

# A New Organocatalyzed Michael–Michael Cascade Reaction Generates Highly Substituted Fused Carbocycles

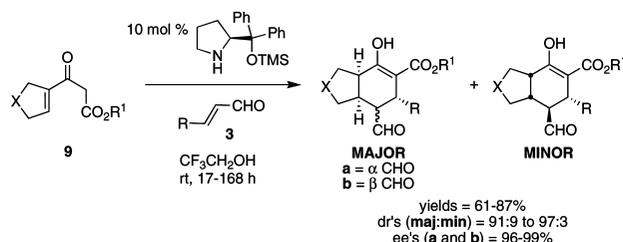
Patrick G. McGarraugh and Stacey E. Brenner\*

Department of Chemistry, Brooklyn College and the City University of New York,  
2900 Bedford Avenue, Brooklyn, New York 11210

sbrenner@brooklyn.cuny.edu

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## ABSTRACT



While  $\beta$ -ketoesters are useful Michael donors, they were previously ineffective in Michael–Michael cascade reactions using  $\alpha,\beta$ -unsaturated aldehydes in conjunction with diphenylprolinol silyl ether organocatalysts. However, through rational modification of substrates and manipulation of the catalytic cycle, we developed an efficient Michael–Michael cascade reaction using  $\beta$ -ketoesters of type **9**. In this transformation, highly substituted fused carbocycles are generated in a single step in up to 87% yield and 99% ee.

Organocatalyzed cascade reactions are a powerful synthetic tool in green chemistry, as environmentally inert catalysts are used in the formation of multiple bonds and stereocenters in a single reaction flask.<sup>1</sup> Diphenyl prolinol silyl ethers such as **1a** (Scheme 1) have recently emerged as highly effective catalysts for organocascade reactions. This class of catalysts has been employed in cascade processes in which the formation of multiple C–C single bonds generates 3-, 5-, or 6-membered carbocycles. These include Michael–S<sub>N</sub>2 alkylation,<sup>2</sup> Michael–aldol,<sup>3</sup> Michael–Knoevenagel,<sup>4</sup> Michael–Mannich,<sup>5</sup> Michael–Henry,<sup>6</sup> Michael–Wittig,<sup>7</sup> and Michael–Michael<sup>8</sup> cascade reactions.

Among the latter class of reactions, of those cascades initiated by activation of an  $\alpha,\beta$ -unsaturated aldehyde through iminium catalysis, a  $\beta$ -dicarbonyl compound was used as a Michael

donor in only one example<sup>8b</sup> (reaction 1, Scheme 1), despite the fact that this type of Michael donor is commonly employed in organocatalytic conjugate addition reactions.<sup>9</sup> However, when the unsaturation was relocated relative to the  $\beta$ -dicarbonyl moiety in an attempt to form substituted cyclohexanes, the

(1) For a review, see: Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581.

(2) (a) Xie, H.; Zu, L.; Li, H.; Wang, J.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 5835–5839. (b) Vesely, J.; Zhao, G.-L.; Bartoszewicz, A.; Córdova, A. *Tetrahedron Lett.* **2008**, *49*, 4209–4212. (c) Ibrahim, I.; Zhao, G.-L.; Rios, R.; Vesely, J.; Sundén, H.; Dziedzic, P.; Córdova, A. *Chem.–Eur. J.* **2008**, *14*, 7867–7879.

(3) (a) Marigo, M.; Bertelsen, S.; Landa, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 5475–5479. (b) Enders, D.; Narine, A. A.; Benninghaus, T. R.; Raabe, G. *Synlett* **2007**, 1667–1670. (c) Wang, J.; Li, H.; Xie, H.; Zu, L.; Shen, X.; Wang, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 9050–9053. (d) Hong, B.-C.; Nimje, R. Y.; Sadani, A. A.; Liao, J.-H. *Org. Lett.* **2008**, *10*, 2345–2348. (e) Zhao, G.-L.; Dziedzic, P.; Ullah, F.; Eriksson, L.; Córdova, A. *Tetrahedron Lett.* **2009**, *50*, 3458–3462. (f) Rueping, M.; Kuenkel, A.; Tato, F.; Bats, J. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 3699–3702. (g) Enders, D.; Wang, C.; Bats, J. W. *Synlett* **2009**, 1777–1780.

