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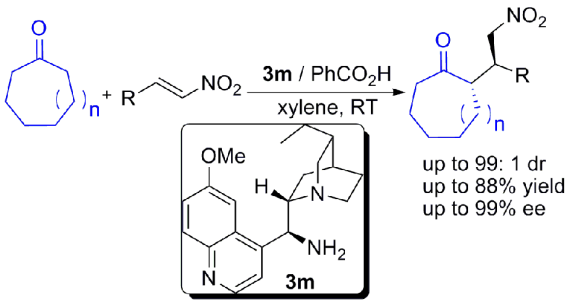


An organocatalytic Michael reaction of cycloheptanone and cyclooctanone with nitrodienes and nitroolefins catalyzed by primary amine catalysts has been accomplished.

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# Highly Enantioselective Michael Reaction Employing Cycloheptanone and Cyclooctanone as Nucleophiles

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An organocatalytic Michael reaction of cycloheptanone and cyclooctanone with nitrodienes and nitroolefins catalyzed by a hydroquinine-based primary amine catalyst has been accomplished. The corresponding Michael adducts were obtained in good yields (up to 88%) with good to excellent diastereoselectivities (up to >100:1) and enantioselectivities (up to >99% ee). The absolute configuration of the Michael product was assigned by TDDFT simulation of the ECD spectrum. And the Michael products can be readily converted into analogs of cycloalkano[b] fused pyrrolidines.

## Introduction

Over the past decade, chemists have witnessed a rapid development in organocatalysis, a powerful and attractive field involving the synthesis of chiral building blocks, natural products, and biologically active compounds using inexpensive and environmentally benign organocatalysts under mild conditions. Numerous elegant enantiocontrol organocatalytic methodologies have been developed.[1] The Michael reaction has been widely used to build valuable carbon-carbon bonds in modern organic chemistry.[2] Accordingly, the asymmetric organocatalytic Michael reaction has attracted considerable attention, and significant progress has been widely exploited over the past 10 years with a diverse combination of Michael donors and acceptors.[3] Specifically, the asymmetric organocatalytic Michael addition of carbonyl compounds to nitroalkenes has stimulated extensive interest because the chiral adducts (γ-nitrocarbonyl compounds) serve as key precursors of various key complex organic targets.[4]

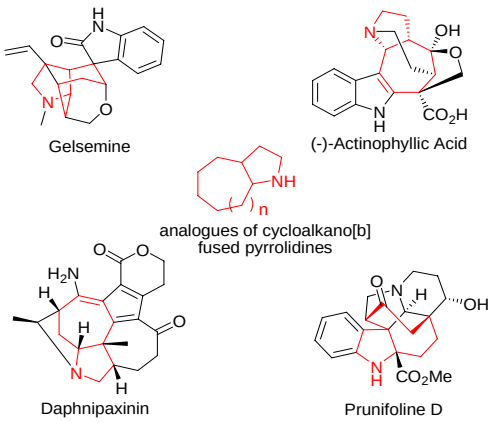



**Figure 1.** Examples of biologically active compounds containing seven- and eight-membered carbocycles

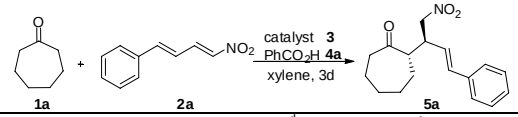
Therefore, much effort has been directed to determine new transformations to prepare these powerful intermediates.[5] To date, poor enantioselectivity is achieved in most cases when the cycloheptanone or cyclooctanone serves as the Michael donor.[6] Recently, Wang reported one example of secondary amine catalysed asymmetric Michael addition of cycloheptanone with nitroolefin, giving excellent enantioselectivity.[6e] However, numerous biologically active compounds, both naturally occurring and artificial, contain complex seven- and eight-membered carbocycles in their core structures, such as cycloalkano[b]fused pyrrolidines (Figure 1)[7] and α-methylene butyrolactones[8]. Consequently, the development of an efficient organocatalytic method for the Michael reaction of cycloheptanone and cyclooctanone with electrophiles with high enantioselectivity remains challenging and indispensable.

