Organocatalysis

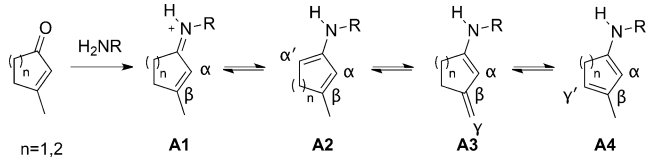
Deutsche Ausgabe: DOI: 10.1002/ange.201605790
Internationale Ausgabe: DOI: 10.1002/anie.201605790

# γ′-Selective Functionalization of Cyclic Enones: Construction of a Chiral Quaternary Carbon Center by [4+2] Cycloaddition/Retro-Mannich Reaction with 3-Substituted Maleimides

*Chuncheng Zou, Chuikun Zeng, Zhen Liu, Min Lu, Xiaohua Sun, and Jinxing Ye**

***Abstract:*** *The first example of organocatalyzed γ′-selective functionalization of cyclic enones with 3-substituted maleimides results in the stereoselective construction quaternary carbon center is presented. The reactions provided γ′-functionalized cyclic enones and β-functionalized cyclopentenones in good to excellent yields with excellent diastereo- and enantioselectivities. DFT calculations indicated that the reaction might proceed as a [4+2] cycloaddition/retro-Mannich reaction which could explain the unexpected product with a chiral quaternary carbon center and the excellent stereoselectivity.*

One of the major challenges in modern asymmetric catalysis is the selective activation and functionalization of reactants having multiple activation sites. Cyclic enones are potential synthons in natural products synthesis[1] and have multiple reactive sites,[2] and the researches about them have attracted the attention of chemists in the past decades. Pioneered by MacMillan et al. and List et al. organocatalytic β- and α,β-functionalizations of cyclic enones have been described to proceed via the LUMO-lowered iminium ion **A1**[3] and α′,β-functionalization via the HOMO-raised cross-conjugated dienamine **A2** (Scheme 1).[4] The groups of Melchiorre and Bencivenni further presented γ-regioselective direct vinylogous Michael additions or aldol reactions via the thermodynamic linear *exo*-dienamine **A3**.[5] After that, Chen reported a method enabling α′,γ′-functionalizations of cyclic enones, by using a cascade reaction, via the intermediate **A2** and subsequent extended *endo*-dienamine **A4**.[6] Recently, we reported the γ′-functionalization of 3-phenyl-2-cyclopentenone by vinylogous Michael addition to γ-butyrolactam, but it was not suitable for 3-phenyl-2-cyclohexenone.[7] To the best of our knowledge, direct catalytic asymmetric γ′-selective functionalization of simple cyclic enones is unprecedented. Thus we were fascinated by an organocatalytic pathway involving the formation of the intermediate **A4** to achieve the selective γ′-functionalization of cyclic enones.




***Scheme 1.*** Potential iminium ion and dienamine intermediates of cyclic enones under organocatalysis.

[4+2] Cycloaddition/retro-Mannich reactions have shown extensive application in the synthesis of complex natural products,[8] and offered a high level of stereochemical control and atom economy. In 2006, Jørgensen and co-workers reported the first organocatalytic γ-functionalization of α,β-unsaturated aldehydes by [4+2] cycloaddition/retro-Mannich reaction.[9] Selective activation of the remote γ-site and obtaining a high stereochemical outcome without racemization were the challenges of the reaction. Interestingly, for cyclic enones under organocatalysis, another challenge was the selective activation of the γ′-site instead of the γ-site. Indeed, when comparing the intermediates **A3** and **A4**, [4+2] cycloaddition between **A3** (*trans*-dienamine as diene) and dienophiles is unfavorable, whereas it is favorable for **A4** (*cis*-dienamine). Herein, we envisioned that the γ′-selective functionalization would proceed by an organocatalytic asymmetric [4+2] cycloaddition/retro-Mannich reaction via **A4**, and an α,β-unsaturated ketone motif would remain in the product for additional functionalization for constructing complex chiral molecules.

In the current study, we report the first example of γ′-selective functionalization of cyclic enones with 3-substituted maleimides for the construction of chiral quaternary carbon centers.[10] DFT calculations indicate that the reaction might proceed as a [4+2] cycloaddition/retro-Mannich reaction, and could explain the unprecedented construction of chiral quaternary carbon center with excellent diastereo- and enantioselectivity.