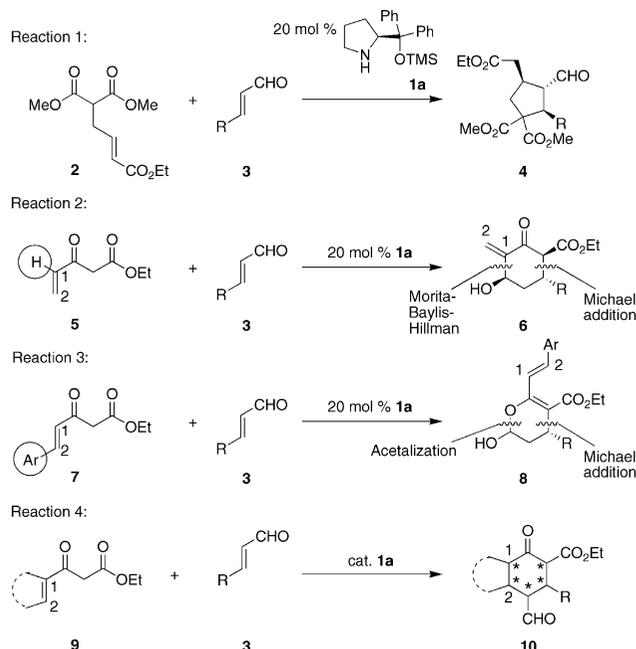
(4) (a) Hayashi, Y.; Toyoshima, M.; Hiroaki, G.; Ishikawa, H. *Org. Lett.* **2009**, *11*, 45–48. (b) Łukasz, A.; Richter, B.; Vila, C.; Krawczyk, H.; Jørgensen, K. A. *Chem.–Eur. J.* **2009**, *15*, 3093–3102.

(5) Ibrahim, I.; Rios, R.; Vesely, J.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 6252–6257.

(6) (a) Hayashi, Y.; Okano, Y.; Aratake, S.; Hazelard, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 4922–4925. (b) Reyes, E.; Jiang, H.; Milelli, A.; Elsner, P.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 9202–9205.

(7) Liu, Y.-k.; Ma, C.; Jiang, K.; Liu, T.-Y.; Chen, Y.-C. *Org. Lett.* **2009**, *11*, 2848–2851.

### Scheme 1. 1a-Catalyzed Cascade Reactions



desired transformation (i.e., reaction 4) was surprisingly not observed. When conjugated  $\beta$ -ketoesters with terminal, mono-substituted olefins (**5**) were used, the initial Michael addition was instead followed by a Morita–Baylis–Hillman reaction (reaction 2).<sup>10</sup> Alternatively, when conjugated  $\beta$ -ketoesters with internal olefins (**7**) were used, subsequent to the initial Michael addition, acetal formation occurred in lieu of another Michael addition (reaction 3).<sup>11</sup> Presumably, the second Michael addition is kinetically slow and/or thermodynamically unfavorable, as it would disrupt the highly conjugated system.

We reasoned that using conjugated  $\beta$ -ketoesters of type **9**, in which the olefin is part of a carbocycle, would modulate the reactivity of these substrates and might enable the desired Michael–Michael cascade reaction. First, disubstitution at the 1-position of the alkene would preclude the undesired Morita–Baylis–Hillman pathway. Additionally, the fact that the alkene is cyclic and is not part of a system with extended conjugation

