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Organocatalytic Enantioselective Domino Michael-aldol Condensation of 5-Oxoalkanal and α,β-Unsaturated Aldehydes. Efficient Assembly of Densely Functionalized Cyclohexenes†

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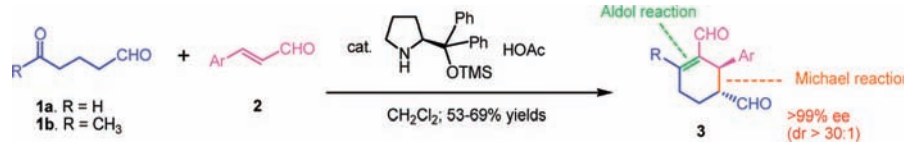
ABSTRACT



Organocatalytic Michael reaction of glutaraldehyde and 3-arylpropenal followed by the subsequent intramolecular aldol condensation provided 2-arylcyclohex-3-ene-1,3-dicarbaldehydes. Reactions with the 5-oxohexanal variant afforded the highly functionalized cyclohexenedicarbaldehydes in high diastereoselectivity and high enantioselectivity (>99% ee). Structure of the adduct 3j was confirmed unambiguously by X-ray analysis.

The field of asymmetric organocatalysis has grown rapidly and it has become the eminent strategy in contemporary organic synthesis.[1] The concepts of iminium activation[2] and enamine catalysis[3] have been applied to a broad range of chemical reactions. Among them, many studies have been devoted to the Michael addition,[4] with particular emphasis on the reaction with nitrostyrenes.[5] In contrast to nitrostyrene, fewer examples of Michael acceptors employing α,β-unsaturated carbonyl compounds have been reported. Moreover, the nucleophiles used in organocatalytic Michael additions to α,β-unsaturated aldehydes have generally been limited to π-nucleophiles (such as pyrroles, indoles, anilines, and silyloxyfurans),[6] nitroalkanes, malonate,[7] cyclopentadiene,[8] and more recently, aminonitrile (the glyoxylate d[1]-synthon).[9] A few examples of the organocatalytic Michael addition of an aldehyde to alkyl vinyl ketones (α,β-unsaturated ketones, mainly on methyl vinyl ketone) have appeared.[10] Nevertheless, examples of the organocatalytic intermolecular Michael addition of aldehydes (α-position) to

† Dedicated to Professor E. J. Corey on the occasion of his 80th birthday.

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(4) For recent reviews in asymmetric organocatalytic 1,4-conjugate additions, see: (a) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (b) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, 2065. (c) Almasi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (d) Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123. (e) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877.

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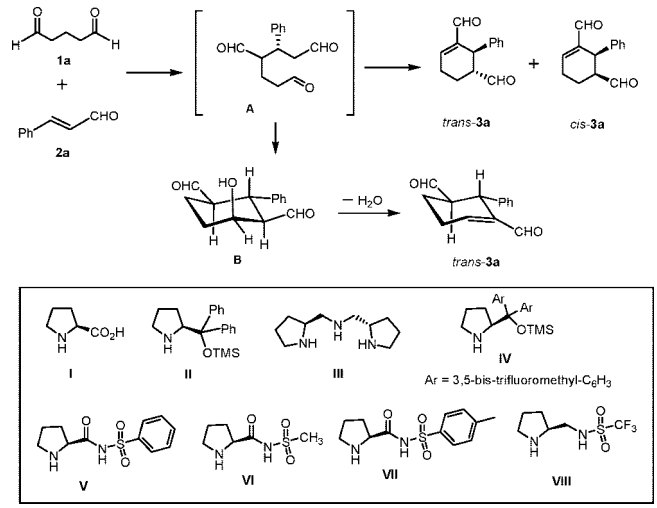
α,β-unsaturated aldehydes remain elusive.[11,12] Despite numerous publications dealing with organocatalytic reactions, only a few examples have focused on the domino (or tandem) reaction as the strategic tactic.[13] A chef d'oeuvre was established by Enders et al. in a triple cascade organocatalytic Michael−Michael−aldol reaction of a linear aldehyde, an α,β-unsaturated aldehyde, and nitrostyrene for the synthesis of tetrasubstituted cyclohexenecarbaldehydes with four stereogenic centers in high diastereo- and enantioselectivity.[14]

In conjunction with our continuing efforts to explore new organocatalytic annulations,[15] we embarked upon a domino strategy in the tandem Michael−aldol condensation. Herein, we report the development of a new domino organocatalytic conjugate addition and aldol condensation for the diastereo- and enantioselective synthesis of highly functionalized cyclohexene derivatives.