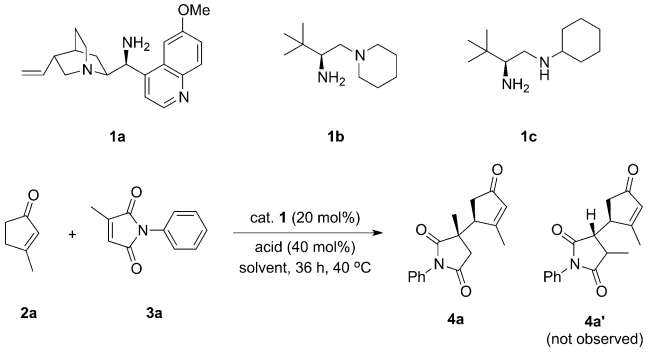
The initial screening using a variety of dienophiles[11] showed that the 3-methyl-maleimide **3a** was a good partner in the reaction with 3-methyl-2-cyclopentenone (**2a**; see Table 1). The γ′-functionalized product **4a**, to our surprise, which results from the formation of chiral quaternary carbon center at C3 of **3a**, rather than at C4 (**4a′**), was obtained in excellent conversion (88%) with excellent diastereoselectivity (>19:1) and moderate enantioselectivity (entry 1) by using the cinchona-based primary amine catalyst 9-amino (deoxy)quinine (**1a**) and benzoic acid in toluene at 40°C. Another primary-tertiary diamine catalyst (**1b**) derived from L-leucine slowed down the reaction, but led to a slightly improved *ee* value of 77% (entry 2). While using a primary-

[*] C. Zou, C. Zeng, M. Lu, X. Sun, Prof. Dr. J. Ye
Engineering Research Centre of Pharmaceutical Process Chemistry, Ministry of Education; Shanghai Key Laboratory of New Drug Design; School of Pharmacy, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237 (China)
E-mail: yejx@ecust.edu.cn
Prof. Dr. Z. Liu
State Key Laboratory of Chemical Engineering, East China University of Science and Technology, Shanghai, 200237 (China)

Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201605790.

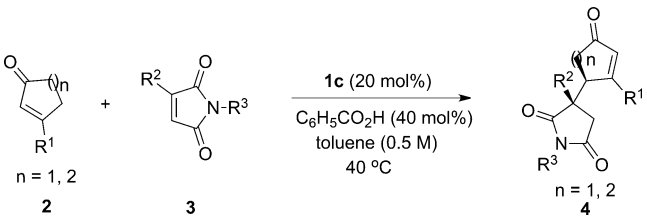
***Table 1:*** Screening studies of [4+2] cycloaddition/retro-Mannich reaction of 3-methyl-2-cyclopentenone to 3-methyl-maleimide.[a]




| Entry | Cat. | Acid | Solvent | Conv.[b] [%] | *ee*[c] [%] |
|---|---|---|---|---|---|
| 1 | **1a** | $C_6H_5CO_2H$ | toluene | 88 | 70 |
| 2 | **1b** | $C_6H_5CO_2H$ | toluene | 40 | 77 |
| 3 | **1c** | $C_6H_5CO_2H$ | toluene | >99 | >99 |
| 4 | **1c** | $C_6H_5CO_2H$ | 1,4-dioxane | 30 | >99 |
| 5 | **1c** | $C_6H_5CO_2H$ | EtOH | >99 | 92 |
| 6 | **1c** | $C_6H_5CO_2H$ | DCE | >99 | 98 |
| 7 | **1c** | $C_6H_5CO_2H$ | EtOAc | >99 | 98 |
| 8 | **1c** | 4-$OMeC_6H_4CO_2H$ | toluene | >99 | 97 |
| 9 | **1c** | 4-$NO_2C_6H_4CO_2H$ | toluene | >99 | 98 |

[a] Reactions were performed with **2a** (0.1 mmol), **3a** (0.2 mmol), Cat. **1** (20 mol%), and acids (40 mol%) in 200 μL of solvent. [b] Determined by GC analysis. [c] Determined by chiral-phase HPLC analysis. All d.r. > 19:1 determined by $^1$H NMR analysis of the crude reaction mixture. DCE = 1,2-dichloroethane.

