeed, alkyl thiourea **5** exhibited superior performance to the well-recognized aromatic thiourea catalyst **1h** with much improved enantioselectivity in the Michael addition of 3-substituted oxindole to nitrostyrene (Scheme 1).



Scheme 1. Development of a new alkyl thiourea catalyst **5** and its catalytic application.

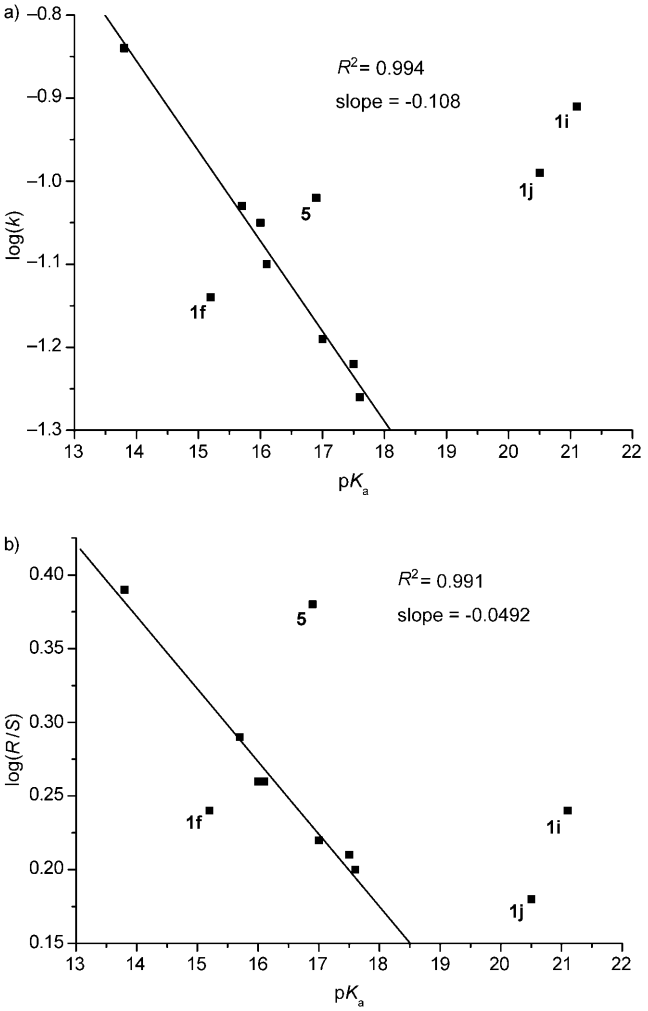


Figure 2. Correlation of pK_a values of thioureas **1** with reaction rate (a) and enantioselectivity (b) for Michael addition reaction of ethyl α-phenyl cyanoacetate to methyl vinyl ketone.

In conclusion, we have experimentally determined the first pK_a scale of a range of asymmetric thiourea catalysts. Correlations of pK_a with catalytic activity and stereoselectivity were presented. Collectively, 1) LFERs were observed for both pK_a–$\log(k)$ and pK_a–$\log(R/S)$ correlations in *meta*- and/or *para*-substituted aromatic thioureas; whereas 2) deviations from the LFERs were observed with *ortho*-substituted aromatic thioureas and alkyl thioureas; 3) structurally distinct thioureas demonstrated highly consistent LFERs with uniform negative slopes in both pK_a–$\log(k)$ and pK_a–$\log(R/S)$ correlations, 4) negative slopes were obtained in all the LFERs, indicating that more acidic catalysts in a structurally related series with remotely varied substituents are generally favored leading to faster reaction and better enantioselectivity; and 5) LFERs as well as the deviation phenomena hold for different Michael addition reactions. Based on the above results, we propose herein that LFERs should be prevalent in other bifunctional thiourea

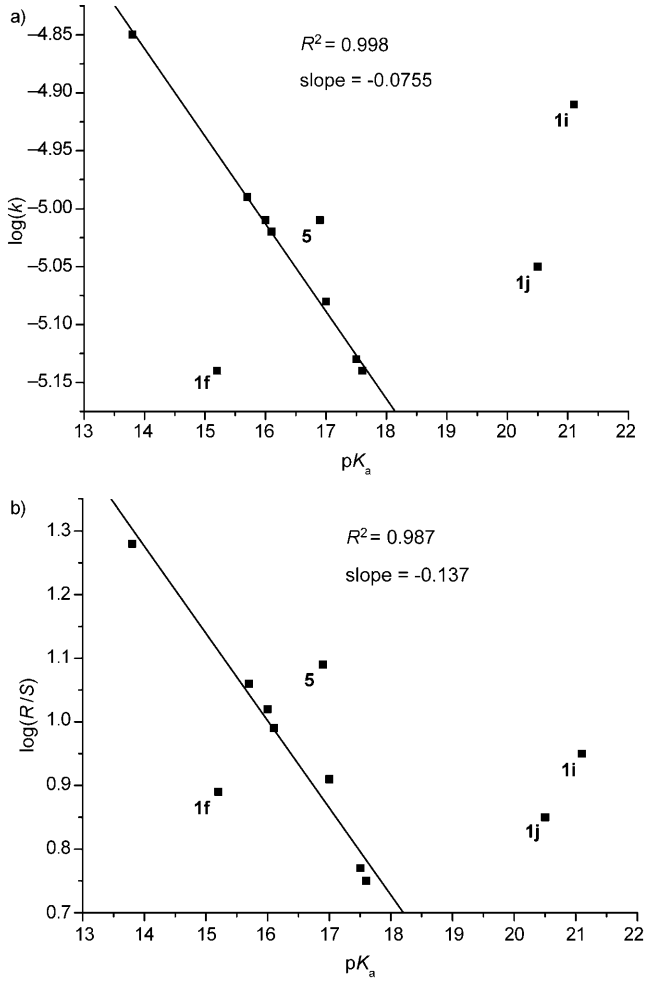


Figure 3. Correlations of pK_a values of thiourea **1** with reaction rate (a) and enantioselectivity (b) for Michael addition reaction of CH_3NO_2 to chalcone.

catalysis and a highly conserved catalytic mode is probably involved in these reactions. In addition, alkyl-substituted thioureas were identified as favorable structures for asymmetric bifunctional catalysis and a significantly improved catalyst **5** was evolved by simple electronic tuning of the alkyl group, demonstrating superior performance in the Michael addition of 3-substituted oxindoles in our preliminary test.

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Keywords: bifunctional catalysis · hydrogen bonds · linear free energy relationships · organocatalysis · pK_a

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