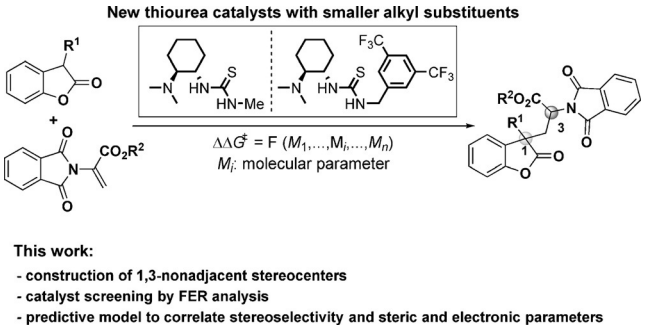
Asymmetric Catalysis

International Edition: DOI: 10.1002/anie.201601028
German Edition: DOI: 10.1002/ange.201601028

Asymmetric Conjugate Addition of Benzofuran-2-ones to Alkyl 2-Phthalimidoacrylates: Modeling Structure–Stereoselectivity Relationships with Steric and Electronic Parameters

Chen Yang, En-Ge Zhang, Xin Li, and Jin-Pei Cheng**

Abstract: *A highly predictive model to correlate the steric and electronic parameters of tertiary amine thiourea catalysts with the stereoselectivity of Michael reactions of 3-substituted benzofuranones and alkyl 2-phthalimidoacrylates is described. As predicted, new 3,5-bis(trifluoromethyl)benzyl- and methyl-substituted tertiary amine thioureas turned out to be highly suitable catalysts for this reaction and enabled the synthesis of enantioenriched α-amino acid derivatives with 1,3-nonadjacent stereogenic centers.*



Scheme 1. Catalyst screening for the Michael addition of 3-substituted benzofuranones and alkyl 2-phthalimidoacrylates by FER analysis.

Benzofuran-2(3*H*)-ones with quaternary stereogenic centers at the 3-position are very important structural motifs of biologically interesting compounds[1] and frequently utilized as versatile chiral building blocks for asymmetric synthesis.[2] Accordingly, various methods have been well established for the synthesis of these compounds.[3] The generation of chiral benzofuranones with one quaternary stereogenic center or two adjacent stereogenic centers has been frequently documented. However, in sharp contrast, highly diastereo- and enantioselective syntheses of chiral benzofuran-2-ones with nonadjacent stereogenic centers in the 1- and 3-position have not been achieved. One conceivable strategy to solve this problem might be the conjugate addition of 3-substituted benzofuran-2-ones to α-branched Michael acceptors. This process has been considered to be a great challenge as it proceeds by tandem conjugate addition–protonation and requires the simultaneous controlled formation of two separated stereogenic centers (Scheme 1).

Chiral bifunctional thioureas with tertiary amine substituents have received particular attention owing to their ability to activate several functionalities, enabling a great variety of asymmetric reactions.[4] However, the dependence of the stereoselectivity of such reactions on the catalyst structure has not be carefully elucidated thus far. The use of free energy relationship (FER) analyses[5] in the realm of asymmetric catalysis has provided some understanding in recent years, which has greatly promoted the rational design of new catalysts and enabled reasonable predictions of new chemical transformations.[6,7] In this context, Sigman and co-workers have made remarkable contributions in finding correlations between the outcomes of asymmetric reactions and two-, three-, or multiple dimensional models by employing a set of steric, electronic, and molecular vibration parameters.[7] Although the increased research activity in this area is reflected by a number of recent investigations, reports that focus on organocatalysis and on bifunctional thiourea catalysts in particular are still limited.[6c,e–g,o,7d,e,j]

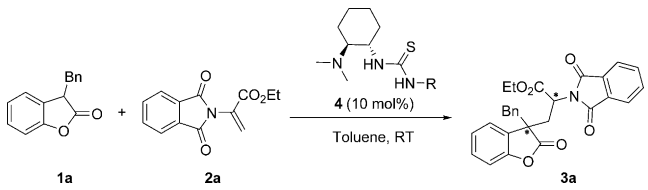
Herein, we report the highly stereoselective Michael addition of 3-substituted benzofuranones to alkyl 2-phthalimidoacrylates that is catalyzed by new bifunctional tertiary amine thioureas with two simple alkyl substituents, which could be applied to synthesize α-amino acid derivatives with tetrasubstituted γ-carbon atoms. The discovery of the new catalysts was based on a FER analysis to determined the catalytic performance of bifunctional thioureas; this approach is completely different from the traditional catalyst screening process (Scheme 1).