***Table 2:*** Substrate scope of [4+2] cycloaddition/retro-Mannich reaction.[a]




| Entry | n | $R^1$, $R^2$, $R^3$ | *t* [h] | Yield [%] | *ee* [%] | d.r. |
|---|---|---|---|---|---|---|
| 1 | 1 | Me, Me, Ph | 36 | **4a**, 95 | >99 | >19:1 |
| 2 | 1 | Et, Me, Ph | 36 | **4b**, 90 | 97 | 9:1 |
| 3 | 1 | *n*Bu, Me, Ph | 50 | **4c**, 92 | >99 | >19:1 |
| 4 | 1 | *i*Pr, Me, Ph | 36 | **4d**, 93 | >99 | 10:1 |
| 5 | 1 | Ph, Me, Ph | 36 | **4e**, 92 | 94 | 5:1 |
| 6 | 1 | 1-naphthyl, Me, Ph | 48 | **4f**, 82 | 90 | >19:1 |
| 7 | 1 | styryl, Me, Ph | 48 | **4g**, 84 | 99 | >19:1 |
| 8 | 1 | 4-*t*Bu-styryl, Me, Ph | 48 | **4h**, 81 | 93 | >19:1 |
| 9 | 2 | Ph, Me, Ph | 72 | **4i**, 80 | 99 | >19:1 |
| 10 | 2 | 3,5-$(OMe)_2C_6H_3$, Me, Ph | 72 | **4j**, 52 | 99 | >19:1 |
| 11 | 2 | styryl, Me, Ph | 72 | **4k**, 78 | 98 | >19:1 |
| 12 | 2 | phenylethynyl, Me, Ph | 72 | **4l**, 64 | 99 | >19:1 |
| 13 | 2 | Ph, Me, Me | 72 | **4m**, 72 | 99 | >19:1 |
| 14 | 2 | styryl, Me, H | 72 | **4n**, 78 | 98 | >19:1 |
| 15 | 2 | styryl, Me, *p*-$BrC_6H_4$ | 72 | **4o**, 65 | 99 | >19:1 |
| 16 | 1 | Me, Et, Ph | 36 | **4p**, 93 | >99 | >19:1 |
| 17 | 1 | Me, *n*Bu, Ph | 40 | **4q**, 90 | 96 | >19:1 |
| 18 | 1 | Me, *i*Pr, Ph | 48 | **4r**, 90 | 97 | >19:1 |
| 19 | 1 | Me, Me, H | 48 | **4s**, 94 | 96 | 7:1 |
| 20 | 1 | Me, Me, Me | 48 | **4t**, 92 | 97 | 11:1 |
| 21 | 1 | Me, Me, Bn | 48 | **4u**, 91 | 95 | >19:1 |
| 22 | 1 | Me, Me, *p*-$BrC_6H_4$ | 36 | **4v**, 92 | 98 | >19:1 |
| 23 | 1 | Me, Me, *o*-$FC_6H_4$ | 48 | **4w**, 90 | 98 | >19:1 |
| 24 | 1 | Me, Me, *m*-$CF_3C_6H_4$ | 36 | **4x**, 96 | 97 | 13:1 |
| 25 | 2 | styryl, Me, *m*-$ClC_6H_4$ | 72 | **4y**, 78 | 93 | 10:1 |
| 26 | 2 | styryl, Et, Ph | 72 | **4z**, 85 | 98 | >19:1 |

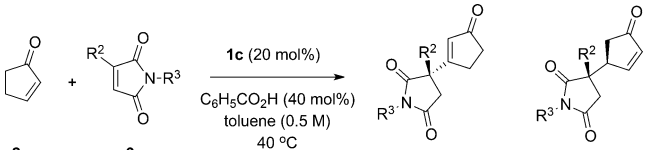
[a] Reactions performed using 1.0 equiv of **2** (0.2 mmol, 0.5 M), 2.0 equiv of **3**, 0.2 equiv of **1c**, and 0.4 equiv of benzoic acid in toluene at 40 °C. Yields of isolated products are given. The *ee* values were determined by chiral-phase HPLC analysis. The d.r. values were determined by $^1$H NMR analysis of the crude reaction mixture.

secondary diamine catalyst (**1c**) derived from L-leucine and cyclohexylamine,[12] both the conversion and enantioselectivity were excellent. Solvent effects were then explored, and it was found that 1,4-dioxane had a detrimental effect on the reaction rate, but the enantioselectivity was maintained (entry 4). It was pleasing that other solvents, such as ethyl alcohol, 1,2-dichloroethane, and ethyl acetate, did not affect the reaction rate and the enantioselectivities ranged from 92 to 98% (entries 5–7). Other acids such as 4-methoxy and 4-nitrobenzoic acids did not affect the diastero- and enantioselectivities (entries 8 and 9).

