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# Sequential Organocatalytic Stetter and Michael-Aldol Condensation Reaction: Asymmetric Synthesis of Fully Substituted Cyclopentenes via a [1 + 2 + 2] Annulation Strategy

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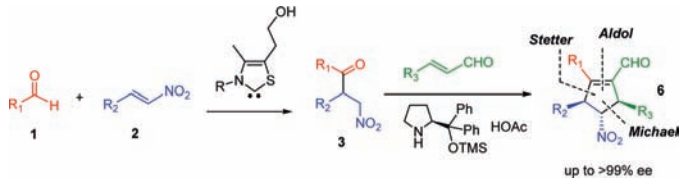
## ABSTRACT




**A stereoselective synthesis of fully substituted cyclopentenes has been achieved by a sequential organocatalyzed Stetter and Michael-aldol condensation of aromatic aldehydes, nitroalkenes, and α,β-unsaturated aldehydes via the [1 + 2 + 2] annulation strategy with excellent diastereoselectivities and enantioselectivities (up to >99% ee).**

Among the vast number of organocatalytic reactions reported, the reactions catalyzed by *N*-heterocyclic carbenes (NHCs)[1] represent a unique category, especially, the umpolung of classical carbonyl activity, which includes benzoin condensation,[2] homoenolate reactions,[3] and Stetter reactions.[4] The asymmetric intramolecular Stetter reaction was first introduced by Enders[5] and later studied by Rovis,[6] and many other examples have since been demonstrated.[7] However, much less success has been reported for the organocatalytic enantioselective intermolecular Stetter reaction.[8,9] Only one example of the intermolecular Stetter reaction of aromatic heterocyclic aldehydes and nitroolefins has been uncovered.[10,11] On the other hand, organocatalyzed [3 + 2] annulations toward cyclopentane and cyclopentene derivatives have been accomplished recently via Michael-aldol,[12] Michael/α-alkylation,[13] double Michael,[14] Michael−Henry,[15] homoenolate Micha-

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el-aldol,[16] benzoin-oxy-Cope,[17] phosphane-catalyzed [3 + 2] dipolar cycloaddition,[18] and iminium-enamine metal-catalyzed enyne cycloisomerization.[19] The cyclopentanes prepared from these methods were highly functionalized, but these compounds still bore an unfunctionalized methylene moiety in the five-membered ring systems. Therefore, an alternative annulation method toward fully functionalized (fully substituted) cyclopentane derivatives is certainly attractive.[20] Taking into account the above observations in the context of asymmetric synthesis, especially for multicomponent reactions,[21] we envisioned an approach to fully substituted cyclopentenes that could be accomplished by a sequential Stetter and Michael-aldol condensation reaction[22] of aromatic aldehydes, nitroalkenes, and α,β-unsaturated aldehydes via the unprecedented multicomponent [1 + 2 + 2] annulation strategy (Scheme 1). Initially, a β-nitroketone could be prepared from the intermolecular Stetter reaction of an aldehyde with a nitroalkene followed by the cascade organocatalytic Michael-aldol reactions of the β-nitroketone with an α,β-unsaturated aldehyde to provide the fully functionalized cyclopentenes. In this paper, we explore the feasibility of such an idea; this work culminates in the asymmetric synthesis of fully substituted cyclopentenes with an unusual kinetic resolution of 2-alkyl-3-nitroalkanone, a base-sensitive β-nitroketone.[23] Our initial efforts focused on the systematic evaluation of various catalysts and reaction conditions to optimize the intermolecular Stetter reaction of **1** and **2** (Table 1). We began our preparation of β-nitroketones by screening several thiazolium- and imidazolium-based precatalysts, e.g., **I**−**III**. The initial reaction provided **3a** in moderate yield (55%) from **1a** and **2a** with the precatalyst **I** and $Cs_2CO_3$ (Table 1, entry 1). The same reaction with other base additives, e.g., $K_2CO_3$, $Et_3N$, and DIEPA, unfortunately gave lower yields of **3a** (Table 1, entries 2−4). The β-nitroketone compounds are somewhat sensitive to basic conditions, and a large amount of 1-phenyl-2-methylenepentan-1-one (**4**) was obtained in these reactions. The same reaction using the precatalyst **II** provided a