Taking the addition of 3-benzylbenzofuranone (**1a**) to 2-phthalimidoacrylate **2a** as the model reaction, we conducted an FER analysis to investigate the effect of structural parameters, that is, steric and electronic factors, on the stereoselectivity achieved with a particular catalyst. (*S*,*S*)-Cyclohexane-1,2-diamine-based tertiary amine thiourea catalysts with different substituents were evaluated first (Table 1, entries 1–9). The choice of proper steric parameters is very important to quantify the correlation.[7h] The extensively used Charton values were unsuitable for our steric analysis (Supporting Information, Figure S1) because they consider the substituents to be spherical. On the other hand, the multifaceted Sterimol parameters (B_1, B_5, L)[8] have been shown to be more robust in the description of steric effects in recent correlative steric analyses. We thus applied this set of parameters in the following analysis.[9]

[*] C. Yang, E.-G. Zhang, Prof. X. Li, Prof. J.-P. Cheng
State Key Laboratory of Elemento-organic Chemistry
Department of Chemistry, Nankai University, and Collaborative Innovation Center of Chemical Science and Engineering
Tianjin 300071 (China)
E-mail: xin_li@nankai.edu.cn
chengjp@nankai.edu.cn

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201601028.

Table 1: Catalyst optimization.[a]



Entry	R	Cat.	Yield[b] [%]	d.r.[c]	$\Delta\Delta G^{\neq}$ (d.r.)[d]	e.r.[e]	$\Delta\Delta G^{\neq}$ (e.r.)[d]
1	Me	**4a**	99	6.71	1.12	13.07	1.52
2	Et	**4b**	99	5.58	1.02	10.28	1.38
3	*i*Pr	**4c**	92	3.07	0.66	5.32	0.99
4	Bn	**4d**	99	4.47	0.89	11.44	1.44
5	*c*Hex	**4e**	89	2.20	0.47	4.72	0.92
6	Ph	**4f**	79	3.67	0.77	4.60	0.89
7	*t*Bu	**4g**	70	2.00	0.41	2.76	0.60
8	CEt_3	**4h**	57	1.05	0.03	1.69	0.31
9	*i*Bu	**4i**	93	4.82	0.93	9.67	1.34
10	4-$MeC_6H_4CH_2$	**4j**	96	4.26	0.86	11.04	1.42
11	4-$ClC_6H_4CH_2$	**4k**	97	4.89	0.94	13.74	1.55
12	4-$CF_3C_6H_4CH_2$	**4l**	98	5.80	1.04	14.86	1.60
13	3,4,5-$F_3C_6H_2CH_2$	**4m**	99	5.07	0.96	16.27	1.65
14	3,5-$(CF_3)_2C_6H_3CH_2$	**4n**	99	4.28	0.86	18.53	1.73
15	CF_3CH_2	**4o**	99	3.66	0.77	15.67	1.63
16	$C_2F_5CH_2$	**4p**	93	3.62	0.76	12.02	1.47
17	3,5-$(CF_3)_2C_6H_3$	**4q**	82	4.61	0.90	8.09	1.24

[a] The reactions were conducted with **1a** (0.1 mmol), **2a** (0.15 mmol), and 10 mol% of the catalyst in toluene (0.5 mL) at RT for 3 days. [b] Yield of isolated product as the average of three runs. [c] Determined by HPLC analysis, averaged over three runs. [d] $\Delta\Delta G^{\neq} = RT\ln$(d.r. or e.r.), $R = 0.001986$ kcal K^{-1} mol^{-1}, $T = 298.15$ K. [e] For the major diastereomer, determined by HPLC analysis on a chiral stationary phase, averaged over three runs.