After optimization of the reaction conditions for the [4+2] cycloaddition/retro-Mannich reaction, the substrate scope with respect to the cyclic enones was investigated (Table 2, entries 1–15). Under the optimized reaction conditions, **4a** was isolated with 95% yield. It was convenient to scale up the reaction, and 2.52 grams of **4a** were obtained (*ee* = 98%, d.r. > 19:1).[11] We first systematically investigated the effect of different substituents at the 3-position of 2-cyclopentenone. 3-butyl-2-cyclopentenone gave similar results (**4c**). Ethyl, isopropyl, and phenyl substituents decreased the diastereoselectivities, while yields and enantioselectivities remained high (**4b**, **4d**, **4e**). Moreover, naphthyl (**4f**) and styryl (**4g**) substituents did not affect the stereochemical outcome. It was encouraging that for 3-substituted 2-cyclohexenones, the reactions were also feasible. We investigated the effect of aryl, styryl, and alkynyl groups (**4i–l**), and the yields were found to be moderate to good, though comparatively lower than that of 3-substituted 2-cyclopentenone, and they gave excellent diastereo- (>19:1) and enantioselectivities (98–99%). In addition, different N-substituents, such as methyl, hydrogen, and 4-bromophenyl, on the 3-methyl-maleimides did not affect the yields and stereoselectivities (**4m–o**). In contrast, the substrate scope of 3-substituted maleimides was thoroughly investigated. The reactions gave excellent yields and good to excellent stereoselectivities independent of 3-position substituents of maleimides as ethyl, butyl, isopropyl groups (**4p–r**), and N-substituents as hydrogen, methyl, benzyl, aryl groups (**4s–x**). With 3-styryl-2-cyclohexenone as a model substrate, the diastereo- and enantioselectivities remained excellent, while the yields were as good as 78–85% (**4y**,**z**), which were slightly lower than those obtained with 3-methyl-2-cyclopentenone. The absolute configurations of **4o** and **4v** were determined by X-ray crystallographic analysis.[11]

Interestingly and unexpectedly, for 2-cyclopentenone (**2aa**), β-substituted 2-cyclopentenones (**5**) rather than γ′-

***Table 3:*** Substrate scope of isomerization reaction between 2-cyclopentenone and 3-substituted malemides.[a]

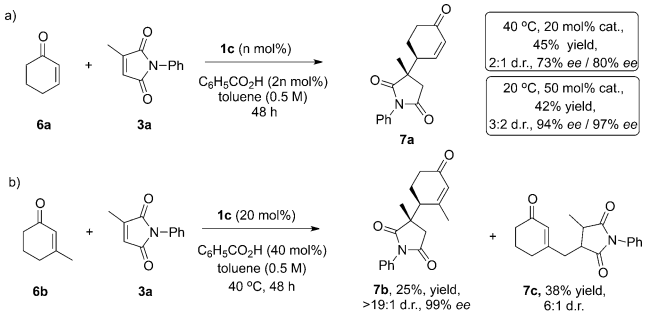



| Entry | $R^2$, $R^3$ | *t* [h] | Yield [%] | *ee* [%] |
|---|---|---|---|---|
| 1 | Me, Ph | 48 | **5a**, 93 | 96 |
| 2 | Et, Ph | 48 | **5b**, 90 | 95 |
| 3 | *n*Bu, Ph | 48 | **5c**, 91 | 95 |
| 4 | Me, Me | 48 | **5d**, 87 | 98 |
| 5 | Me, *p*-$ClC_6H_4$ | 48 | **5e**, 88 | 96 |

[a] Reactions performed using 1.0 equiv of 2-cyclopentenone **2aa** (0.2 mmol, 0.5 M), 2.0 equiv of **3**, 0.2 equiv of **1c**, and 0.4 equiv of benzoic acid in toluene at 40 °C. Yields of isolated products were given. The *ee* values were determined by chiral-phase HPLC analysis. The absolute configuration of **5e** was determined by X-ray analysis.

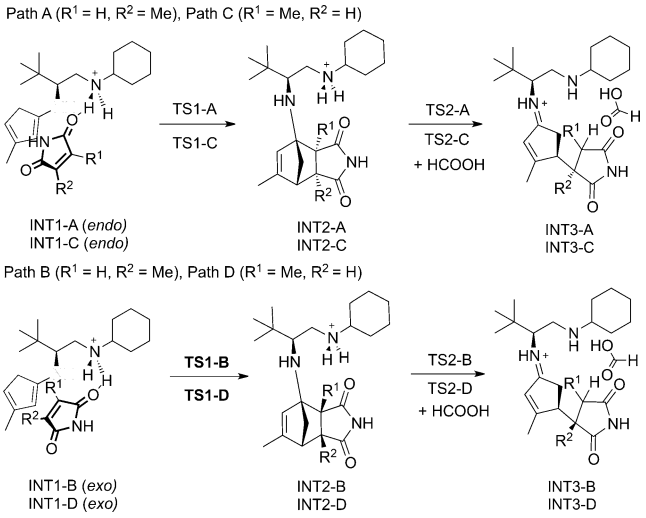
substituted 2-cyclopentenones (**5′**) were obtained with a chiral center attached to C3 of 2-cyclopentenone (Table 3). Regardless of the 3-substituent (methyl, ethyl, and butyl; **5a–c**) on the maleimides and the N-substituents (methyl and aryl groups; **5d,e**), the enantioselectivities remained excellent (95–98 %), and the yields ranged from 87 to 93 %. To the best of our knowledge, there are no methods for synthesizing these kinds of chiral compounds.