## Results and Discussion

We initiated our study using catalyst **3** for the Michael reaction of cycloheptanone **1a** with nitrodiene **2a** (Scheme 1).[9] Table 1 shows that the secondary amine catalysts L–prolinol **3a**, L–proline **3b**, Jørgensen-Hayashi catalyst **3c**, and MacMillan catalyst **3d** were almost completely inactive (entries 1 to 4) for the Michael transformation. The multifunctional Xu catalysts **3e** and **3f** led to moderate catalytic activity (10% and 52% yield) and good enantioselectivity (70% ee and 67% ee) (entries 5 and 6). The chiral primary amine catalyst **3g** and the chiral primary amine-thiourea bifunctional catalyst **3h** could not promote the reaction (entries 7 and 8). By contrast, higher selectivity were obtained using the Cinchona alkaloid-based primary amine catalysts **3i**, **3j**, **3k**, **3l**, and **3m**,[10] which promoted the formation of **5a** with high diastereoselectivity (9:1 dr to 29:1

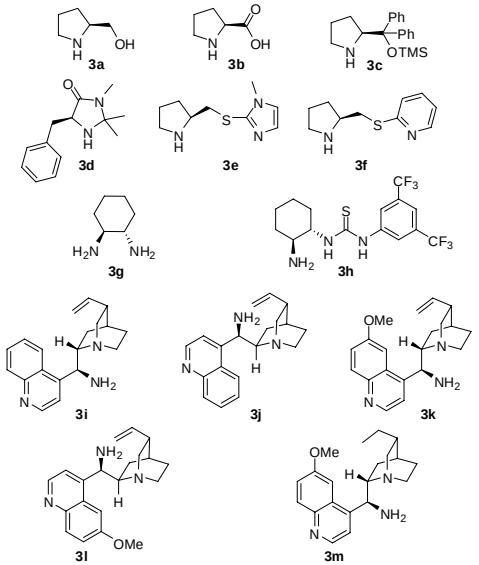
dr) and enantioselectivity (67% ee to 88% ee), although low yields (11% to 19%) were obtained (entries 9 to 13). The loadings of catalysts **3i**, **3k**, and **3m** were then verified, and the results showed that the yield increased with increasing loadings of catalysts **3i**, **3k**, and **3m** were then verified, and the results showed that the yield increased with increasingcatalyst loading. The yield and enantioselectivity rose from19% and 86% ee to 73% and 89% ee, respectively, when the loading amount of catalyst **3m** increased from 20 mol% to 50 mol% (entries 13 to 18). Additionally, increasing the reaction temperature led to higher yield but lower selectivity (entry 19 vs. entry 17). Notably, xylene and $PhCO_2H$ were found to be the comparatively suitable solvent and additive, respectively, among a series of organic solvents and acids (see the Supporting Information).[11] Thus, an efficient catalyst **3m** / $PhCO_2H$ / xylene system was developed for the highly enantioselective Michael reaction.

**Table 1.** Catalyst screening and reaction optimization[a]



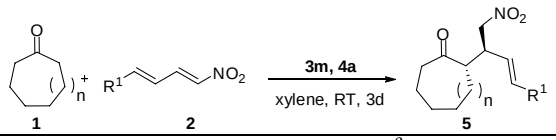

| Entry | Catalyst | T (℃) | Yield[d] (%) | *dr*[e] (*anti*:*syn*) | ee[e] (%) (*anti*) |
|---|---|---|---|---|---|
| 1 | **3a** | 25 | 5< | n.d. | n.d. |
| 2 | **3b** | 25 | trace | n.d. | n.d. |
| 3 | **3c** | 25 | trace | n.d. | n.d. |
| 4 | **3d** | 25 | trace | n.d. | n.d. |
| 5 | **3e** | 25 | 10 | 4:1 | 70 |
| 6 | **3f** | 25 | 52 | 3:1 | 67 |
| 7 | **3g** | 25 | trace | n.d. | n.d. |
| 8 | **3h** | 25 | trace | n.d. | n.d. |
| 9 | **3i** | 25 | 16 | 24:1 | 85[f] |
| 10 | **3j** | 25 | 12 | 9:1 | 69[f] |
| 11 | **3k** | 25 | 11 | 29:1 | 88 |
| 12 | **3l** | 25 | 12 | 9:1 | 67 |
| 13 | **3m** | 25 | 19 | 13:1 | 86 |
| 14[b] | **3i** | 25 | 23 | 8:1 | 83[f] |
| 15[b] | **3k** | 25 | 25 | 8:1 | 89 |
| 16[b] | **3m** | 25 | 37 | 11:1 | 88 |
| 17[c] | **3k** | 25 | 48 | 6:1 | 90 |
| 18[c] | **3m** | 25 | 73 | 7:1 | 89 |
| 19[c] | **3k** | 50 | 70 | 4:1 | 83 |

[a]Unless otherwise stated, the reaction was conducted by stirring in xylene (0.5 ml) using **1a** (0.5 mmol) and **2a** (0.13 mmol) with 20 mol% catalyst **3** and 20 mol% $PhCO_2H$ **4a** at room temperature. [b]30 mol% catalyst **3** and 30 mol% $PhCO_2H$ **4a** were used. [c]50 mol% catalyst **3** and 50 mol% $PhCO_2H$ **4a** were used. [d]Isolated yield. [e]Determined by HPLC analysis on a Chiralcel AS-H. [f]The opposite configuration.