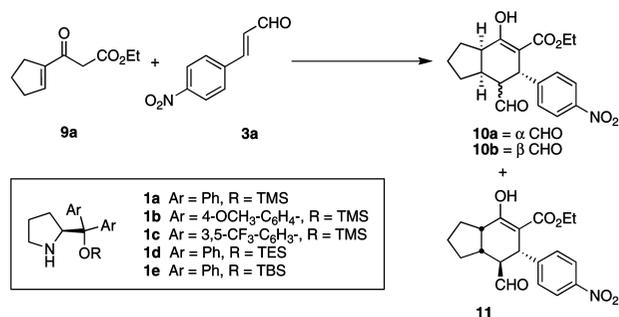
(8) (a) Enders, D.; Hüetl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861–863. (b) Zu, L.; Li, H.; Xie, H.; Wang, J.; Jiang, W.; Tang, Y.; Wang, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3732–3734. (c) Carlone, A.; Cabrera, S.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1101–1104. (d) Bor-Cheng, H.; Nimje, R. Y.; Wu, M.-F.; Sadani, A. A. *Eur. J. Org. Chem.* **2008**, 1449–1457. (e) Penon, O.; Carlone, A.; Mazzanti, A.; Locatelli, M.; Sambri, L.; Bartoli, G.; Melchiorre, P. *Chem.–Eur. J.* **2008**, *14*, 4788–4791. (f) Zhao, G.-L.; Ibrahim, I.; Dziedzic, P.; Sun, J.; Bonneau, C.; Córdova, A. *Chem.–Eur. J.* **2008**, *14*, 10007–10011. (g) Bencivenni, G.; Wu, L.-Y.; Mazzanti, A.; Giannichi, B.; Pescioli, F.; Song, M.-P.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1–5. (h) Hong, B.-C.; Nimje, R. Y.; Liao, J.-H. *Org. Biomol. Chem.* **2009**, 3095–3101.

(9) For a review of organocatalyzed conjugate addition reactions, including those involving  $\beta$ -dicarbonyl compounds as Michael donors, see Almási, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299–365.

(10) Cabrera, S.; Alemán, J.; Bolze, P.; Bertelsen, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 121–125.

(11) Zhu, M.-K.; Wei, Q.; Gong, L.-Z. *Adv. Synth. Catal.* **2008**, *350*, 1281–1285.

### Table 1. Catalyst Optimization<sup>a</sup>



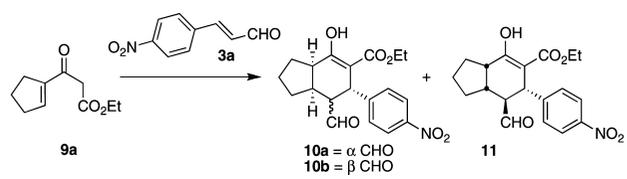
entry	catalyst	solvent	time (h)	% conversion <sup>b</sup>	dr (10:11) <sup>b</sup>	% ee (10a) <sup>c</sup>	% ee (10b) <sup>c</sup>
1 <sup>d</sup>	<b>1a</b>	DCE	240	13	78:22	nd	nd
2	<b>1a</b>	DCE	168	25	84:16	99	99
3	<b>1a</b>	EtOH	168	61	78:22	99	99
4	<b>1b</b>	EtOH	168	20	85:15	87	99
5	<b>1c</b>	EtOH	168	0	nd	nd	nd
6	<b>1d</b>	EtOH	168	66	79:21	99	98
7	<b>1e</b>	EtOH	216	65	80:20	87	96

<sup>a</sup> Reaction conditions: **3a** (1 equiv), **9a** (1 equiv), cat. (20 mol %), PhCOOH (20 mol %), solvent (0.3 M), rt. <sup>b</sup> Determined by <sup>1</sup>H NMR of crude reaction mixture. <sup>c</sup> Determined by chiral HPLC. <sup>d</sup> Reaction run without PhCOOH.

may alter the kinetic and thermodynamic preference, respectively, for the desired Michael addition pathway relative to the undesired acetalization pathway. Moreover, substrates of type **9** would produce highly substituted fused carbocycles, with a chiral catalyst, as well as the thermodynamic preference for the ring junction, establishing multiple stereocenters.