For 2-cyclohexenone (**6a**) and 3-alkyl-2-cyclohexenone, the results were quite complicated and intriguing (Scheme 2). For **6a**, the enantioselectivities were moderate at 40 °C, but excellent at 20 °C, albeit with poor diastereoselectivities (Scheme 2a). When using 3-methyl-2-cyclohexenone (**6b**) and **3a** as reaction partners, the result was a mixture of γ and γ′ products (Scheme 2b). Even though the yield of the γ′ product **7b** was as low as 25 %, was isolated with excellent diastereo- (> 19:1) and enantioselectivity (99 %). Melchiorre et al. reported the vinylogous Michael addition to to the γ-site of 3-alkyl-2-cyclohexenone, and explained that the γ-carbon atom had more electronic density than any other carbon atoms as determined by DFT calculations.[5a] Even though we succeeded in getting the γ′-product in low yield and with excellent stereoselectivity, further efforts are needed for the development of a general γ′-selective functionalization of 3-alkyl-2-cyclohexenone in high yield.




***Scheme 2.*** [4+2] Cycloaddition/retro-Mannich reaction of 2-cyclohexenone and 3-alkyl-2-cyclohexenone.

DFT calculations were carried out to elucidate the most plausible reaction mechanism. The calculations indicated that the reaction proceeds by a [4+2] cycloaddition/retro-Mannich reaction,[13] which is shown in Scheme 3. There are two possible mechanisms for the retro-Mannich reaction: 1) acid-assisted proton transfer (TS2, Path A–D) and 2) direct proton transfer (TS3, Path A′–D′; discussed in the Supporting Information). As shown in Figure 1, the Δ*G* of TS2 varies




***Scheme 3.*** Reaction pathways for reaction of **2a** and **3e** catalyzed by **1c**.

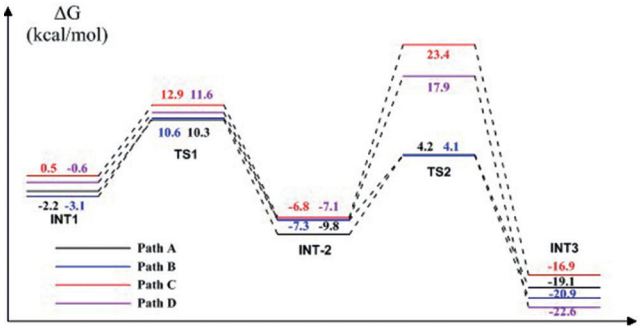


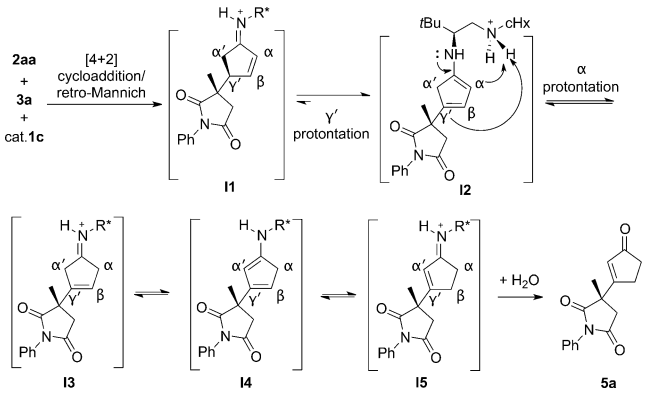

***Figure 1.*** Gibbs free-energy profile of [4+2] cycloaddition/retro-Mannich Reaction of **2a** to **3e** catalyzed by **1c**.