Initially, to a solution of glutaraldehyde (**1a**)[16] and cinnamaldehyde (**2a**) in CH_3CN (4 mL, 0.25 M) was added L-proline (0.5 equiv), and the solution was stirred at 25 °C for 72 h. As expected, the tandem Michael−aldol condensation product **3a** was obtained in trace amount (8% yield, Table 1, entry 1). Most of the glutaraldehyde was consumed (decomposed), but much of the cinnamaldehyde remained.

Table 1. Screening of the Catalyst, Solvent, and Reaction Conditions for the Tandem Michael−Aldol Condensation[a]



entry	cat.	additive[b]	solvent	time (h)	yield (%)[c]	dr[d]	ee (%)[f,g]
1	**I**		CH_3CN	72	8	85:15	n.d.
2	**I**	TEA	CH_3CN	8	19	90:10	n.d.
3	**II**	HOAc	CH_3CN	12	30	90:10	85[h]
4	**II**	HOAc	toluene	6	55	67:33	43[h]/44[i]
5	**II**	HOAc	CH_2Cl_2	6	**66**	**>99:1**	**89**[h]
6	**II**	$C_6H_5CO_2H$	CH_2Cl_2	4	62	99:1	88[h]
7	**II**	HFIP	CH_2Cl_2	24	53	95:5	80[h]
8	**II**		Et_2O	10	31	80:20	63[h]
9	**II**		CH_2Cl_2	10	43	99:1	89[h]
10	**III**	HOAc	CH_3CN	12	~0[e]	n.a.	n.a.
11	**IV**	HOAc	CH_2Cl_2	72	10	n.d.	n.d.
12	**V**		CH_3CN	48	~0[e]	n.a.	n.a.
13	**VI**		CH_3CN	48	~0[e]	n.a.	n.a.
14	**VII**		CH_3CN	48	~0[e]	n.a.	n.a.
15	**VIII**		CH_3CN	30	52	60:40	−6[h]/25[i]

[a] The reactions were performed in 0.25 M **2a** at 25 °C. [b] The same equivalents of catalysts were applied. [c] Isolated yields. [d] Diastereomeric ratio (dr) of trans/cis, determined by ^{1}H NMR prior to workup. [e] No reaction and recovery of cinnamaldehyde. [f] Enantiomeric excess (ee) determined by HPLC with chiral column (Chiracel OD). [g] ee were measured by GC−MS (Shimadzu QP 5000, chiral capillary column, γ-cyclodextrin trifluoroacetyl, Astec type G-TA, size 30 m × 0.25 mm, flow rate 24 mL/min, temperature range: 100−150 °C, gradient: 3 °C /min). [h] ee of *trans*-**3a**. [i] ee of *cis*-**3a**.

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(10) For Michael addition of aldehydes to alkyl vinyl ketones, see: (a) Hong, B.-C.; Chen, F.-L.; Chen, S.-H.; Liao, J.-H.; Lee, G.-H. *Org. Lett.* **2005**, *7*, 557. (b) Chi, Y.; Gellman, S. H. *Org. Lett.* **2005**, *7*, 4253. (c) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296. (d) Nicolaou, K. C.; Sarlah, D.; Shaw, D. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4708.

(11) For an intramolecular example, see:(a) Fonseca, M. T. H.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3958. (b) A tandem reaction involving the intermolecular conjugate addition of a nitroaldehyde intermediate (γ-position of aldehyde) to an α,β-unsaturated aldehyde (nitroalkane conjugate addition) was reported by Enders, see ref 14.

(12) For a recent example of organocatalytic conjugate addition of aldehyde to maleimides, see: Zhao, G.-L.; Xu, Y.; Sundén, H.; Eriksson, L.; Sayah, M.; Córdova, A. *Chem. Commun.* **2007**, 734.

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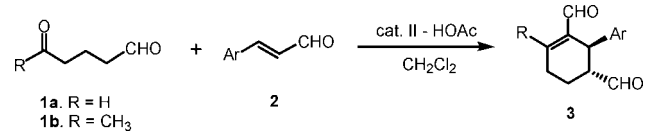
(16) Extracted and concentrated from commercially available 25% aqueous solution.