Using conjugated  $\beta$ -ketoester **9a**, the **1a**-catalyzed Michael–Michael cascade reaction with **3a** in DCE did generate **10** and **11**, albeit in very low conversion even after 10 days (entry 1, Table 1). While the initial Michael addition was complete within 12 h, the subsequent Michael addition was exceedingly sluggish. To promote this second step, a preliminary screen of additives known to facilitate catalyst turnover (i.e., benzoic acid) or to enhance enamine formation (i.e., Et<sub>3</sub>N, NaOAc) was carried out. While basic additives did not accelerate the reaction (data not shown), with benzoic acid, enhanced diastereomeric ratios and excellent ee's of the major diastereomer, **10b**, and its epimer, **10a**, were achieved (entry 2). Although the conversion was also improved, it was still low after extended reaction times. As suspected, ethanol, a protic solvent that can participate in hydrogen bonding interactions with the  $\beta$ -ketoester moiety, further accelerated the second Michael addition and greatly improved conversion (entry 3).

The use of a more electron-rich catalyst, **1b**, drastically slowed both Michael additions in the cascade reaction (entry 4), while the use of a more electron-deficient catalyst, **1c**, completely suppressed the second Michael addition (entry 5). Catalysts with different silyl groups did not provide both **10a** and **10b** in 99% ee, as had catalyst **1a** (entries 6 and 7). In all cases, the ee of the minor diastereomer, **11**, was diminished relative to that of **10a** and **10b**, ranging from 33% (using **1d**) to 82% (using **1b**).

**Table 2.** Optimization of Reaction Conditions<sup>a</sup>


entry	mol % of <b>1a</b>	additive	solvent	time (h)	% conversion <sup>b</sup>	dr ( <b>10a</b> : <b>11</b> ) <sup>b</sup>	ee ( <b>10a</b> ) <sup>c</sup>	ee ( <b>10b</b> ) <sup>c</sup>
1	20	PhCO <sub>2</sub> H	toluene	168	5	80:20	nd	nd
2	20	PhCO <sub>2</sub> H	Et <sub>2</sub> O	168	<1	nd	nd	nd
3	20	PhCO <sub>2</sub> H	THF	168	0	nd	nd	nd
4	20	PhCO <sub>2</sub> H	MeCN	168	32	93:7	99	99
5	20	PhCO <sub>2</sub> H	CF <sub>3</sub> CH <sub>2</sub> OH	2	12	89:11	nd	nd
6	20	PhCO <sub>2</sub> H	CF <sub>3</sub> CH <sub>2</sub> OH	41	17	91:9	99	99
7	20		CF <sub>3</sub> CH <sub>2</sub> OH	17	85	90:10	99	99
8	10		CF <sub>3</sub> CH <sub>2</sub> OH	17	87	91:9	99	99
9	5		CF <sub>3</sub> CH <sub>2</sub> OH	17	80	91:9	99	99
10	1		CF <sub>3</sub> CH <sub>2</sub> OH	88	25	88:12	99	99
11 <sup>d</sup>	5		CF <sub>3</sub> CH <sub>2</sub> OH	46	76	92:8	99	99

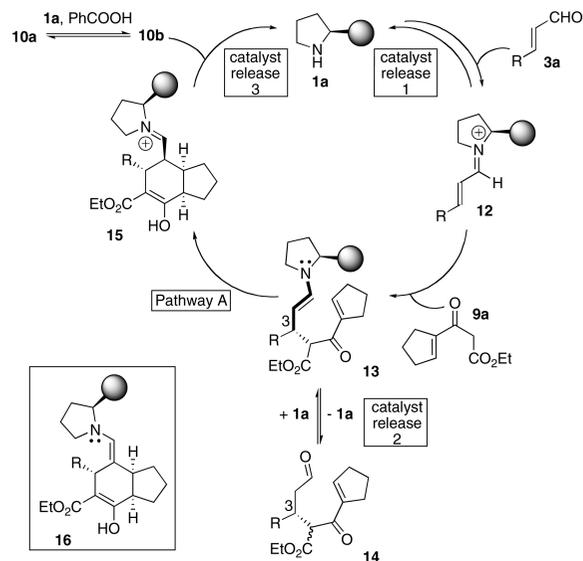
<sup>a</sup> Reaction conditions: **3a** (1 equiv), **9a** (1 equiv), **1a**, additive (20 mol %), solvent (0.3 M), rt. <sup>b</sup> Determined by <sup>1</sup>H NMR of crude reaction mixture. <sup>c</sup> Determined by chiral HPLC. <sup>d</sup> Reaction run at 0 °C.