**Scheme 1.** The catalysts used in this study

**Table 2.** Substrate scope of nitrodienes in Michael reaction[a]

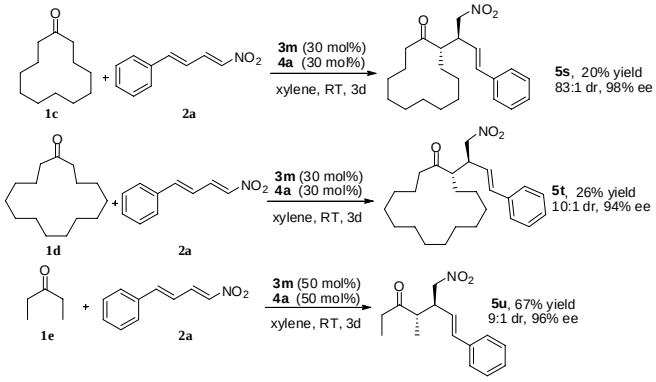



| Entry | n/**1** | $R^1$ | Product | Yield[c] (%) | *dr*[d] (*anti*:*syn*) | ee[d] (%) (*anti*) |
|---|---|---|---|---|---|---|
| 1 | 1/**1a** | $C_6H_5$ | **5a**[b] | 73 | 7:1 | 89 |
| 2 | 1/**1a** | 4-$MeC_6H_4$ | **5b**[b] | 72 | 8:1 | 90 |
| 3 | 1/**1a** | 4-$MeOC_6H_4$ | **5c**[b] | 67 | 7:1 | 87 |
| 4 | 1/**1a** | 4-$FC_6H_4$ | **5d**[b] | 80 | 7:1 | 89 |
| 5 | 1/**1a** | 4-$ClC_6H_4$ | **5e**[b] | 75 | 6:1 | 90 |
| 6 | 1/**1a** | 4-$BrC_6H_4$ | **5f**[b] | 62 | 6:1 | 88 |
| 7 | 1/**1a** | 3-$FC_6H_4$ | **5g**[b] | 78 | 7:1 | 86 |
| 8 | 1/**1a** | 3-$ClC_6H_4$ | **5h**[b] | 75 | 6:1 | 91 |
| 9 | 1/**1a** | 3-$BrC_6H_4$ | **5i**[b] | 60 | 6:1 | 86 |
| 10 | 1/**1a** | Pr | **5j**[b] | 84 | 8:1 | 80 |
| 11 | 1/**1a** | *i*Pr | **5k**[a] | 78 | 9:1 | 83 |
| 12 | 1/**1a** | $CO_2Et$ | **5l**[a] | 88 | 2:1 | 78 |
| 13 | 2/**1b** | $C_6H_5$ | **5m**[a] | 45 | 23:1 | 92 |
| 14 | 2/**1b** | 4-$MeC_6H_4$ | **5n**[a] | 41 | 47:1 | 93 |
| 15 | 2/**1b** | 4-$FC_6H_4$ | **5o**[a] | 23 | 99:1 | 91 |
| 16 | 2/**1b** | 4-$ClC_6H_4$ | **5p**[a] | 37 | 99:1 | 92 |
| 17 | 2/**1b** | 4-$BrC_6H_4$ | **5q**[a] | 23 | 26:1 | 94 |
| 18 | 2/**1b** | *i*Pr | **5r**[a] | 83 | 99:1 | 99 |

[a]Unless otherwise stated, the reaction was conducted by stirring in xylene(0.5 ml) using **1** (0.5 mmol) and **2** (0.13 mmol) with 30 mol% catalyst **3m** and 30 mol% $PhCO_2H$ **4a** at room temperature. In the case of racemic samples, 50 mol% pyrrolidine and 50 mol% $PhCO_2H$ **4a** were used. [b]50 mol% catalyst **3m** and 50 mol% $PhCO_2H$ **4a** were used. [c]Isolated yield. [d]Determined by HPLC analysis.

