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Control of Four Stereocenters in an Organocatalytic Domino Double Michael Reaction: Efficient Synthesis of Multisubstituted Cyclopentanes

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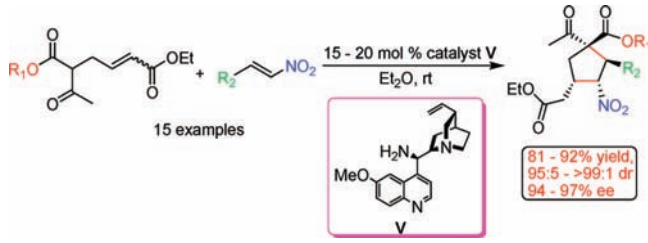
ABSTRACT



A highly enantioselective and diastereoselective domino organocatalytic double Michael reaction which provides expedited access to multifunctionalized five-membered rings catalyzed by 9-amino-9-deoxyepiquinine (V) has been developed. Simple operational procedures, high yields (81−92%), excellent enantioselectivity (90−97% ee), diastereoselectivities (95:5−>99:1 dr), and immense potential of synthetic versatility of the products render this new methodology highly appealing for asymmetric synthesis.

The asymmetric organocatalytic domino reaction has emerged as a powerful paradigm in accelerating the development of new methods for the synthesis of diverse chiral molecules.[1] With the benefits of ease operation, ready availability, and low toxicity of reactants and catalysts, these organocatalytic reactions are attractive methods in modern synthetic chemistry and have received remarkable attention during the past decade.[2] Of the developed strategies for asymmetric tandem reactions, Enders et al. have performed the synthesis of substituted cyclohexenes by applying a three-component domino reaction[3a,b] while Hayashi et al. described a two-component multistep Michael-Henry sequence for the synthesis of cyclohexane derivatives by using pentane-1,5-dial and 2-substituted nitroalkenes.[3e]

Although several other elegant organocatalytic tandem reactions have also been reported recently,[4] the development of new methodologies for the generation of molecules with multiple stereogenic carbons[3] including quaternary centers in a cascade manner remains a big challenge at the forefront of synthetic chemistry. The Michael addition reaction, being one of the most general and versatile methods for formation

(1) For a recent review, see: (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (b) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1.

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(3) (a) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (b) Enders, D.; Hüttl, M. R. M.; Runsink, J.; Raabe, G.; Wendt, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 467. (c) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1272. (d) Marigo, M.; Bertelsen, S.; Landa, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 5475. (e) Hayashi, Y.; Okano, T.; Aratake, S.; Hazelard, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 4922. (f) Cao, C.-L.; Sun, X.-L.; Kang, Y.-B.; Tang, Y. *Org. Lett.* **2007**, *9*, 4151.

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of C−C bonds in organic synthesis, has received much attention in the development of enantioselective catalytic protocols.[5] Domino Michael−Michael (also called "double Michael") reactions have been explored and demonstrated as a powerful tool in organic synthesis.[6] Efficient asymmetric double Michael processes have been achieved by relying on the use of chiral auxiliaries[7] and chiral precursors[8] for stereocontrol. However, the development of organocatalytic enantioselective versions of the reactions proved to be a challenging task, and there have been very few reports[9] regarding the formation of quaternary and tertiary stereocenters with both excellent enantioselectivity and diastereoselectivity using α,β-unsaturated esters as Michael acceptors.

In conjunction with our continuing efforts in exploring new organocatalytic domino reactions,[10] we investigated the domino double Michael reaction. Herein we wish to report the results of an investigation that has led to a novel organocatalytic diastereo- and enantioselective cascade double Michael reaction, in which two C−C bonds and four contiguous stereogenic centers (containing one adjacent quaternary and tertiary stereocenters) were efficiently created in a one-pot operation with an efficient control of stereochemistry. This new catalytic methodology serves as a facile approach to synthetically useful, highly functionalized chiral cyclopentanes.[11]