**Scheme 1.** [1 + 2 + 2] Annulation Approach to Cyclopentenes

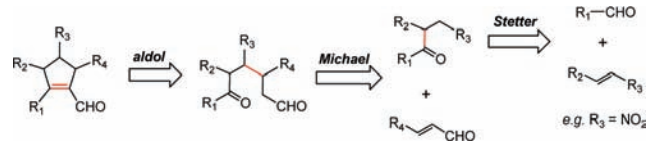
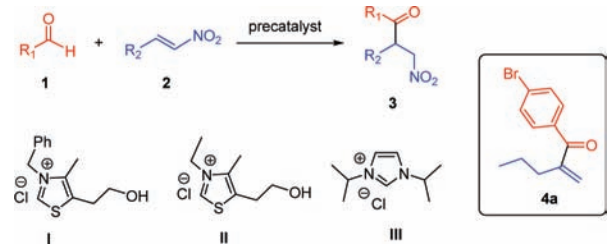



**Table 1.** Screening of Catalysts and Conditions for the Stetter Reaction of **1** and **2**[a]




| entry | product | cat. | additive (20 mol %) | time (h) | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **3a** $R_1 = p$-$BrC_6H_4$; $R_2 = n$-Pr | **I** | $Cs_2CO_3$ | 0.25 | 55 |
| 2 | **3a** $R_1 = p$-$BrC_6H_4$; $R_2 = n$-Pr | **I** | $K_2CO_3$ | 8 | 16 |
| 3 | **3a** $R_1 = p$-$BrC_6H_4$; $R_2 = n$-Pr | **I** | $Et_3N$ | 6 | 12 |
| 4 | **3a** $R_1 = p$-$BrC_6H_4$; $R_2 = n$-Pr | **I** | DIEPA | 3 | 24 |
| 5 | **3a** $R_1 = p$-$BrC_6H_4$; $R_2 = n$-Pr | **II** | $Cs_2CO_3$ | 0.5 | 16 |
| 6 | **3a** $R_1 = p$-$BrC_6H_4$; $R_2 = n$-Pr | **III** | $Cs_2CO_3$ | 10 | 0 |
| 7 | **3b** $R_1 = p$-$BrC_6H_4$; $R_2 = n$-$C_6H_{13}$ | **I** | $Cs_2CO_3$ | 0.33 | 52 |
| 8 | **3c** $R_1 = p$-$ClC_6H_4$; $R_2 = n$-$C_6H_{13}$ | **I** | $Cs_2CO_3$ | 0.5 | 48 |

[a] Unless otherwise noted, the reactions were performed in 0.13 M **1** with a ratio 1:1.2 of **1**/**2** at 25 °C. [b] Isolated yields of the adducts **3**.

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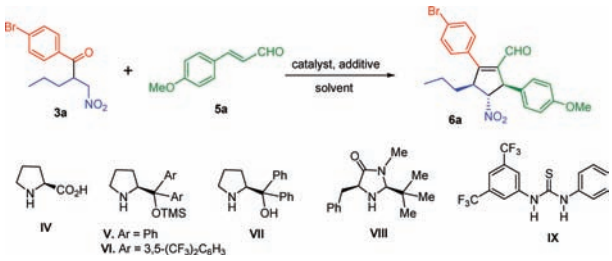
lower yield, and attempts with precatalyst **III** afforded no product **3** (Table 1, entries 5−6). Several $\beta$-nitroketones (**3b**, **3c**) were prepared via the **I**−$Cs_2CO_3$ conditions (Table 1, entries 7 and 8).

With the $\beta$-nitroketone **3a** in hand, several catalysts and reaction conditions were screened to explore the feasibility of the domino Michael-aldol condensation (Table 2). At the outset of this study,