With optimal catalyst **1a** in hand, optimization of other reaction conditions ensued. Both nonpolar solvents and polar aprotic solvents led to substantially reduced conversions relative to reactions run in ethanol (entries 1–4, Table 2). Switching to trifluoroethanol, a solvent that is a stronger hydrogen bond donor than ethanol, gave surprising results.

After only 2 h, product formation was detected (entry 5). Additionally, the ratio of **10a**:**10b** was 1:29, whereas in all previous experiments the ratios of **10a**:**10b** ranged from 1:1.4 to 1.7:1. After 41 h, there was little improvement in conversion, but the ratio of **10a**:**10b** was 1:5 (entry 6). Moreover, the first Michael addition had not gone to completion under these conditions; the single Michael adduct along with substantial amounts of **3a** and **9a** were present after 41 h. As the diastereomeric ratio and ee's were both excellent in this solvent, we sought to improve the conversion. Consideration of these, and other, observations with respect to the proposed mechanism of this transformation (Scheme 2) provided insight as to how to accomplish this.

First, the observation that the initial Michael addition had not gone to completion indicated that either the “catalyst release 1” pathway of iminium **12** competes with the Michael addition to **12** or that **14** can revert back to starting materials. Subjecting single Michael adduct **14** to catalyst **1a** and benzoic acid in trifluoroethanol resulted in rapid conversion to **10** only, revealing that the formation of **14** is not reversible. Thus, the “catalyst release 1” pathway appears to be favored in the presence of benzoic acid in trifluoroethanol more so than in other solvents.

When the initial Michael addition does occur to provide **13**, if pathway A is followed, the second Michael addition occurs. In trifluoroethanol, this second Michael addition is rapid, as evidenced by the conversion to **10** within 2 h. However, in this solvent, as in other solvents, **13** prefers the “catalyst release 2” pathway, which provides single Michael adduct **14**. Compound

**Scheme 2.** Proposed Catalytic Cycle

**14** can react with **1a** to re-enter the catalytic cycle and go on to product, as rapidly occurs in the absence of **3a**. However, for reasons explained above, in trifluoroethanol and benzoic acid, there would be a substantial amount of **3a** in solution, which evidently competes for the catalyst. Together, this accounts for the presence of **14** after 41 h and for the plateau in conversion to **10** (entry 6, Table 2).

Finally, since epimerization of **10a** and **10b** occurs in the presence of benzoic acid and **1a**, but not benzoic acid alone, we speculated that it proceeds via an enamine intermediate (**16**), and not via a keto–enol equilibrium. The fact that the conversion to **10a** and **10b** did not change dramatically over the course of 39 h under these conditions, while the ratio of **10a** to **10b** did, suggests that **10b** formed first and was slowly converted to, and reaching equilibrium with, **10a**. It would therefore appear that in the presence of benzoic acid in trifluoroethanol, “catalyst release 3” predominates over formation of enamine **16** either from **15** prior to catalyst release or from **10b** (via **15**) after its ejection from the catalytic cycle.

Thus, whereas in other solvents a sluggish second Michael addition hampered conversion, these observations collectively implied that under these conditions, catalyst release (i.e., turnover) was the culprit. Impeding catalyst release from **12** and from **13** should enable a rapid, efficient, and highly selective Michael–Michael cascade reaction. We therefore ran the reaction in the absence of benzoic acid, which, as mentioned earlier, is known to facilitate catalyst turnover. Gratifyingly, this led to 85% conversion, 9:1 dr, and 99% ee of **10a** and **10b** (present in a 1:1.1 ratio) in only 17 h (entry 7, Table 2)!