According to Eq. (1), the dependence of the stereoselectivity ($\Delta\Delta G^{\neq}$) on steric effects can be evaluated, and the coefficients can be determined by performing a stepwise regression (for details, see the Supporting Information).

$$\Delta\Delta G^{\neq} = a\,B_1 + b\,B_5 + c\,L + d \quad (1)$$

$$\Delta\Delta G^{\neq}\,(\text{e.r.}) = -0.73\,B_1 - 0.13\,L + 3.2 \quad (2)$$

$$\Delta\Delta G^{\neq}\,(\text{d.r.}) = -0.62\,B_1 - 0.12\,L + 2.5 \quad (3)$$

For the enantioselectivity, the best fit [Eq. (2)] included B_1 and L terms with $R^2 = 0.92$ and $p = 1.7 \times 10^{-3}$ with a confidence level of 95% (determined by an f-test, similarly hereinafter). A plot of the predicted and experimentally measured $\Delta\Delta G^{\neq}$ values shows a very good linear correlation with a slope of 0.92, a *y* intercept at 0.076, and $R^2 = 0.92$ (Figure 1a). The slope is close to 1.0, and the intercept value is very small, indicating the high predictive power of Eq. (2), which was corroborated by the analysis of additional data (Table 1, entry 9). The negative coefficients of the B_1 and L parameters indicated that a substituent with minimum width and length should be optimal to induce high enantioselectivity. Based on similar principles, we conducted a quantitative analysis of the diastereoselectivity. It was found that the same terms (B_1 and L) are statistically significant for the diastereoselectivity with $R^2 = 0.94$ and $p = 1.0 \times 10^{-3}$ [Eq. (3)]. Good diastereoselectivity should thus be achieved with substituents similar required to those for high enantioselectivity. Comparison of the predicted and experimental diastereoselectivities provided a slope of 0.94, indicating that the predictive power of Eq. (3) is also rather high (Figure 1b). Of particular note is that the observed correlation between the diastereoselectivity and the steric parameters enriched the scope of quantitative structure–selectivity analyses for the first time. Collectively, the analyses of the stereoselectivity suggest that methyl, ethyl, and benzyl substituents, with minimum widths and lengths, should be considered for further optimization.

We tried to further modify these promising candidates by electronic perturbation (Table 1, entries 10–16). The benzyl-substituted thiourea was chosen as the starting point rather than the optimal catalyst **4a** because it is much easier to tune its electronic properties by introducing substituents on the benzyl ring. Interestingly, even though benzyl-substituted squaramide catalysts have been used for a long time,[10] modified benzyl thioureas have never been described (entries 10–14).[11] A very

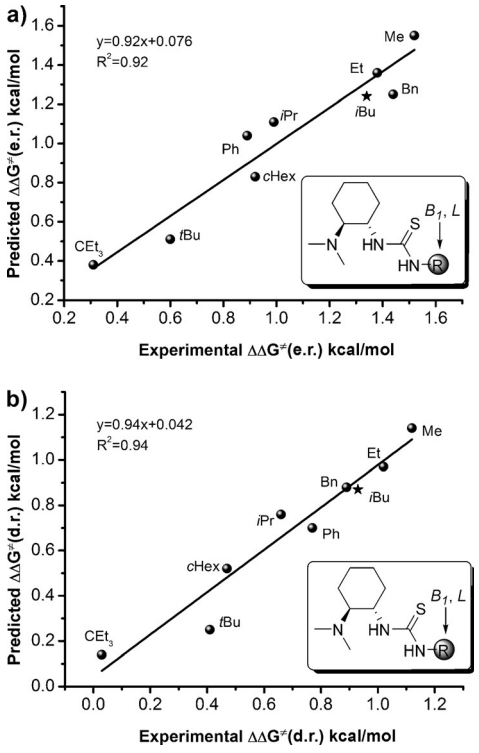


Figure 1. FER analysis of steric effects.

good linear FER was found between the $\Delta\Delta G^{\neq}$(e.r.) values and the Hammett constants for a set of benzyl thioureas (Figure 2). As expected, the introduction of more electron-

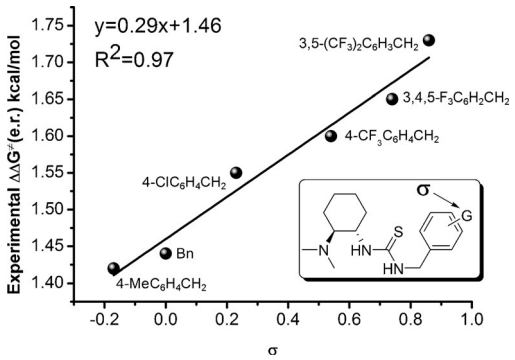


Figure 2. FER analysis of the electronic effects of benzyl-substituted thioureas.