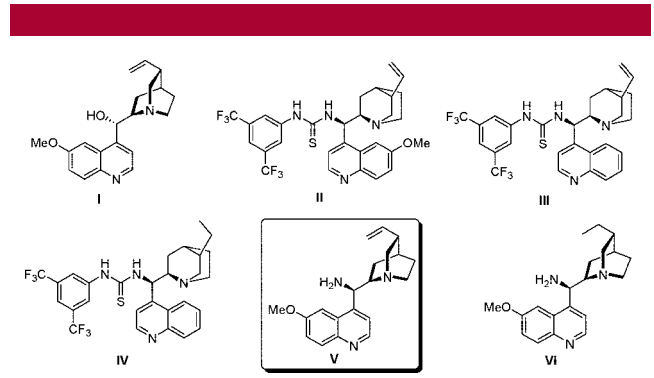

Figure 1. Cinchona alkaloid and derivative catalysts tested in the domino double Michael reactions.

The design of a catalytic cascade double Michael addition reaction required the consideration of several factors. The reactivity of the α,β-unsaturated substrates that participates in the second conjugate addition reaction must be reactive enough to allow the intramolecular Michael reaction. In the meanwhile, these substrates should be less reactive than nitroolefins. Recognition of this reactivity profile allows the design of systems capable of undergoing efficient double Michael addition sequences. Furthermore, a carbon nucleophile should be sufficiently active to only engage in the first Michael addition reaction. To address this concern, we employed easily enolized acetoacetate ester to replace the α,β-unsaturated ester.

Readily accessible cinchona alkaloid and catalyst derivatives, which were developed recently in several research groups, have been identified as efficient bifunctional organocatalysts in asymmetric Michael reactions. To probe the feasibility of the proposed Michael-Michael cascade reacton, we started our inverstigation by reacting nitrostyene with diethyl 5-acetylhex-2-enedioate **2** (*E*:*Z* = 6:1) in the presence of cinchona alkaloid catalyst **I** (15 mol%) at the room temperature (22 °C). To our delight, we were able to isolate the desired product in 81% yield as a single diastereoisomer, even though it is not enantiomerically pure (Table 1, entry 1). In attempts to improve the yield and enantioselectivity, we screened several catalysts and reaction conditions. Catalyst **II** proved to be a very efficient catalyst for Michael reaction. Therefore, we chose **II** as the most promising catalyst to sceen other conditions. However, the results were not improved significantly when the reaction was carried out in different solvents or at different reaction temperatures (Table 1, entries 2−5). As such, we turned our attention to screen more catalysts (in Figure 1, **III**−**VI**) at room temperature. Catalyst **V**[12] was found to be an excellent candidate to catalyze this domino reaction with the highest stereoselectivity (97% ee, >99:1 dr) among all the cases inves-

(4) For a review of tandem reactions, see: (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. For selected examples of tandem reactions, see: (b) Ramachary, D. B.; Chowdari, N. S.; Barbas III, C. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 4233. (c) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. J. *Am. Chem. Soc.* **2004**, *126*, 5962. (d) Zhong, G.; Yu, Y. *Org. Lett.* **2004**, *6*, 1637. (e) Zhong, G. *Chem. Commun.* **2004**, 626. (f) Reyes, E.; Jiang, H.; Milelli, A.; Elsner, P.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 9202. (g) Cabrera, S.; Alemán, J.; Bolze, P.; Bertelsen, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 121. (h) Aroyan, C. E.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 256. (i) Dudding, T.; Hafez, A. M.; Taggi, A. E.; Wagerle, T. R.; Lectka, T. *Org. Lett.* **2002**, *4*, 387. (j) Wang, J.; Xie, H.; Li, H.; Zu, L.; Wang, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4177. (k) Li, H.; Zhang, Y.; Vogel, P.; Sinay, P.; Bleriot, Y. *Chem. Commun.* **2007**, 183. (l) Marigo, M.; Schulte, T.; Franzen, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710. (m) Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1343. (n) Yang, J. W.; Hechavarria, M.; Fonseca, T.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036. (o) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (p) Brandau, S.; Maerten, E.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 14986. (q) Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5168.