**Table 2.** Screening of Catalysts and Optimization for the Domino Michael-Aldol Reaction[a]



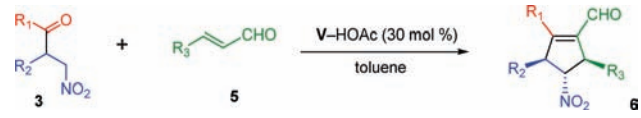

| entry | cat. (mol %) | additive[b] | solvent | time (h) | yield[c] (%) |
|---|---|---|---|---|---|
| 1 | **IV** (30) | | $CH_3CN$ | 160 | ~0 |
| 2 | **V** (30) | $CH_3CO_2H$ | EtOH | 160 | ~0 |
| 3 | **V** (30) | $CH_3CO_2H$ | DMF | 164 | ~0 |
| 4 | **V** (30) | $CH_3CO_2H$ | $CH_2Cl_2$ | 165 | trace |
| 5 | **V** (30) | $CH_3CO_2H$ | $CH_3CN$ | 171 | trace |
| 6 | **V** (30) | $CH_3CO_2H$ | $CHCl_3$ | 96 | 18 |
| 7 | **V** (30) | $CH_3CO_2H$ | $Et_2O$ | 98 | 19 |
| 8 | **V** (30) | $CH_3CO_2H$ | toluene | 144 | 36 |
| 9 | **V** (30) | $PhCO_2H$ | toluene | 105 | 26 |
| 10 | **V** (30) | PNBA | toluene | 153 | 27 |
| 11 | **V** (30) | DABCO | toluene | 90 | ~0 |
| 12 | **VI** (30) | $CH_3CO_2H$ | toluene | 100 | trace |
| 13 | **VII** (30) | $CH_3CO_2H$ | toluene | 100 | ~0 |
| 14 | **VIII** (30) | $CF_3CO_2H$ | toluene | 120 | trace |
| 15 | **IX** (30) | − | toluene | 120 | ~0 |

[a] Unless otherwise noted, the reactions were performed in 0.25 M **5a** with a ratio 2.4:1 of **3a**/**5a** at 25 °C. [b] Additive/catalyst = 1:1. [c] Isolated yields of the adducts **6a**.

reaction of **3a** and **5a** with L-Pro (**IV**) in $CH_3CN$ gave the disappointing outcome of no expected product **6a** (Table 2, entry 1). The same reaction with the Jørgensen−Hayashi catalyst (**V**) and acetic acid in EtOH, DMF, $CH_2Cl_2$, and $CH_3CN$ also provided no or only trace amounts of **6a** (Table 2, entries 2−5). Satisfyingly, the same reaction conditions in $CHCl_3$, $Et_2O$, or toluene provided **6a**, although in moderate yields (Table 2, entries 6−8). Replacement of acetic acid with benzoic acid or *p*-nitrobenzoic acid did not improve the yields (Table 2, entries 9 and 10). When DABCO was substituted for the acid, no product **6a** was observed (Table 2, entry 11). Moreover, the reactions with other catalysts, e.g., **VI**−**IX**, were fruitless (Table 2, entries 12−14).

Having established the optimal reaction conditions for **6a**, although moderate yields only were obtained, we investigated the use of the $\beta$-nitroketone **3** and $\alpha,\beta$-unsaturated aldehydes **5** for synthesizing a variety of fully substituted cyclopentene derivatives **6**. The all-*trans* isomers (**6a**−**k**) were, in all cases, the only observable diastereoisomers with high enantioselectivities (92% to >99% ee, entries 1−11, Table 3). Because $\beta$-nitroketones **3** was somewhat unstable and a certain amount of material tended to be diverted to the production of **4**, a ratio 2.4:1 of racemic **3** to **5** was

**Table 3.** Scope of the Domino Michael-Aldol Condensation[a]




| entry | product | time (h) | yield[b] %[c] (%)[d] | ee (%)[d] |
|---|---|---|---|---|
| 1 | **6a** $R_1$ = *p*-$BrC_6H_4$; $R_2$ = *n*-Pr; $R_3$ = 4-$OMeC_6H_4$ | 170 | 54 (36) | >99[e] |
| 2 | **6b** $R_1$ = *p*-$BrC_6H_4$; $R_2$ = *n*-Pr; $R_3$ = 3,4-$(OMe)_2C_6H_4$ | 168 | 60 (24) | 97[f] |
| 3 | **6c** $R_1$ = *p*-$BrC_6H_4$; $R_2$ = *n*-Pr; $R_3$ = 3,4,5-$(OMe)_3C_6H_4$ | 162 | 62 (31) | 96[f] |
| 4 | **6d** $R_1$ = *p*-$BrC_6H_4$; $R_2$ = *n*-Pr; $R_3$ = pyridin-3-yl | 157 | 56 (24) | >99[f] |
| 5 | **6e** $R_1$ = *p*-$BrC_6H_4$; $R_2$ = *n*-Pr; $R_3$ = 3-OMe-4-$OAcC_6H_4$ | 165 | 63 (21) | 98[f] |
| 6 | **6f** $R_1$ = *p*-$BrC_6H_4$; $R_2$ = *n*-Pr; $R_3$ = 3-OMe-4-$OEt$-$C_6H_4$ | 168 | 72 (30) | 99[f] (77)[g] |
| 7 | **6g** $R_1$ = *p*-$BrC_6H_4$; $R_2$ = *n*-hexyl; $R_3$ = 4-$OMeC_6H_4$ | 163 | 55 (25) | 99[f] |
| 8 | **6h** $R_1$ = *p*-$BrC_6H_4$; $R_2$ = *n*-hexyl; $R_3$ = 3-OMe-4-$OEt$-$C_6H_4$ | 173 | 65 (22) | 97[f] |
| 9 | **6i** $R_1$ = *p*-$BrC_6H_4$; $R_2$ = *n*-Pr; $R_3$ = 3-$NO_2$-$C_6H_4$ | 148 | 48 (19) | >99[f] |
| 10 | **6j** $R_1$ = *p*-$ClC_6H_4$; $R_2$ = *n*- hexyl; $R_3$ = 3-OMe-4-$OEt$-$C_6H_4$ | 172 | 68 (25) | 96[f] |
| 11 | **6k** $R_1$ = *p*-$BrC_6H_4$; $R_2$ = *n*-Pr; $R_3$ = 4-$NMe_2$-$C_6H_4$ | 169 | 58 (23) | 92[e] |