withdrawing groups improved the enantioselectivity. Similarly, catalysts with fluorinated ethyl and propyl substituents also followed this rule (entries 15 and 16). The 3,5-bis(trifluoromethyl)benzyl-substituted tertiary amine thiourea **4n**,[12] which had never been synthesized and applied in asymmetric catalysis, was calculated to be a favorable catalyst for the current Michael addition. It is noteworthy that the performance of the Takemoto catalyst **4q**[12,13] (entry 17) is worse than that of the new catalyst **4n**.[14]

Furthermore, we noted that the model considering only steric parameters cannot be compatible with R groups that induce electronic perturbation (Figure S2). We then tried to develop a new model to unite steric and electronic effects by introducing IR vibrations and NBO charges (Table S2).[15–17] After a stepwise regression analysis, Eq. (4) and Eq. (5) were obtained. The good correlation between the predicted and experimental stereoselectivities indicates that these models can handle cases where both steric and electronic parameters play a role (Figure 3) as the equations delineated the activation of substrates by hydrogen bonds and the disadvantages of repulsive interactions. An inspection of the corresponding parameters revealed that this model also indicates that the introduction of small electron-withdrawing groups will generate high enantioselectivities as the aforementioned two-step analysis did.

$$\Delta\Delta G1^{\neq}\,(\text{e.r.}) = -0.40\,B_1 + 0.0076\,\nu_{N2-H2} + 35\,NBO_{N1} - 4.0 \quad (4)$$

$$\Delta\Delta G1^{\neq}\,(\text{d.r.}) = -0.085\,L + 44\,NBO_{C{*}N2} + 75\,NBO_{N1\times H1} + 27 \quad (5)$$

The screening of several widely used bifunctional organocatalysts under identical conditions confirmed the conclusion drawn from our free-energy analysis (Table S6), namely that **4n** performs best in terms of both catalytic reactivity and stereoselectivity. With **4n** as the optimal catalyst, a further screen of the reaction conditions, including solvent, temperature, and additive and catalyst loadings (Table S7), revealed the most suitable reaction conditions to entail the use of **4n** (3 mol%) and 3 Å molecular sieves (40 mg) in chlorobenzene