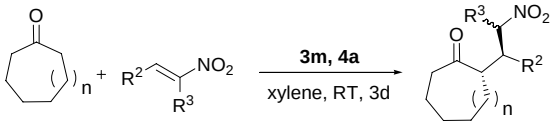
The scope of the reaction with respect to nitrodiene was explored using the established optimized reaction conditions (Table 2). With cycloheptanone **1a**, aryl and alkyl substituents were well tolerated on nitrodiene reactants and provided the respective Michael product **5a**–**l** with moderate to high yields (60% to 88%), diastereoselectivities (2:1 to 9:1 dr), and enantioselectivities (78% to 91% ee) (entries 1 to 12). Apparently, electron-donating and electron-withdrawing substituents on the aromatic ring of the nitrodienes had limited effect on yield and selectivity (entries 1 to 9). Accordingly, the nitrodiene scope was further explored using cyclooctanone **1b** as substrate (entries 13 to 18). In this case, various nitrodiene derivatives with different substitution patterns on the aromatic ring all provided the expected products **5m** to **5q** with excellent levels of diastereoselectivity (23:1 to 99:1 dr) and enantioselectivity (91% to 94% ee) (entries 13 to 17). Notably, alkyl-substituted nitrodiene could also be used as reaction partner, and the product 5r was obtained in 83% yield with 99:1 dr and 99% ee (entry 18). Compared with the previous results with **1a**, the use of **1b** as substrate generally led to enhanced diastereoselectivities and enantioselectivities.

The macrocyclic ketones **1c** and **1d** could also readily participate in the Michael transformation as nucleophiles, which resulted in the additional products **5s** and **5t** with high ee values of 98% and 94% and dr values of 83:1 and 10:1, respectively. Acyclic ketone **1e** also served as a suitable carbon nucleophile for the Michael reaction, and afforded the corresponding adduct **5u** with good results in terms of yield (67%), diastereoselectivity (9:1 dr), and enantioselectivity (96% ee).




**Scheme 2.** Further investigation of the substrate scope

**Table 3.** Substrate scope of nitroolefins in Michael reaction[a]

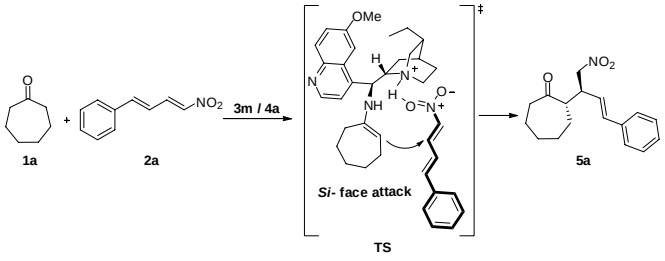


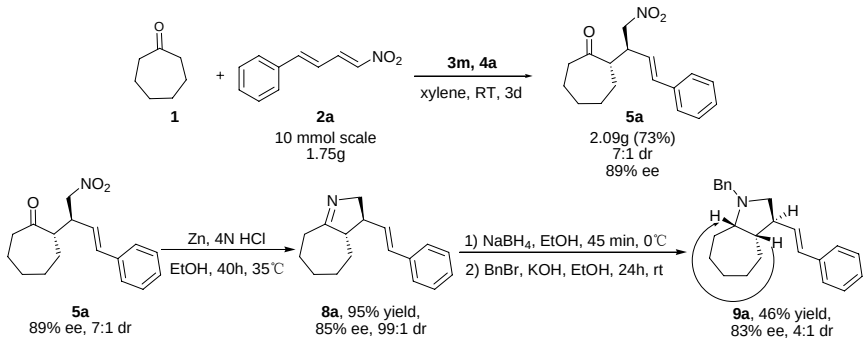

**1** **6** **7**

| Entry | n/**1** | $R^2$ | $R^3$ | Product | Yield[c] (%) | *dr*[d] (*anti*:*syn*) | ee[d] (%) (*anti*) |
|---|---|---|---|---|---|---|---|
| 1 | 1/**1a** | $C_6H_5$ | H | **7a**[b] | 70 | 19:1 | 89 |
| 2 | 1/**1a** | 4-$MeC_6H_4$ | H | **7b**[b] | 69 | 30:1 | 84 |
| 3 | 1/**1a** | 4-$MeOC_6H_4$ | H | **7c**[b] | 84 | 20:1 | 90 |
| 4 | 1/**1a** | 4-$FC_6H_4$ | H | **7d**[b] | 76 | 38:1 | 92 |
| 5 | 1/**1a** | 4-$ClC_6H_4$ | H | **7e**[b] | 79 | 24:1 | 87 |
| 6 | 1/**1a** | 4-$BrC_6H_4$ | H | **7f**[b] | 79 | 38:1 | 83 |
| 7 | 1/**1a** | 3-$MeOC_6H_4$ | H | **7g**[b] | 75 | 22:1 | 81 |
| 8 | 1/**1a** | 3-$BrC_6H_4$ | H | **7h**[b] | 50 | 57:1 | 86 |
| 9 | 2/**1b** | $C_6H_5$ | H | **7i**[a] | 67 | 86:1 | 99 |
| 10 | 2/**1b** | 4-$MeC_6H_4$ | H | **7j**[a] | 60 | 59:1 | 95 |
| 11 | 2/**1b** | 4-$MeOC_6H_4$ | H | **7k**[a] | 57 | >100:1 | 99 |
| 12 | 2/**1b** | 4-$FC_6H_4$ | H | **7l**[a] | 39 | 43:1 | 99 |
| 13 | 2/**1b** | 4-$BrC_6H_4$ | H | **7m**[a] | 54 | 26:1 | 99 |
| 14 | 2/**1b** | 3-$ClC_6H_4$ | H | **7n**[a] | 58 | >100:1 | >99 |
| 15 | 2/**1b** | 3-$BrC_6H_4$ | H | **7o**[a] | 50 | 16:1 | 98 |
| 16 | 1/**1a** | $C_6H_5$ | Me | **7p**[a] | 34 | 3:1 | 93 |
| 17 | 2/**1b** | $C_6H_5$ | Me | **7q**[a] | 38 | 8:1 | 99 |