In an independent reaction, addition of Et_3N to the reaction mixture facilitated the reaction (decreasing the reaction time to 8 h) and slightly increased the yield to 19% (Table 1, entry 2). Recently, the chiral pyrrolidine derivatives, e.g., diarylprolinol TMS ether, have emerged as promising general enamine organocatalyst for asymmetric reactions.[17,18] Consequently, in exploratory efforts directed toward improving better yields and enantioselectivity, a series of organocatalysts,[19] additives, and various conditions were screened (Table 1, entries 3−15). Interestingly, catalyst **II**−HOAc was the most promising candidate for the transformation. A survey of solvents revealed that the reaction media had significant effects on the yields of this process. For example, the reaction with **II**−HOAc carried out in CH_2Cl_2 gave the highest yield (66%) and gave *trans*-**3a** predominately, whereas moderate diastereoselectivity and yields were observed for the reactions in CH_3CN and toluene (Table 1, entries 3−5). In addition, an acid additive was required to facilitate the formation of the key intermediates: iminium ion and enamine. Evaluation of three acids (HOAc, $C_6H_5CO_2H$ and HFIP) revealed that acetic acid is the best acid additive in this reaction (Table 1, entries 5−7). Reaction with **II** without the acid additive gave much lower yields (Table 1, entries 8−9). Other catalysts (**III** to **VII**) gave either no reactions or very low yields (Table 1, entries 10−14). Notably, catalyst **IV**, the bistrifluoromethyl derivative of **II**, gave very slow conversion after 3 days (less than 10% yield in 3 days, Table 1, entry 11). Reaction with catalyst **VIII** provided 52% yield of the product **3a** in low regioselectivity (60:40) and enantioselectivity (−6% ee for *trans*-**3a** and 25% ee for *cis*-**3a**, Table 1, entry 15).

Having established the optimal reaction conditions, a series of aryl acrylaldehydes (**2**) were reacted with glutaraldehyde (**1a**) in the presence of catalyst **II**−HOAc in CH_2Cl_2 at ambient temperature to probe the generality of this asymmetric catalytic variant reaction (Table 2, entries 1−7). Significantly, the majority of the examples, independent of the nature of substituents on the phenyl ring, gave excellent enantioselectivity and diastereoselectivity (>30:1). However, for the reaction with (*E*)-3-(furan-2-yl)acrylaldehyde (**2e**), moderate enantioselectivity (74% ee) and yield (55%, along with lots of polymerization products) were obtained (Table 2, entry 5).[20] Interestingly, the reactions with 5-oxohexanal (**1b**) gave much better enantioselectivites than the counterpart reactions with glutaraldehyde (**1a**)

Table 2. Tandem Michael−Aldol Reaction of **1** and **2**



1a. R = H
1b. R = CH_3

2

3

entry	product	time (h)	yield[a] (%)	ee[b] (%)
1	*trans*-**3a**, R = H, Ar = Ph	6	66	89
2	**3b**, R = H, Ar = (*p*-OMe)C_6H_4	10	65	93[c]
3	**3c**, R = H, Ar = (*p*-Me)C_6H_4	10	63	93
4	**3d**, R = H, Ar = (*o*-OTBS)C_6H_4	8	68	97[c]
5	**3e**, R = H, Ar = furanyl	6	55[d]	74
6	**3f**, R = H, Ar = (*o*-NO_2)C_6H_4	6	69	96
7	**3g**, R = H, Ar = (*p*-Br)C_6H_4	4	61	94
8	**3h**, R = CH_3, Ar = Ph	24	60	95
9	**3i**, R = CH_3, Ar = furanyl	36	53[d]	92
10	**3j**, R = CH_3, Ar = (*o*-NO_2)C_6H_4	30	62	>99
11	**3k**, R = CH_3, Ar = (*p*-Br)C_6H_4	34	58	>99
12	**3l**, R = CH_3, Ar = (*p*-OMe)C_6H_4	30	60	>99

[a] Reaction at 25 °C, isolated yields, diastereomeric ratio (dr) >99%. [b] Unless otherwise noted, enantiomeric excesses (ee) were measure by HPLC with chiral column (Chiracel OD). [c] ee were measured by GC−MS (Shimadzu QP 5000, chiral capillary column, γ-cyclodextrin trifluoroacetyl, Astec type G-TA, size 30 m × 0.25 mm, flow rate 24 mL/min, temperature range: 100−150 °C, gradient: 3 °C /min). [d] With many polymerization products.

(Table 2, entries 8−12). Significantly, the reaction of **1b** and **2e** gave **3i** with much better enantioselectivity than **3e** prepared from **1a** and **2e**, (Table 2, entries 9 and 5). More interestingly, the reaction succeeded with the cinnamaldehyde derivatives with ortho electron-donating substituents (e.g., OTBS, Table 2, entry 4). Typically, C-alkylation via conjugate addition on these ortho electro-donating substituted phenyl α,β-unsaturated aldehydes is difficult due to both the steric and inductive effects and has never been reported. The structure of **3j** was unambiguously assigned by its single-crystal X-ray analysis (Figure 1).