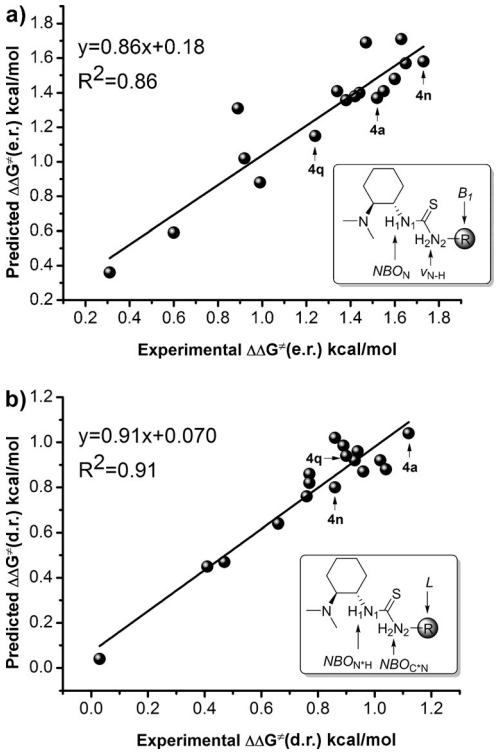


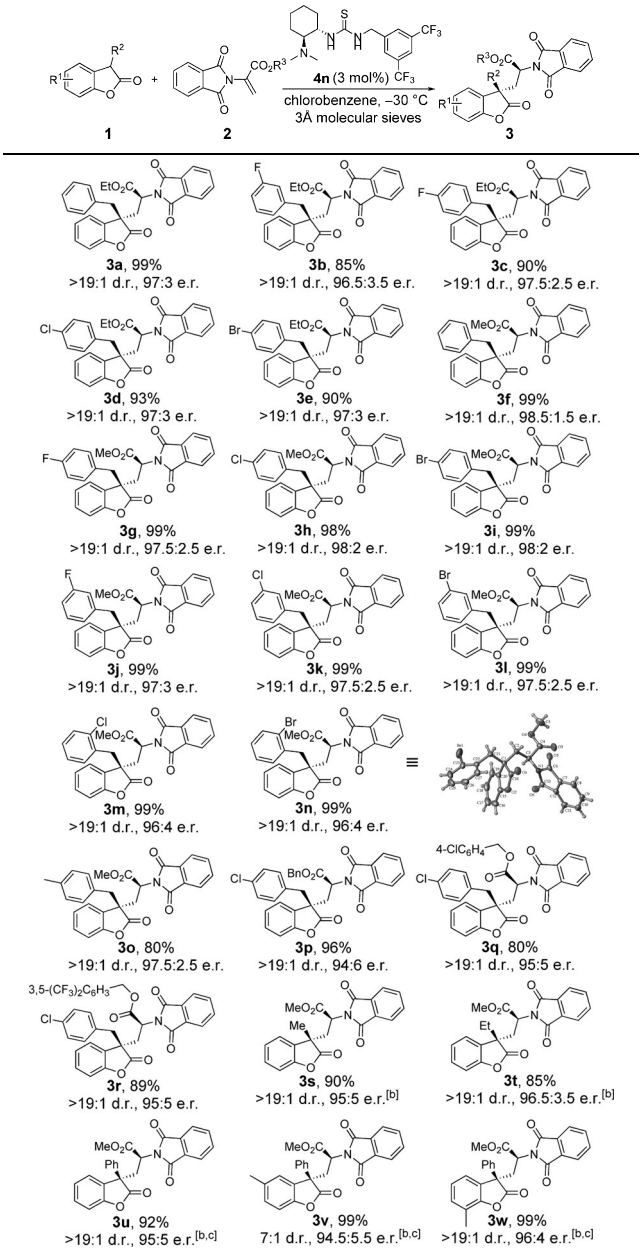
Figure 3. FER analysis for all catalysts.

at −30 °C, which gave **3a** in 99% yield, >19:1 d.r., and 97:3 e.r.

With the optimized reaction conditions in hand, we subsequently evaluated the substrate scope of the addition reaction of 3-substituted benzofuran-2-ones to 2-phthalimidoacrylates. As shown in Table 2, at a catalyst loading of 3 mol%, electron-withdrawing and -donating groups at the 2-, 3- and 4-position of the benzyl substituent R^2 of substrate **1** were tolerated, and their addition to ethyl and methyl 2-phthalimidoacrylates proceeded to give the corresponding products **3a–3o** in excellent yields (up to 99%) with excellent diastereoselectivities (>19:1 d.r.) and enantioselectivities (96:4–98.5:1.5 e.r.). Different benzyl 2-phthalimidoacrylates were also investigated. As expected, these 1,3-conjugate addition reactions catalyzed by **4n** under the standard conditions proceeded smoothly, and afforded the desired products **3p–3r** in high yields (up to 96% yield) and stereoselectivities (up to >19:1 d.r. and 95:5 e.r.). Our further exploration of the reaction scope focused on methyl- and ethyl-substituted benzofuran-2-ones. Whereas the catalyst loading had to be increased to 5 mol% to maintain acceptable reactivities, the diastereo- and enantioselectivities of the desired products **3s** and **3t** were still very good. Under modified reaction conditions (Table S8), 3-aryl-substituted benzofuranones can also be employed in this conjugate addition strategy, and the Michael products **3u–3w** were obtained in high yields and stereoselectivities.

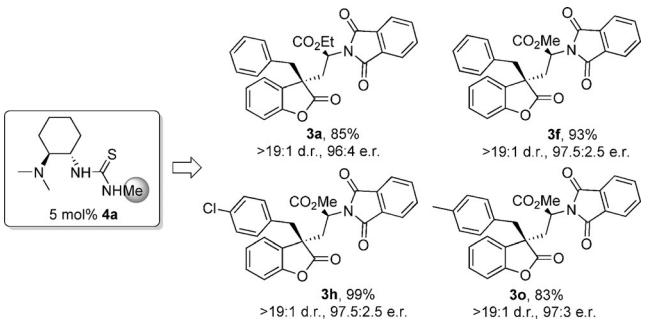
It is noteworthy that whereas large substituents are generally employed in ligand and catalyst design to achieve better stereoselectivities, our steric analysis showed that the smallest, methyl-substituted catalyst **4a** gave **3a** with the best

Table 2: Substrate scope.[a]



[a] Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), **4n** (3 mol%), 3 Å molecular sieves (40 mg), chlorobenzene (1.0 mL), −30°C, 5 days. The absolute configuration was determined by X-ray analysis.[18] Yields of isolated products are given. The stereoselectivities were determined by HPLC analysis on a chiral stationary phase. [b] **4n** (5 mol%). [c] In chlorobenzene/toluene (6:4, 1.0 mL).