[a] Unless otherwise noted, the reactions were performed in 0.25 M of **5** with a ratio 2.4:1 of **3**/**5** at 25 °C. [b] Isolated yields of the adducts **6**. [c] Isolated yields by Method B: catalyst **V** was added in seven portions (a total accumulated quantity of 30 mol %) in 24 h intervals. [d] Isolated yields by Method A in parentheses (30 mol % **V** was added at once in the beginning). [e] Determined by HPLC with a chiral column (Chiracel OD-H). [f] Determined by HPLC with a chiral column (Chiralpak IA). [g] Values in parentheses indicate the enantiomeric excess of the recovered **3a** after 168 h reaction, analyzed by Chiracel OD-H.

applied in the reactions. The high enantiomeric excess of **6** obtained under these conditions provided evidence for the kinetic asymmetric transformation in the domino Michael-aldol condensation of racemic **3** with **5**.[24] This transformation contributes to the few examples of organocatalytic aldol condensation of aromatic ketones with aldehydes.[25] On the other hand, the observation of an intermediate **7**[26] in these reactions implied that the moderate isolated yields (19−36%) probably arose because formation of the stable **7** by consumption of the catalyst **V** resulted in early termination of the catalytic cycle during the domino reaction process.[27] Unfortunately, the parasitical dead-end product **7** of the cascade reaction was quite stable with respect to a variety of acid and moisture conditions, and several attempts to modify the reaction conditions to regenerate the active catalyst **V** from **7** in the reaction sequence were in vain. To sustain sufficient quantities of catalyst during the reaction progress, catalyst **V** was added in seven portions (a total accumulated quantity of 30 mol %, the same amount of catalyst used previously) in 24 h intervals (Method B). The reaction series was repeated using the new method, and the resulting yields

(24) An enantiomeric excess of 77% for the recovered **3a** was observed after 168 h of reaction.

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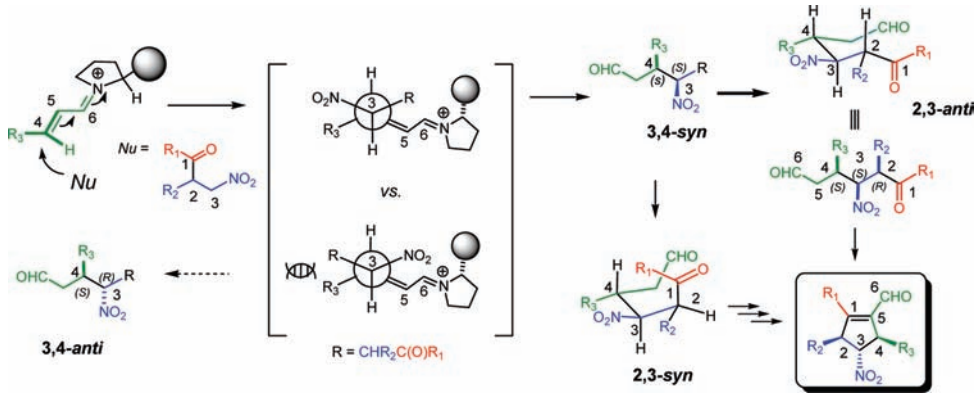
**Scheme 2.** Plausible Reaction Mechanism




doubled or even tripled in all cases with good yields and with the same high enantioselectivities (Table 3, entries 1−11, 48−72% yields).