largely, $\Delta G = 4.2$ and 4.1 kcal mol$^{-1}$ for paths A and B, respectively, versus $\Delta G = 23.4$ and 17.9 kcal mol$^{-1}$ for paths C and D, respectively, because of the steric bulk of methyl group in the proton-transfer mechanism, which involves an extra acid molecule to assist the proton transfer process. In the experiment, the reaction rate was faster with 2 equivalents of acid than with 1 equivalent of acid, and there was no reaction without acid. The acid-assisted protonation could proceed with a low-lying transition state, TS2 (Δ*G*, 4.1–4.2 kcal mol$^{-1}$). Therefore, the [4+2] cycloaddition becomes the rate-limiting step, and the ratio of the products is determined by the relative height of TS1 on the energy diagram. Here, we calculated a slightly higher-energy transition state, TS1, in

path B than that in path A, and it explains the favored path A. It was worth noting that, between INT2-A and TS2-A in path A, there exists an negligible quasi-transition state of synchronous C–C bond cleavage and enolization with a $\Delta G$ value of 2.5 kcal mol$^{-1}$ and a resting state $\Delta G$ value of 2.1 kcal mol$^{-1}$ (see Figure S3). The unstable states could go back to INT2-A, or go further to a real transition state such as TS2-A, with $\Delta G$ 4.2 kcal mol$^{-1}$, by proton attacking from acid and undergo a protonation to last intermediate INT3-A with $\Delta G$ −19.1 kcal mol$^{-1}$.

We propose a possible mechanism, as illustrated in Scheme 4, to explain the interesting isomerization. Firstly, the intermediate **I1** is obtained with the catalyst **1c** according to the mechanism shown in Scheme 3 (path A). Then **I1** forms the α,γ′-dienamine **I2**, which is then protonated at the α-site to give the intermediate **I3**.[7a] However, **I3** equilibrates with either the α′,β-dienamine **I4** or α,γ′-dienamine **I2.** **I2** can join in the catalytic cycle and **I4** offers the imine **I5** by protonation at β-site. Finally, **I5** is hydrolyzed to give **5a**.




***Scheme 4.*** Proposed mechanism for isomerization reaction.

In short, we have established the first example of a γ′-selective functionalization of cyclic enones by an organocatalytic asymmetric [4+2] cycloaddition/retro-Mannich reaction to give 3-substituted maleimides. The methodology provides easy access to chiral 3,4-disubstituted cyclic enones with a quaternary carbon center adjacent to C4 of the cyclic enones, and chiral 3-substituted cyclopentenone with a quaternary carbon center adjacent to C3 in good to excellent yields with excellent diastereo- and enantioseletivities.

## Acknowledgements

This work was supported by the National Natural Science Foundation of China (21272068, 21572056), the Program for New Century Excellent Talents in University (NCET-13-0800), the Fundamental Research Funds for the Central Universities.

**Keywords:** asymmetric catalysis · cycloaddition · DFT calculations · isomerization · organocatalysis

**How to cite:** *Angew. Chem. Int. Ed.* **2016**, *55*, 14257 – 14261
*Angew. Chem.* **2016**, *128*, 14469 – 14473

[1] For selected examples, see: a) H. Suginome, Y. Nakayama, *Tetrahedron* **1994**, *50*, 7771 – 7782; b) A. Kolb, W. Zuo, J. Siewert, K. Harms, P. von Zezschwitz, *Chem. Eur. J.* **2013**, *19*, 16366 – 16373; c) J. Buter, R. Moezelaar, A. J. Minnaard, *Org. Biomol. Chem.* **2014**, *12*, 5883 – 5890; d) Y. Liu, S.-J. Han, W.-B. Liu, B. M. Stoltz, *Acc. Chem. Res.* **2015**, *48*, 740 – 751; e) T. Nemoto, R. Muramoto, T. Ruengsatra, Y. Hamada, *Tetrahedron* **2016**, *72*, 1991 – 1997.

[2] For selected reviews on aminocatalysis, see: a) W. Notz, F. Tanaka, C. F. Barbas, *Acc. Chem. Res.* **2004**, *37*, 580 – 591; b) D. W. C. MacMillan, *Nature* **2008**, *455*, 304 – 308; c) S. Bertelsen, K. A. Jorgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178 – 2189; d) J.-L. Li, T.-Y. Liu, Y.-C. Chen, *Acc. Chem. Res.* **2012**, *45*, 1491 – 1500; e) L. Zhang, S. Luo, *Synlett* **2012**, 1575 – 1589; f) J. Alemán, S. Cabrera, *Chem. Soc. Rev.* **2013**, *42*, 774 – 793; g) L. Zhang, N. Fu, S. Luo, *Acc. Chem. Res.* **2015**, *48*, 986 – 997.