stereoselectivity (Figure 1). This exciting result prompted us to further investigate the application of this simple catalyst in the current Michael addition. Under optimized reaction conditions, several substrates were examined (Scheme 2). To our delight, the Michael additions catalyzed by 5 mol% of **4a** proceeded with very good reactivities and stereocontrol, and the corresponding products (**3a**, **3f**, **3h**, and **3o**) were obtained in high yields with very good diastereo- and enantioselectivities. The very good stereoselectivities induced by **4a** are very interesting. Based on the observations in this



Scheme 2. Catalytic performance of methyl catalyst **4a**. Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), **4a** (5 mol%), 3 Å molecular sieves (40 mg), chlorobenzene (1.0 mL), −30°C, 5 days.

study and previous computational mechanistic studies on the activation model of tertiary amine thiourea catalysts,[19] a preliminary mechanism was proposed (Figure S6).[20]

In summary, the free-energy relationships between the stereoselectivities and the properties of tertiary amine thiourea catalysts were investigated by combining steric and electronic parameters for the first time. Thioureas with small, strongly electron-withdrawing N substituents were shown to be optimal catalysts for the Michael addition of 3-substituted benzofuranones and alkyl 2-phthalimidoacrylates. As a result, the methyl- and 3,5-bis(trifluoromethyl)benzyl-substituted tertiary amine thioureas identified during the free-energy analysis were successfully applied for the synthesis of α-amino acid derivatives with a benzofuran-2-one in the γ-position and 1,3-nonajacent stereogenic centers in high yields and stereoselectivities. Comprehensive studies of the mechanism are ongoing in our laboratory.

Acknowledgements

This work was supported by the National Basic Research Program of China (2012CB821600) and the National Natural Science Foundation of China (21390400 and 21421062). We thank Prof. S. Z. Luo (ICCAS), Dr. L. Zhang (ICCAS), and Dr. S. S. Hu (UC Berkeley) for helpful discussions.

Keywords: amino acids · asymmetric catalysis · enantioselectivity · free-energy relationships · hydrogen bonds

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 6506–6510
Angew. Chem. **2016**, *128*, 6616–6620

[1] a) Z. Shen, C. P. Falshaw, E. Haslam, M. J. Begley, *J. Chem. Soc. Chem. Commun.* **1985**, 1135; b) N. Lindquist, W. Fenical, G. D. Van Duyne, J. Clardy, *J. Am. Chem. Soc.* **1991**, *113*, 2303; c) S. Piacente, P. Montoro, W. Oleszek, C. Pizza, *J. Nat. Prod.* **2004**, *67*, 882; d) B. Sontag, M. Rüth, P. Spiteller, N. Arnold, W. Steglich, M. Reichert, G. Bringmann, *Eur. J. Org. Chem.* **2006**, 1023; e) B. Wu, S. He, X.-D. Wu, D.-K. Wu, Y.-J. Pan, *Helv. Chim. Acta* **2007**, *90*, 1586; f) Y.-J. Kwon, M.-J. Sohn, C.-J. Zheng, W.-G. Kim, *Org. Lett.* **2007**, *9*, 2449; g) H.-M. Ge, C.-H. Zhu, D.-H. Shi, L.-D. Zhang, D.-Q. Xie, J. Yang, S.-W. Ng, R.-X. Tan, *Chem. Eur. J.* **2008**, *14*, 376.

[2] a) K. C. Nicolaou, Q. Kang, T. R. Wu, C. S. Lim, D. Y. K. Chen, *J. Am. Chem. Soc.* **2010**, *132*, 7540; b) L. Li, Q. Yang, Y. Wang, Y.

Jia, *Angew. Chem. Int. Ed.* **2015**, *54*, 6255; *Angew. Chem.* **2015**, *127*, 6353.