The structure and relative stereochemistry of the reaction adduct was revealed by single-crystal X-ray analysis of the racemic (±)-**6a**, prepared by pyrrolidine−HOAc catalysis (Figure 1). In addition, the absolute configuration of the product was assigned unambiguously on the basis of an X-ray analysis of (+)-**6c** (Figure 1). Thus, the origin of the stereoselectivity in this nitro-Michael reaction by catalyst **V** was similar to that observed in other examples of organocatalysis.[28] To explain the stereochemistry of this transformation, a plausible mechanism was proposed, as shown in Scheme 2. The reaction was initiated from the iminium activation of the α,β-unsaturated aldehyde by catalyst **V** followed by the nitro-Michael addition of the nitroalkane nucleophile from the *re* face under the control of the catalyst to give an intermediate with a 4-*S* configuration. It is interesting to note that the stereochemistry of the 3,4-*syn* alkanal adduct was consistent with the relative topicity previously observed for other organocatalytic nitro-Michael additions.[28] Nevertheless, the formation of the (2*R*,3*S*,4*S*)-alkanal with 2,3-*anti* stereoselectivity in these reactions is unprecedented. The resulting intermediate subsequently underwent intramolecular aldol condensation of the aldehyde and ketone to give the cyclopent-1-enecarbaldehyde **6**.[29]

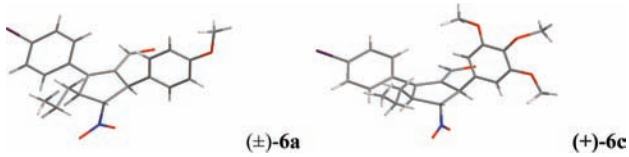



**Figure 1.** Stereoplots of the X-ray crystal structures of (±)-**6a** and (+)-**6c**: C, gray; N, blue; O, red; Br, purple.

In conclusion, we have discovered an unprecedented sequential organocatalytic Stetter and Michael-aldol condensation reaction with evidence of a kinetic asymmetric transformation. Remarkably, this methodology constitutes the first organocatalytic formal [1 + 2 + 2] annulation and provides a simple and direct protocol for the stereoselective construction of fully functionalized cyclopentene derivatives in a multicomponent operation. The presence of three contiguous chiral centers with high enantioselectivity is especially noteworthy. An increase in the yields of the organocatalytic Michael-aldol condensation was achieved by the portionwise addition of the organocatalysts. This methodology is the first of its kind reported for organocatalysis reactions and may constitute a useful technique for overcoming those organocatalytic reactions that are limited by early terminated catalytic cycles. Further exploration of its synthetic applications is underway.

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**Supporting Information Available:** Experimental procedures, characterization data, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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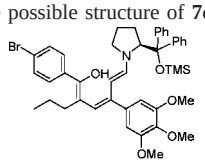
(26) For example, the possible structure of **7c** (*E*/*Z* mixtures) is




(27) For the study of reactive intermediates in organocatalysis with diarylprolinol ethers, see: (a) Groselj, U.; Seebach, D.; Badine, D. M.; Schweizer, W. B.; Beck, A. K.; Krossing, I.; Klose, P.; Hayashi, Y.; Uchimaru, T. *Helv. Chim. Acta* **2009**, *92*, 1225. (b) Seebach, D.; Groselj, U.; Badine, D. M.; Schweizer, W. B.; Beck, A. K. *Helv. Chim. Acta* **2008**, *91*, 1999. (c) Lakhdar, S.; Tokuyasu, T.; Mayr, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 8723.

(28) (a) Han, B.; Xiao, Y.-C.; He, Z.-Q.; Chen, Y.-C. *Org. Lett.* **2009**, *11*, 4660. (b) Zu, L.; Xie, H.; Li, H.; Wang, J.; Wang, W. *Adv. Synth. Catal.* **2007**, *349*, 2660. (c) Enders, D.; Wang, C.; Bats, J. W. *Synlett* **2009**, 1777. (d) Gotoh, H.; Okamura, D.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2009**, *11*, 4056.

(29) The possibility remained that the less stable *cis* adduct **6**, if formed from the 2,3-*syn* adduct, could epimerize to the more stable *trans*-adduct **6** during the reaction condition.