[a]Unless otherwise stated, the reaction was conducted by stirring in xylene(0.5 ml) using **1** (0.5 mmol) and **6** (0.13 mmol) with 30 mol% catalyst **3m** and 30 mol% $PhCO_2H$ **4a** at room temperature. In the case of racemic samples, 50 mol% pyrrolidine and 50 mol% $PhCO_2H$ **4a** were used. [b]50 mol% catalyst **3m** and 50 mol% $PhCO_2H$ **4a** were used. [c]Isolated yield. [d]Determined by HPLC analysis.

**Scheme 3**. Proposed transition state for the reaction






**Scheme 4**. Enantioselective gram-scale synthesis of **5a**, and derivatization of Michael adduct **5a** to cycloalkano[b]fused pyrrolidine **9a**[11]

With the above success, the reaction scope was further extended to nitroolefins. As illustrated in Table 3, the reaction of cycloheptanone **1a** or cyclooctanone **1b** with nitroolefins were performed under the above optimal reaction conditions. The reactions proceeded smoothly in moderate to high yields (up to 84% yield), high to excellent diastereoselectivities (up to >100: 1 dr) and good to excellent enantioselectivities (up to >99 ee) (entries 1 to 15). It is noteworthy that reactions between **1b** and nitroolefins gave better results to those nitrodienes were used as the nucleophiles(table 3, entries 9 to 15 vs table 2, entries 13 to 18), and reactions between **1a** and nitroolefins obtained better diastereoselectivities than those between **1a** and nitrodienes (table 3, entries 1 to 8 vs table 2, entries 1 to 9). The reactions of β-disubstituted nitroalkenes including β-methyl nitroalkene (table 3, entries 16 and 17) reacted successfully to give the corresponding products **7p** and **7q** in good to high diastereoselectivities with high to excellent enantioselectivities.

The absolute configuration (AC) of the Michael product **5a** was determined to be S, S by comparing the experimental CD spectrum with the results of time-dependent density functional theory (TDDFT) calculations of electronic circular dichroism (ECD) spectra.[11, 12] As shown in Figure 2 (Figure 6S), in the selected data in the 200-390 nm UV region, the experimental CD spectrum is consistent with the calculated data of 1-SS. Then, a transition state model was proposed (Scheme 3). Nitrodiene **2a** was activated well through the hydrogen-bonding interaction between the protonated bridgehead nitrogen atom of **3m** and nitro group of **2a**. Therefore, the enamine formed from **3m** and **1a** attacked the activated **2a** from the *Si* face to afford the major stereoisomer of Michael adduct **5a** with the configuration of (S, S).

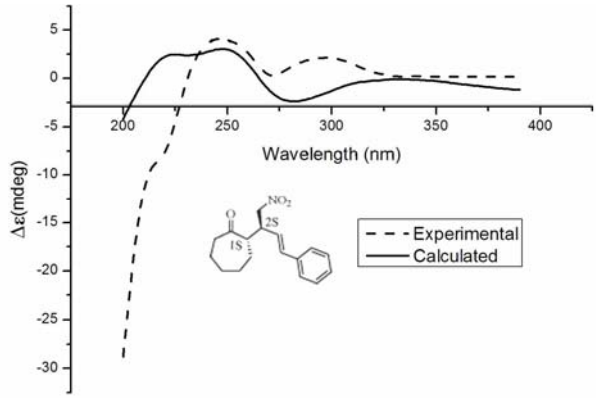



**Figure 2**. Experimental (dotted trace) and calculated ECD spectra (full trace) of the Michael product **5a**

The enantioselective Michael reaction can be performed successfully on gram-scale to obtain 2.09 g of **5a** (73% yield) with the same diastereoselectivity and enantioselectivity under modified conditions (Scheme 4). The synthetic utility of this Michael reaction was also demonstrated in the synthesis of chiral cycloalkano[b]fused pyrrolidine **9a** (Scheme 4).[13] The transformation involves the Zn/HCl-mediated reductive cyclization of adduct **5a** to obtain imine **8a** in 95% yield. A reduction of imine **8a** with $NaBH_4$ followed by Bn protection resulted in **9a** with good overall yield and without racemization.