[3] a) I. D. Hills, G. C. Fu, *Angew. Chem. Int. Ed.* **2003**, *42*, 3921; *Angew. Chem.* **2003**, *115*, 4051; b) S. A. Shaw, P. Aleman, E. Vedejs, *J. Am. Chem. Soc.* **2003**, *125*, 13368; c) S. A. Shaw, P. Aleman, J. Christy, J. W. Kampf, P. Va, E. Vedejs, *J. Am. Chem. Soc.* **2006**, *128*, 925; d) B. M. Trost, N. Cramer, S. M. Silverman, *J. Am. Chem. Soc.* **2007**, *129*, 12396; e) C.-L. Zhu, F.-G. Zhang, W. Meng, J. Nie, D. Cahard, J.-A. Ma, *Angew. Chem. Int. Ed.* **2011**, *50*, 5869; *Angew. Chem.* **2011**, *123*, 5991; f) G. Bergonzini, P. Melchiorre, *Angew. Chem. Int. Ed.* **2012**, *51*, 971; *Angew. Chem.* **2012**, *124*, 995; g) X.-F. Cheng, Y. Li, Y.-M. Su, F. Yin, J.-Y. Wang, J. Sheng, H. U. Vora, X.-S. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 1236; h) K. Ohmatsu, M. Ito, T. Kunieda, T. Ooi, *J. Am. Chem. Soc.* **2013**, *135*, 590; for a review, see: i) Y. Li, X. Li, J.-P. Cheng, *Adv. Synth. Catal.* **2014**, *356*, 1172.

[4] a) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; *Angew. Chem.* **2006**, *118*, 1550; b) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999; c) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; d) S. J. Connon, *Chem. Commun.* **2008**, 2499; e) H. Miyabe, Y. Takemoto, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 785; f) P. R. Schreiner, Z. Zhang, *Chem. Soc. Rev.* **2009**, *38*, 1187; g) P. M. Pihko, *Hydrogen Bonding in Organic Synthesis*, Wiley-VCH, Weinheim, **2009**.

[5] a) A. Williams, *Free Energy Relationships in Organic and Bio-organic Chemistry*, The Royal Society of Chemistry, London, **2003**; b) E. N. Bess, M. S. Sigman, *Linear free energy relationships (LFERs) in asymmetric catalysis. Asymmetric Synthesis II: More Methods and Applications*, Wiley-VCH, Weinheim, **2012**; c) K. C. Harper, M. S. Sigman, *J. Org. Chem.* **2013**, *78*, 2813.

[6] a) K. Mikami, Y. Motoyama, M. Terada, *J. Am. Chem. Soc.* **1994**, *116*, 2812; b) M. Palucki, N. S. Finney, P. J. Pospisil, M. L. Güler, T. Ishida, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 948; c) K. H. Jensen, M. S. Sigman, *Angew. Chem. Int. Ed.* **2007**, *46*, 4748; *Angew. Chem.* **2007**, *119*, 4832; d) S. Rodríguez-Escrich, K. S. Reddy, C. Jimeno, G. Colet, C. Rodríguez-Escrich, L. Solá, A. Vidal-Ferran, M. A. Pericàs, *J. Org. Chem.* **2008**, *73*, 5340; e) S. J. Zuend, E. N. Jacobsen, *J. Am. Chem. Soc.* **2009**, *131*, 15358; f) R. R. Knowles, E. N. Jacobsen, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20678; g) R. R. Knowles, S. Lin, E. N. Jacobsen, *J. Am. Chem. Soc.* **2010**, *132*, 5030; h) X. Li, H. Deng, B. Zhang, J. Li, S. Z. Luo, J.-P. Cheng, *Chem. Eur. J.* **2010**, *16*, 450; i) H. Huang, H. Zong, G. Bian, L. Song, *J. Org. Chem.* **2012**, *77*, 10427; j) M. C. Holland, S. Paul, W. B. Schweizer, K. Bergander, C. Mück-Lichtenfeld, S. Lakhdar, H. Mayr, R. Gilmour, *Angew. Chem. Int. Ed.* **2013**, *52*, 7967; *Angew. Chem.* **2013**, *125*, 8125; k) H. Li, C. Mazet, *Org. Lett.* **2013**, *15*, 6170; l) R. K. Akhani, M. I. Moore, J. G. Pribyl, S. L. Wiskur, *J. Org. Chem.* **2014**, *79*, 2384; m) M. Mulzer, J. R. Lamb, Z. Nelson, G. W. Coates, *Chem. Commun.* **2014**, *50*, 9842; n) H. Huang, H. Zong, G. Bian, H. Yue, L. Song, *J. Org. Chem.* **2014**, *79*, 9455; o) A. Claraz, G. Sahoo, D. Berta, Á. Madarász, I. Pápai, P. M. Pihko, *Angew. Chem. Int. Ed.* **2015**, *55*, 669; *Angew. Chem.* **2015**, *128*, 679.