[3] For selective β-functionalization of cyclic enones via an iminium ion, see: a) M. Yamaguchi, T. Shiraishi, M. Hirama, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1176 – 1178; *Angew. Chem.* **1993**, *105*, 1243 – 1245; b) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2003**, *42*, 661 – 665; *Angew. Chem.* **2003**, *115*, 685 – 689; c) N. J. A. Martin, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13368 – 13369; d) J. B. Tuttle, S. G. Ouellet, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 12662 – 12663; e) P. Li, Y. Wang, X. Liang, J. Ye, *Chem. Commun.* **2008**, 3302 – 3304; f) M. W. Paixão, N. Holub, C. Vila, M. Nielsen, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2009**, *48*, 7338 – 7342; *Angew. Chem.* **2009**, *121*, 7474 – 7478; g) H. Huang, Z. Jin, K. Zhu, X. Liang, J. Ye, *Angew. Chem. Int. Ed.* **2011**, *50*, 3232 – 3235; *Angew. Chem.* **2011**, *123*, 3290 – 3293; h) C. B. Jacobsen, M. Nielsen, D. Worgull, T. Zweifel, E. Fisker, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 7398 – 7404; i) P. Kwiatkowski, K. Dudziński, D. Łyżwa, *Org. Lett.* **2011**, *13*, 3624 – 3627; j) W. Wu, X. Li, H. Huang, X. Yuan, J. Lu, K. Zhu, J. Ye, *Angew. Chem. Int. Ed.* **2013**, *52*, 1743 – 1747; *Angew. Chem.* **2013**, *125*, 1787 – 1791; k) X. Li, M. Lu, Y. Dong, W. Wu, Q. Qian, J. Ye, D. J. Dixon, *Nat. Commun.* **2014**, *5*, 4479 – 4487; l) L. Cui, L. Zhang, S. Luo, J.-P. Chen, *Eur. J. Org. Chem.* **2014**, 3540 – 3545; m) X. Gu, Y. Dai, T. Guo, A. Franchino, D. J. Dixon, J. Ye, *Org. Lett.* **2015**, *17*, 1505 – 1508; n) J. J. Murphy, D. Bastida, S. Paria, M. Fagnoni, P. Melchiorre, *Nature* **2016**, *532*, 218 – 222; for α, β-functionalization see: o) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 2458 – 2460; p) W. Chen, W. Du, Y.-Z. Duan, Y. Wu, S.-Y. Yang, Y.-C. Chen, *Angew. Chem. Int. Ed.* **2007**, *46*, 7667 – 7670; *Angew. Chem.* **2007**, *119*, 7811 – 7814; q) F. Pesciaioli, F. De Vincentiis, P. Galzerano, G. Bencivenni, G. Bartoli, A. Mazzanti, P. Melchiorre, *Angew. Chem. Int. Ed.* **2008**, *47*, 8703 – 8706; *Angew. Chem.* **2008**, *120*, 8831 – 8834; r) X. Wang, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 6070 – 6071.

[4] a) Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5962 – 5963; b) G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli, P. Melchiorre, *Angew. Chem. Int. Ed.* **2009**, *48*, 7200 – 7203; *Angew. Chem.* **2009**, *121*, 7336 – 7339; c) D.-Q. Xu, A.-B. Xia, S.-P. Luo, J. Tang, S. Zhang, J.-R. Jiang, Z.-Y. Xu, *Angew. Chem. Int. Ed.* **2009**, *48*, 3821 – 3824; *Angew. Chem.* **2009**, *121*, 3879 – 3882; d) X. Feng, Z. Zhou, R. Zhou, Q.-Q. Zhou, L. Dong, Y.-C. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 19942 – 19947; e) D. B. Ramachary, Y. V. Reddy, *Eur. J. Org. Chem.* **2012**, 865 – 887; f) A.-B. Xia, D.-Q. Xu, C. Wu, L. Zhao, Z.-Y. Xu, *Chem. Eur. J.* **2012**, *18*, 1055 – 1059; g) R. Mose, M. E. Jensen, G. Preegel, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2015**, *54*, 13630 – 13634; *Angew. Chem.* **2015**, *127*, 13834 – 13838.

[5] a) G. Bencivenni, P. Galzerano, A. Mazzanti, G. Bartoli, P. Melchiorre, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20642 – 20647; b) D. Bastida, Y. Liu, X. Tian, E. Escudero-Adán, P. Melchiorre, *Org. Lett.* **2013**, *15*, 220 – 223; c) X. Tian, P. Melchiorre, *Angew. Chem. Int. Ed.* **2013**, *52*, 5360 – 5363; *Angew. Chem.* **2013**, *125*, 5468 – 5471; d) N. Di Iorio, P. Righi, A. Mazzanti, M. Mancinelli, A. Ciogli, G. Bencivenni, *J. Am. Chem. Soc.* **2014**, *136*, 10250 – 10253.