## Conclusions

In summary, an organocatalytic enantioselective Michael reaction of nucleophiles, cycloheptanone or cyclooctanone, with nitrodienes and nitroolefins catalyzed by hydroquinine-based primary amine catalyst has been established. The corresponding adducts were obtained in good yields (up to 88%) with good to excellent diastereoselectivities (up to >100:1 dr) and good to excellent enantioselectivities (up to >99% ee). The product can be readily converted into analogs of cycloalkano[b] fused pyrrolidines, which further enhances the utility of this transformation for the synthesis of potentially valuable chiral molecules.

## Experimental section

### General information

The $^1$H **NMR** and $^{13}$C **NMR** spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane. GC-MS experiments were performed on a GC system with a mass selective detector. HRMS data were measured using a TOF mass spectrometer. Column chromatography and flash chromatography experiments were performed on silica gel (200-300 mesh) eluting with ethyl ether and petroleum ether. TLC experiments were carried out on glass-backed silica plates. In each case, enantiomeric ratio was determined on a chiral column in comparison with authentic racemates by chiral HPLC. Chemicals were used without purification as commercially available. Nitrodienes,[14] and organocatalysts **3d**,[15] **3e-3f**,[16] **3h**,[17] **3i-3l**,[18] **3m**[19] were synthesized according to literature.

### Typical experimental procedure for the Michael reaction

Xylene (0.5mL) was added to a mixture of cycloheptanone **1a** or cyclooctanone **1b** (0.5 mmol) with nitrodienes **2** or

nitroolefins **6** (0.126 mmol) in the presence of 30 mol % or 50 mol % catalyst 3m and 30 mol % or 50 mol % $PhCO_2H$ **4a** at room temperature with vigorous stirring. The reaction conversion was monitored by GC-MS. After three days, the reaction mixture was extracted with DCM, washed with water, dried and concentrated. The residue was purified by flash chromatography on silica gel (ether/petroleum ether = 1:4 to 1:2 as eluent) to give the slightly white solid of the Michael addition products **5a** – **5i**, **5m** – **5q**, **7a** – **7b**, **7e** – **7f**, **7i** – **7k**, **7n** – **7q**, the slightly yellow liquid products **5j** – **5l**, **5r**, **7g** and colorless oil **7c**, **7l**. The enantiomeric excesses (% ee) was determined by HPLC analysis using chiral stationary phases.

## Acknowledgements

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## Notes and references

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Electronic Supplementary Information (ESI) available: experimental procedures, characterizations, NMR spectra and HPLC spectra are available. See DOI: 10.1039/b000000x/

1 For selected books and reviews on organocatalysis, see: (a) *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis* (Eds: A. Berkessel and H. Gröger) Wiley-VCH, Weinheim, **2004**; (b) *Enantioselective Organocatalysis* (Eds: P. I. Dalko), Wiley-VCH, Weinheim, **2007**; (c) B. List and J. W. Yang, *Science* **2006**, *313*, 1584; (d) M. J. Gaunt, C. C. C. Johansson, A. McNally and N. C. Vo, *Drug Discovery Today* **2007**, *12*, 8; (e) D. W. C. MacMillan, *Nature* **2008**, *455*, 304; (f) A. Dondoni and A. Massi, *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; (g) P. Melchiorre, M. Marigo, A. Carlone and G. Bartoli, *Angew. Chem. Int. Ed.* **2008**, *47*, 6138; (h) S. Bertelsen and K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178; (i) E. Marqués-López, R. P. Herrera and M. Christmann, *Nat. Prod. Rep.* **2010**, *27*, 1138; (j) C. Vaxelaire, P. Winter and M. Christmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 3605; (k) J. Alemán and S. Cabrera, *Chem. Soc. Rev.* **2013**, *42*, 774.

2 *Cinchona Alkaloids in Synthesis and Catalysis*; (Eds: C. E. Song and P. D. Magnus), Wiley-VCH, Weinheim, **2009**.