(5) For selected reviews regarding Michel addition reactions, see: (a) Berner, O.; Tedeschi, M. L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877. (b) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (c) Almasi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (d) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, 2065.

(6) Review of double Michael reactions, see: (a) Ihara, M.; Fukumoto, K. *Angew. Chem., Int. Ed.* **1993**, *32*, 1010.

(7) Examples using chiral auxiliaries for asymmetric double Michael reactions, see: (a) Saito, S.; Hirohara, Y.; Narahara, O.; Moriwake, T. *J. Am. Chem. Soc.* **1989**, *111*, 4533. (b) Dixon, D. J.; Ley, S. V.; Rodriguez, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 4763.

(8) Examples using chiral precursors for asymmetric double Michael reactions, see: (a) Paquette, L. A.; Tae, J.; Arrington, M. P.; Sadoun, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2742. (b) Hagiwara, H.; Kobayashi, K.; Miya, S.; Hoshi, T.; Suzuki, T.; Ando, M. *Org. Lett.* **2001**, *3*, 251. (c) Herzon, S. B.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 5342. (d) Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 8678.

(9) (a) Zu, L.; Xie, H.; Wang, J.; Tang, Y.; Wang, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3732. (b) Li, H.; Zu, L.; Xie, H.; Wang, J.; Jiang, W.; Wang, W. *Org. Lett.* **2007**, *9*, 1833. (c) Hoashi, Y.; Yabuta, T.; Takemoto, Y. *Tetrahedron Lett.* **2004**, *45*, 9185. (d) Hoashi, Y.; Yabuta, T.; Yuan, P.; Miyabe, H.; Takemoto, Y. *Tetrahedron* **2006**, *62*, 365.

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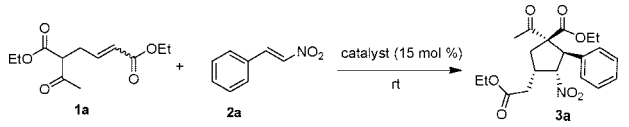
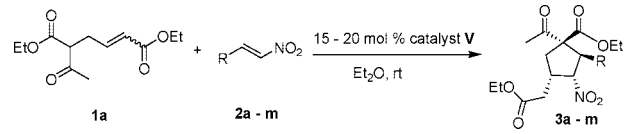
Table 1. Organocatalytic Domino Double Michael Reactions of Ethyl 2-Acetyl-5-oxohexanoate **1a** (*E*:*Z* = 6:1) and *trans*-*β*-Nitrostyrene[a]



entry	catalyst	solvent	*t* (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**I**	neat	6	72	94:6	23
2	**II**	neat	5	73	96:4	79
3	**II**	toluene	8	91	96:4	82
4	**II**	Et_2O	8	90	97:3	83
5[e]	**II**	Et_2O	24	88	97:3	83
6	**III**	Et_2O	8	90	96:4	80
7	**IV**	Et_2O	8	87	96:4	95
8	**V**	Et_2O	16	91	>99:1	97
9	**VI**	Et_2O	16	91	97:3	95
10[f]	**V**	Et_2O	30	85	>99:1	97
11	**V**	toluene	36	86	97:3	90
12[e]	**V**	Et_2O	24	87	>99:1	96
13[g]	**V**	Et_2O	16	82	>99:1	96

[a] Unless otherwise specified, all the reactions were carried out using **1a** (0.3 mmol, 1.0 equiv) and **2a** (0.45 mmol, 1.5 equiv) with 15 mol % of catalyst at room temperature (22 °C). [b] Isolated yields. [c] Determined by NMR and HPLC analysis. [d] Determined by chiral HPLC analysis (major isomer). [e] Reaction at 0 °C. [f] Catalyst (10 mol %) was used. [g] **1a** (0.45 mmol, 1.5 equiv) and **2a** (0.3 mmol, 1.0 equiv) were used.