[7] a) J. J. Miller, M. S. Sigman, *Angew. Chem. Int. Ed.* **2008**, *47*, 771; *Angew. Chem.* **2008**, *120*, 783; b) M. S. Sigman, J. J. Miller, *J. Org. Chem.* **2009**, *74*, 7633; c) K. H. Jensen, J. D. Webb, M. S. Sigman, *J. Am. Chem. Soc.* **2010**, *132*, 17471; d) K. H. Jensen, M. S. Sigman, *J. Org. Chem.* **2010**, *75*, 7194; e) J. L. Gustafson, M. S. Sigman, S. J. Miller, *Org. Lett.* **2010**, *12*, 2794; f) K. C. Harper, M. S. Sigman, *Science* **2011**, *333*, 1875; g) K. C. Harper, M. S. Sigman, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 2179; h) K. C. Harper, E. N. Bess, M. S. Sigman, *Nat. Chem.* **2012**, *4*, 366; i) K. C. Harper, S. C. Vilardi, M. S. Sigman, *J. Am. Chem. Soc.* **2013**, *135*, 2482; j) A. Milo, E. N. Bess, M. S. Sigman, *Nature* **2014**, *507*, 210; k) E. N. Bess, A. J. Bischoff, M. S. Sigman, *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 14698; l) A. Milo, A. J. Neel, F. D. Toste, M. S. Sigman, *Science* **2015**, *347*, 737; m) C. Zhang, C. B. Santiago, J. M. Crawford, M. S. Sigman, *J. Am. Chem. Soc.* **2015**, *137*, 15668.

[8] a) A. Verloop, *Drug Design*, Academic Press, New York, **1976**; b) A. Verloop, J. Tipker, *Biological Activity and Chemical Structure*, Elsevier, Amsterdam, **1977**; c) A. Verloop, *IUPAC Pesticide Chemistry*, Pergamon, Oxford, **1983**.

[9] The Sterimol parameters were calculated with the geometrically optimized structures of the catalysts at the M06-2X/def2-TZVP level of theory using Molecular Modeling Pro software available from ChemSW.

[10] J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416.

[11] B. Qiao, Q. Liu, H. Liu, L. Yan, Z. Jiang, *Chem. Asian J.* **2014**, *9*, 1252.

[12] For a discussion of the privileged 3,5-bis(trifluoromethyl)phenyl group, see: K. M. Lippert, K. Hof, D. Gerbig, D. Ley, H. Hausmann, S. Guenther, P. R. Schreiner, *Eur. J. Org. Chem.* **2012**, 5919.

[13] a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672; b) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119.

[14] **4n** also performed better than **4q** in another two reactions. For details, see Tables S4 and S5.

[15] The IR vibrations and NBO charges were calculated at the M06-2X/def2-TZVP level of theory.

[16] Gaussian 09 (Revision D.01), M. J. Frisch et al., Gaussian, Inc., Wallingford CT, **2009**.

[17] NBO Version 3.1, E. D. Glendening, A. E. Reed, J. Carpenter, E. F. Weinhold.

[18] CCDC 1024960 contains the supplementary crystallographic data for compound **3n**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[19] a) A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151; b) T. A. Rokob, A. Hamza, I. Pápai, *Org. Lett.* **2007**, *9*, 4279; c) B. Kótai, G. Kardos, A. Hamza, V. Farkas, I. Pápai, T. Soós, *Chem. Eur. J.* **2014**, *20*, 5631.

[20] The possible $^{\delta+}$N–CH···O and CH···π interactions[21] between catalyst and substrate may account for the origin of enantioselectivity. For details, see the "Preliminary Discussions on the Mechanism" Section in the Supporting Information.

[21] a) R. C. Johnston, P. H. Y. Cheong, *Org. Biomol. Chem.* **2013**, *11*, 5057; b) E. H. Krenske, K. N. Houk, *Acc. Chem. Res.* **2013**, *46*, 979; c) J. P. Wagner, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2015**, *54*, 12274; *Angew. Chem.* **2015**, *127*, 12446; d) R. C. Wende, A. Seitz, D. Niedek, S. M. M. Schuler, C. Hofmann, J. Becker, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2016**, *55*, 2719; *Angew. Chem.* **2016**, *128*, 2769.

Received: January 29, 2016
Revised: February 29, 2016
Published online: April 15, 2016