3 For selected reviews, see: (a) R. Ballini, G. Bosica, D. Fiorini, A. Palmieri and M. Petrini, *Chem. Rev.* **2005**, *105*, 933; (b) D. Almasi, D. A. Alonso and C. Najera, *Tetrahedron: Asymmetry* **2007**, *18*, 299; (c) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701; (d) J. L. Vicario, D. Badia and L. Carrillo, *Synthesis* **2007**, 2065; (e) B. Westermann, M. Ayaz and S. S. van Berkel, *Angew. Chem. Int. Ed.* **2010**, *49*, 846; (f) J. Wang, P. Li, P. Y. Choy, A. S. C. Chan and F. Y. Kwong, *ChemCatChem* **2012**, 4, 917; (g) C. F. Nising and S. Bräse, *Chem. Soc. Rev.* **2012**, *41*, 988.

4 For selected reviews, see: (a) O. M. Berner, L. Tedeschi and D. Enders, *Eur. J. Org. Chem.* **2002**, 1877; (b) S. Sulzer-Mosse and A. Alexakis, *Chem. Commun.* **2007**, 3123; (c) D. Roca-Lopez, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero and P. Merino, *Tetrahedron: Asymmetry* **2010**, *21*, 2561.

5 For selected reviews, see: (a) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.* **2010**, *2*, 167; (b) Y. Zhang and W. Wang, *Catal. Sci. Technol.* **2012**, *2*, 42.

6 (a) P. Kotrusz, S. Toma, H. -G. Schmalz and A. Adler; *Eur. J. Org. Chem.* **2004**, 1577; (b) J. Wang, H. Li, B. Lou, L. Zu, H. Guo and W. Wang, *Chem. Eur. J.* **2006**, *12*, 4321; (c) L. Gu, Y. Wu, Y. Zhang and G. Zhao, *J Mol Catal A -Chem.* **2007**, *263*, 186; (d) D. -Q. Xu, H. -D. Yue, S. -P. Luo, A. -B. Xia, S. Zhang and Z. -Y. Xu, *Org. Biomol. Chem.* **2008**, *6*, 2054; (e) D. -Z. Xu, S. Shi and Y. Wang, *Eur. J. Org. Chem.* **2009**, 4848; (f) C. Wang, C. Yu, C. Liu and Y. Peng, *Tetrahedron Lett.* **2009**, *50*, 2363; (g) S. Belot, A. Quintard, N. Krause and A. Alexakis, *Adv. Synth. Cat.* **2010**, *352*, 667; (h) A. Lu, R. Wu, Y. Wang, Z. Zhou, G. Wu, J. Fang and C. Tang, *Eur. J. Org. Chem.* **2011**, 122; (i) Y. -M. Chuan, L. -Y. Yin, Y. –M. Zhang and Y. -G. Peng, *Eur. J. Org. Chem.* **2011**, 578; (j) M. Tsakos, M. Trifonidou and C. G. Kokotos, *Tetrahedron* **2012**, *68*, 8630; (k) V. Gauchot, J. Gravel and A. R. Schmitzer, *Eur. J. Org. Chem.* **2012**, 6280.

7 For seven-membered carbocycle example, see: (a) K. E. O. Ylijoki and J. M. Stryke, *Chem. Rev.* **2012**, *113*, 2244; (b) C. L. Martin, L. E. Overman and J. M. Rohde, *J. Am. Chem. Soc.* **2008**, *130*, 7568; (c) T. B. Dunn, J. M. Ellis, C. C. Kofink, J. R. Manning and L. E. Overman, *Org. Lett.* **2009**, *11*, 5658; (d) C. L. Martin, L. E. Overman and J. M. Rohde, *J. Am. Chem. Soc.* **2010**, *132*, 4894; (e) D. S. Belov, E. R. Lukyanenko, A. V. Kurkin and M. A. Yurovskaya, *Tetrahedron* **2011**, *67*, 9214; (f) D. S. Belov, E. R. Lukyanenko, A. V. Kurkin and M. A. Yurovskaya, *J. Org. Chem.* **2012**, *77*, 10125; for eight-membered carbocycle example, see: (g) G. Mehta and V. Singh, *Chem. Rev.* **1999**, *99*, 881; (h) W. G. Earley, J. E. Jacobsen, A. Madin, G. P. Meier, C. J. O'Donnell, T. Oh, D. W. Old, L. E. Overman and M. J. Sharp, *J. Am. Chem. Soc.* **2005**, *127*, 18046; (i) H, Zhou, H. -P. He, N. -C. Kong, Y. -H. Wang, X. -D. Liu and X. -J. Hao, *Helv. Chim. Acta.* **2006**, *89*, 515; (j) K. -H. Lim, O. Hiraku, K. Komiyama, T. Koyano, M. Hayashi and T. -S. Kam, *J. Nat. Prod.* **2007**, *70*, 1302; (k) K. -H. Lim and T. -S. Kam, *Phytochemistry* **2008**, *69*, 558.