Table 2. Domino Double Michael Reaction of Ethyl 2-Acetyl-5-oxohexanoate **1a** (*E*:*Z* = 6:1) and Nitroolefins (**2**) Catalyzed by Catalyst **V**[a]



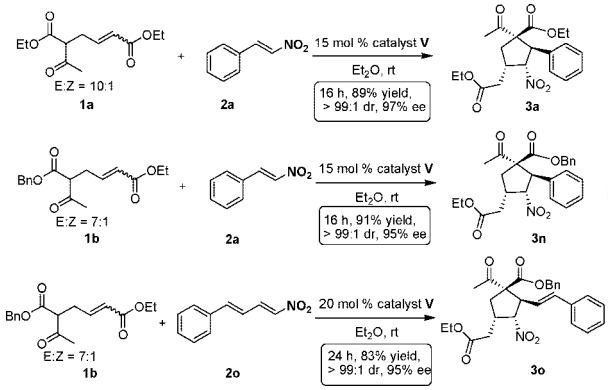
entry	R	**3**	*t* (h)	yield(%)[b]	dr[c]	ee (%)[d]
1	Ph (**2a**)	**3a**	16	91	>99:1	97
2	4-MeC_6H_4 (**2b**)	**3b**	24	89	97:3	95
3	3-MeC_6H_4 (**2c**)	**3c**	24	85	96:4	95
4[e]	4-$MeOC_6H_4$ (**2d**)	**3d**	30	83	96:4	94
5[e]	2-$MeOC_6H_4$ (**2e**)	**3e**	30	81	98:2	90
6	4-BrC_6H_4 (**2f**)	**3f**	16	92	>99:1	95
7	4-ClC_6H_4 (**2g**)	**3g**	16	88	98:2	95
8	2-naphthyl (**2h**)	**3h**	24	84	95:5	95
9	1-naphthyl (**2i**)	**3i**	24	87	97:3	97
10	3-furanyl (**2j**)	**3j**	24	86	98:2	97
11	2-furanyl (**2k**)	**3k**	24	87	95:5	96
12	2-thienyl (**2l**)	**3l**	18	91	>99:1	96
13[e]	4- $O_2NC_6H_4$ (**2m**)	**3m**	36	81	96:4	95

[a] Unless otherwise specified, the reactions were carried out using **1a** (0.3 mmol, 1.0 equiv) and **2** (0.45 mmol, 1.5 equiv) in the presence of 15 mol % of **V** at room temperature in diethyl ether (0.4 mL) (see Supporting Information). [b] Isolated yields. [c] Determined by NMR and HPLC analysis. [d] Determined by chiral HPLC analysis (major isomer). [e] 20 mol % catalyst and 2.0 equiv of **2** were used.

tigated, as shown in the Table 1, entry 10. Further optimization of the reaction conditions elucidated that solvents played a very important role in determining the selectivities of the reaction and yield (diethyl ether, >99:1 dr, 97% ee, 91% yield).

Having estabilizhed the optimal reaction condition, a series of nitroolefins were reacted with unsatuated ester substrates to investigate the generality of the domino double Michael process by using catalyst **V** in diethyl ether. It was observed that most of the reactions are completed within 36 h with good to excellent yields (81−92%), excellent enantioselectivities (90−97% ee) and diastereoselectivities (95:5−>99:1 dr). We would like to highlight that a majority of the examples (shown in Table 2) indicate that the position and electronic property of the substituents on aromatic rings have a very limited effect on the stereoselectivities. Regardless of the types of substituents on the aromatic rings, be it electron-withdrawing (Table 2, entries 6, 7, 13), -donating (entries 2−5), neutral (entry 1, 8, 9) groups and substrates containing a variety of substitution (para, meta, and ortho) groups participated in this reaction efficiently. The heterocyclic thienyl and furanyl groups (Table 2, entries 10−12) also paticipated in this process, giving good yields and enantioselectivities. To our surprise, the presence of the nitro group on the aromatic ring did not cause the enantiomeric excess to decrease. This may be attributed to the primary amine group in the catalyst that can selectively capture the two nitro groups. Interestingly, the ratio (*E*:*Z* = 10:1) of **1a** had no effect on reactivity and selectivity (Scheme 1a). The