Lowering the catalyst loading to 10 mol % slightly improved both conversion and diastereoselectivity (entry 8). A catalyst loading of 5 mol % led to a slight decrease in conversion but maintained the high selectivity of the reaction (entry 9). Further lowering of the catalyst loading to 1 mol % resulted in reduced conversion and a slight erosion of diastereoselectivity (entry

**Table 3.** Substrate Scope<sup>a</sup>

$\text{MAJOR}$   
 $\text{a} = \alpha \text{ CHO}$   
 $\text{b} = \beta \text{ CHO}$

entry	Product (major)	time (h)	yield (%) <sup>b</sup>	dr (maj:min) <sup>c</sup>	% ee (a) <sup>d</sup>	% ee (b) <sup>d</sup>
1		20	82	92:8	99	98
2		17	79	93:7	99	99
3		40	87	92:8	99	98
4		168	79	93:7	99	99
5		142	61	97:3	98	98
6		22	67	97:3	98	98
7		21	76	91:9	97	98
8		28	80	93:7	98	96

<sup>a</sup> Reaction conditions: **3** (1 equiv), **9** (1 equiv), **1a** (10 mol %), CF<sub>3</sub>CH<sub>2</sub>OH (0.3 M), rt. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by <sup>1</sup>H NMR of isolated products. <sup>d</sup> Determined by chiral HPLC.

10). Finally, running the reaction at 0 °C led to a more sluggish reaction with a nominal improvement in diastereoselectivity (entry 11).

Using 10 mol % **1a** and trifluoroethanol as solvent at rt, an investigation of substrate scope was undertaken (Table 3). The **1a**-catalyzed Michael–Michael cascade reaction afforded products in high yields and high selectivity using  $\alpha,\beta$ -unsaturated aromatic aldehydes with electron-withdrawing, electron-releasing, and electronically neutral substitution at either the *meta*- or *para*-position (entries 1–4). However, *ortho* (nitro) substitution was not tolerated. In addition,  $\alpha,\beta$ -unsaturated aldehydes with heteroaromatic and nonaromatic substituents afforded products in slightly reduced yields, but in 98% ee and 97:3 dr (entries 5 and 6). Finally, different ester substituents (entry 7) and, notably, heteroatom substitution in the cyclopentane ring (entry 8) were well-tolerated in this reaction, leading to rapid and highly selective product formation. A ketoester with a cyclohexane (i.e., **9** where X = (CH<sub>2</sub>)<sub>2</sub>) formed additional diastereomers in this reaction (data not shown).

A model for the stereochemical outcome of this reaction is depicted in Scheme 2. The stereochemistry at C3 was assigned by analogy with other **1a**-catalyzed conjugate additions and is assumed to arise from the initial Michael addition occurring from the face opposite the bulky group in iminium **12**. The remaining stereochemistries were established by X-ray crystallography (see the Supporting Information). They are consistent with the intramolecular Michael addition of **13** occurring with the Michael acceptor approaching the enamine from the face opposite, and the proton at C3 projected out toward, the bulky group. Additionally, we established that **10a** and **10b** were epimers by subjecting pure **10a** to benzoic acid in the presence of **1a**, which produced a mixture of **10a** and **10b**.

In conclusion, through rational modification of substrates and manipulation of the catalytic cycle, we developed a new, efficient **1a**-catalyzed Michael–Michael cascade reaction. This transformation generates highly substituted, fused carbocycles with dr's  $\geq 91:9$  and ee's  $\geq 96\%$ . Further investigations into this and other novel, **1a**-catalyzed cascade reaction(s) are presently underway.

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**Supporting Information Available:** General experimental conditions and full characterization data for compounds **9b,9c, 10a, 10b, 11, 17a, 17b, 18a, 18b, 19a, 19b, 20a, 20b, 21a, 21b, 22a, 22b, 23a, 23b, 24a** and **24b**, including an X-ray crystal structure of **10a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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