8 (a) J. A. Marshall and N. Cohen, *J. Org. Chem.* **1965**, *30*, 3475; (b) J. W. Patterson and J. E. Mcmurry, *Chem. Commun.* **1971**, 488; (c) S. Krihnamurthy and H. C. Brown, *J. Am. Chem. Soc.* **1976**, *98*, 3394; (d) T. F. Murray, E. G. Samsel, V. Varma and J. R. Norton, *J. Am. Chem. Soc.* **1981**, *103*, 7520; (e) M. Ando, H. Kusaka, H. Ohara, K. Takase, H. Yamaoka and Y. Yanagit, *J. Org. Chem.* **1989**, *54*, 1952; (f) Y. Higuchi, F. Shimoma and M. Ando, *J. Nat. Prod.* **2003**, *66*, 810.

9 (a) For selected review, see: (a) R. Ballini, N. Araújo, M. V. Gil, Román and E. J. A. Serrano, *Chem. Rev.* **2013**, *113*, 3493; For selected examples of Michael reaction to nitrodienes, see: (b) B. Tan, P. J. Chua, Y. Li and G. Zhong, *Org. Lett.* **2008**, *10*, 2437; (c) S. Belot, A. Massaro, A. Tenti, A. Mordini and A. Alexakis, *Org. Lett.* **2008**, *10*, 4557; (d) H. Ma, K. Liu, F. -G. Zhang, C. -L. Zhu, J. Nie and J. -A. Ma, *J. Org. Chem.* **2010**, *75*, 1402. (e) Z. -B. Li, S. -P. Luo, Y. Guo, A. -B. Xia and D. -Q. Xu, *Org. Biomol. Chem.* **2010**, *8*, 2505.

10 For selected examples, see: (a) S. H. McCooey and S. J. Connon, *Org. Lett.* **2007**, *9*, 599; (b) J. -W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y. -C. Chen, Y. Wu, J. Zhu and J. -G. Deng, *Angew. Chem. Int. Ed.* **2007**, *46*, 389.

11 For more details, please see the Supporting Information.

12 (a) For selected reviews, see: (a) X. -C. Li, D. Ferreira and Y. Ding, *Curr. Org. Chem.* **2010**, *14*, 1678; For selected examples of the use of this technique to assign the absolute configurations of chiral organic molecules, see: (b) F. Furche, R. Ahlrichs, C. Wachsmann, E. Weber, A. Sobanski, F. Vogtle and S. Grimme, *J. Am. Chem. Soc.* **2000**, *122*, 1717; (c) C. Diedrich and S. Grimme, *J. Phys. Chem. A*, **2003**, *107*, 2524.

13 (a) I. H. Sanchez, M. I. Larraza, I. Rojas, F. Kuri Brena, H. J. Flores and K. Jankowski, *Heterocycles* **1985**, *23*, 3033; (b) W. Glassco, J. Suchocki, C. George, B. R. Martin and E. L. May, *J. Med. Chem.* **1993**, *36*, 3381; (c) T. J. Dickerson, T. Lovell, M. M. Meijler, L. Noodleman and K. D. Janda, *J. Org. Chem.* **2004**, *69*, 6603; (d) N. Ruiz, E. Reyes, J. L. Vicario, D. BadÍa, L. Carrillo and U. Uria, *Chem. Eur. J.* **2008**, *14*, 9357; (e) S. V. Pansare, R. Lingampally and R. L. Kirby, *Org. Lett.* **2010**, *12*, 556; (f) P. Chauhana and S. S. Chimnia, *Adv. Synth. Catal.* **2011**, *353*, 3203.

14 S. Belot, A. Massaro, A. Tenti, A. Mordini and A. Alexakis, *Org. Lett.* **2008**, *10*, 4557.

15 K. A. Ahrendt, C. J. Borths and D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243.

16 D. Q. Xu, A. B. Xia, S. P. Luo, J. Tang, S. Zhang, J. R. Jiang and Z. Y. Xu, *Angew. Chem. Int. Ed.* **2009**, *48*, 3821.

17 X. -J. Zhang, S. -P. Liu, J. -H. Lao, G. -J. Du, M. Yan and A. S. C. Chan, *Tetrahedron Asymmetry* **2009**, *20*, 1451.

18 B. Vakulya, S. Varga, A. Csámpai and T. Soós, *Org. Lett.* **2005**, *7*, 1967.

19 S. H. McCooey and S. J. Connon, *Org. Lett.* **2007**, *9*, 599.