Scheme 1. Domino Double Michael Reactions of **1a** with **2a** (*E*:*Z* = 10:1) and **1b** with **2a**/**2o**



domino reaction also proceeded smoothly when **1a** was replaced by **1b**, giving excellent stereoselectivities (95% ee) as displayed in Scheme 1b. Notably, only one double Michael adduct was obtained from the reaction of nitrodiene **2o** in 95% ee value (Scheme 1c). Theoretically, both *β*- and *δ*-

(12) Some papers related to using this type of catalyst: see (a) Xie, J.-W.; Chen, W.; Li, R.; Zeng, M.; Du, W.; Yue, L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Angew. Chem., Int. Ed.* **2007**, *46*, 389. (b) Xie, J.-W.; Yue, L.; Chen, W.; Du, W.; Zhu, J.; Deng, J.-G.; Chen, Y.-C. *Org. Lett.* **2007**, *9*, 413. (c) Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaioli, F.; Sambri, L.; Melchiorre, P. *Org. Lett.* **2007**, *9*, 1403. (d) McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599. (e) Zheng, B.-L.; Liu, Q.-Z.; Guo, C.-S.; Wang, X.-L.; He, L. *Org. Biomol. Chem.* **2007**, *5*, 2913.

positions of **2o** can possibly be attacked due to the congruous two double bonds. This demostrates the high regioselectivity and enantioselectivity of this method.

According to experimental results and the dual activation model,[13] the two substrates involved in the reaction are activaed by catalyst **V** as shown in Figure 2. Nitroolefins

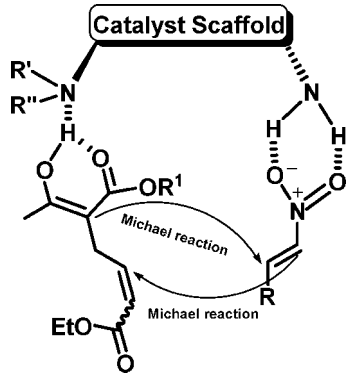


Figure 2. Proposed action of catalyst.

are assumed to interact with the primary amine moiety of **V** via multiple H-bonds. In this case, both the nitro group and β-ketoester group interact with multiple H-bonds so that these two group are on the same side, thus enhancing the electrophilic character of the reacting carbon center and controlling stereochemistry. The carboanion (adjacent to the nitro group) generated from the Michael addition then attacks the double bond of α,β-unsaturated esters to afford double Michael products (Figure 2). The stereochemistry was established by X-ray crystallographic determination of **3g** (Figure 3) and analysis of NMR data of the products.

In summary, we have developed a novel highly enantioselective and diastereoselective organocatalytic domino

(13) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.

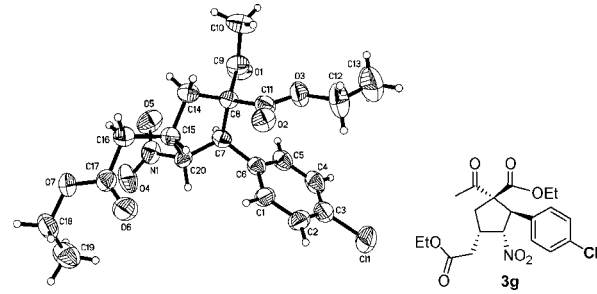


Figure 3. X- ray crystal structure of **3g**.

double Michael reaction that provides expedited access toward highly functionalized cyclopentane derivatives. The structure was confirmed by X-ray analysis of adduct **3g**. Simple operational procedures, high yields (81−91%), excellent enantioselectivity (90−97% ee), diastereoselectivities (95:5−>99:1 dr), and immense potential of synthetic versatility of the products render this new methodology highly appealing for asymmetric synthesis. Further applications of this methodology toward total synthesis of natural products and pharmaceutical agents are currently under active investigation.

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Supporting Information Available: Experimental procedures, characterization, spectra, chiral HPLC conditions, and X-ray crystallograpoic data (CIF file of **3g**: zgf29.cif). This material is available free of charge via the Internet at http://pubs.acs.org.

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