[6] a) P. Renzi, J. Overgaard, M. Bella, *Org. Biomol. Chem.* **2010**, *8*, 980 – 983; b) J. H. Lee, L. Deng, *J. Am. Chem. Soc.* **2012**, *134*, 18209 – 18212; c) X. Yin, Y. Zheng, X. Feng, K. Jiang, X.-Z. Wei, N. Gao, Y.-C. Chen, *Angew. Chem. Int. Ed.* **2014**, *53*, 6245 – 6248; *Angew. Chem.* **2014**, *126*, 6359 – 6362.

[7] a) Z. Qiao, Z. Shafiq, L. Liu, Z.-B. Yu, Q.-Y. Zheng, D. Wang, Y.-J. Chen, *Angew. Chem. Int. Ed.* **2010**, *49*, 7294 – 7298; *Angew. Chem.* **2010**, *122*, 7452 – 7456; b) X. Gu, T. Guo, Y. Dai, A. Franchino, J. Fei, C. Zou, D. J. Dixon, J. Ye, *Angew. Chem. Int. Ed.* **2015**, *54*, 10249 – 10253; *Angew. Chem.* **2015**, *127*, 10387 – 10391.

[8] a) D. L. Comins, R. S. Al-Awar, *J. Org. Chem.* **1992**, *57*, 4098 – 4103; b) H. Arai, M. Kasai, *J. Org. Chem.* **1994**, *59*, 1087 – 1094; c) D. L. Comins, C. A. Brooks, R. S. Al-awar, R. R. Goehring, *Org. Lett.* **1999**, *1*, 229 – 232; d) P. C. B. Page, H. Heaney, M. J. McGrath, E. P. Sampler, R. F. Wilkins, *Tetrahedron Lett.* **2003**, *44*, 2965 – 2970; e) N. Cramer, J. Juretschke, S. Laschat, A. Baro, W. Frey, *Eur. J. Org. Chem.* **2004**, 1397 – 1400; f) M. P. Lalonde, M. A. McGowan, N. S. Rajapaksa, E. N. Jacobsen, *J. Am. Chem. Soc.* **2013**, *135*, 1891 – 1894.

[9] S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973 – 12980.

[10] For catalytic asymmetric reaction examples of 3-substituted maleimides, see: a) R. Shintani, W.-L. Duan, T. Hayashi, *J. Am. Chem. Soc.* **2006**, *128*, 5628 – 5629; b) W.-L. Duan, H. Iwamura, R. Shintani, T. Hayashi, *J. Am. Chem. Soc.* **2007**, *129*, 2130 – 2138; c) S. Mukherjee, E. J. Corey, *Org. Lett.* **2010**, *12*, 632 – 635; d) J. Hernández-Toribio, S. Padilla, J. Adrio, J. C. Carretero, *Angew. Chem. Int. Ed.* **2012**, *51*, 8854 – 8858; *Angew. Chem.* **2012**, *124*, 8984 – 8988.

[11] For more details, see the Supporting Information.

[12] For selected reactions catalyzed by cat. **1c**, see: a) W. Wu, H. Huang, X. Yuan, K. Zhu, J. Ye, *Chem. Commun.* **2012**, *48*, 9180 – 9182; b) F. Yu, H. Hu, X. Gu, J. Ye, *Org. Lett.* **2012**, *14*, 2038 – 2041; c) H. Huang, W. Wu, K. Zhu, J. Hu, J. Ye, *Chem. Eur. J.* **2013**, *19*, 3838 – 3841; d) W. Wu, X. Yuan, J. Hu, X. Wu, Y. Wei, Z. Liu, J. Lu, J. Ye, *Org. Lett.* **2013**, *15*, 4524 – 4527; e) J. Fei, Q. Qian, X. Sun, X. Gu, C. Zou, J. Ye, *Org. Lett.* **2015**, *17*, 5296 – 5299. And see Ref. [3m, 7b].

[13] For selected examples, see: a) S. E. Denmark, A. Thorarensen, *Chem. Rev.* **1996**, *96*, 137 – 166; b) J. Burés, A. Armstrong, D. G. Blackmond, *J. Am. Chem. Soc.* **2011**, *133*, 8822 – 8825; c) J. Burés, A. Armstrong, D. G. Blackmond, *J. Am. Chem. Soc.* **2012**, *134*, 6741 – 6750; d) C. Moberg, *Angew. Chem. Int. Ed.* **2013**, *52*, 2160 – 2162; *Angew. Chem.* **2013**, *125*, 2214 – 2216; e) J. Burés, A. Armstrong, D. G. Blackmond, *Acc. Chem. Res.* **2016**, *49*, 214 – 222.

Received: June 15, 2016
Revised: August 18, 2016
Published online: October 13, 2016