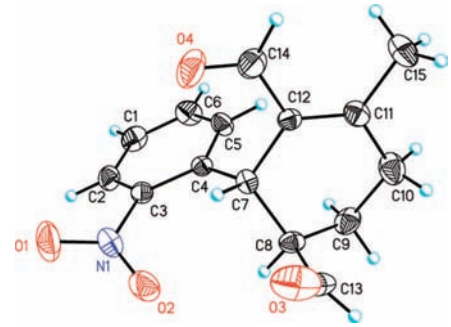


Figure 1. ORTEP of **3j**, thermal ellipsoids draw of 30% probability level.

To determine the absolute stereochemistry of the tandem Michael−aldol adducts, *trans*-**3a** was transformed to the literature-reported alcohols **6** and **7**[21] via a sequence of

(17) For a review, see: Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876.

(18) For recent examples of (*S*)-diphenylpyrrolinol silyl ethers as catalysts in organocatalysis, see: (a) Ibrahem, I.; Córdova, A. *Chem. Commun.* **2006**, 1760. (b) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928. (c) Chi, Y.; S. Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804. (d) Marigo, M.; Bertelsen, S.; Landa, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 5475. (e) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354. (f) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (g) Bertelsen, S.; Dinér, P.; Johansen, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 1536.

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reactions (Figure 2). Decarbonylation[22] of *trans*-**3a** was achieved by Wilkinson's catalyst [$RhCl(PPh_3)_3$][23] in refluxing toluene for 4 h, affording **4** in 70% yield, followed by hydrogenation (H_2, Pd−C, EtOAc, 25 °C, 5 h; 90% yield) to give **5** (diastereomeric ratio 3:1). Reduction of the aldehyde **5** with $NaBH_4$ (EtOH, 25 °C, 1 h) provided alcohols **6** and **7** in 80% yield (trans/cis = 1:3). By comparison with the literature optical data, the absolute stereochemistries of these compounds were discerned as shown in Figure 2.

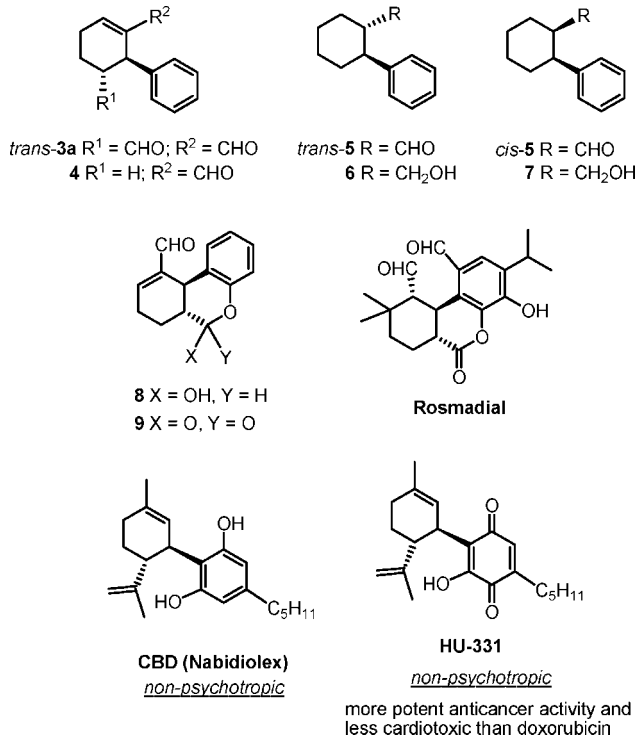

Figure 2. Derivatives of the tandem Michael−aldol adducts.

The cyclohex-2-enylbenzene systems can be found in a variety of natural products and biologically active agents, including rosmadial,[24] nabidiolex,[25] and HU-331[26] (Figure 2). To demonstrate the synthetic versatility of the multifunctional products of this methodology, **3d** was converted to **8** via deprotection (TBAF, THF, 25 °C; 83% yield) and oxidation (PCC, CH_2Cl_2, 25 °C; 85% yield) to give lactone **9** which shares the same skeleton with rosmadial. These successful reactions provide evidence that the current tandem Michael-aldol condensation is a useful methodology in the synthesis of these compounds.

In summary, we have developed a highly diastereoselective and enantioselective domino organocatalytic Michael−aldol condensation that provides expedited access toward highly functionalized and enantiomerically enriched cyclohexene derivatives (>99% ee). The structure was confirmed by X-ray analysis of adduct **3j**. The absolute stereochemistry was revealed by the transformation of adduct *trans*-**3a** to literature compounds. Synthetic applications were demonstrated in the synthesis of **9** with the same skeleton of rosmadial. The simple experimental procedures, high diastereoselectivity and enantioselectivity, and great 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: Crystallographic information files (CIF) for **3j**; experimental procedures and characterization data for the new compounds (**3**−**9**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Cannabidiol (CBD, the non-psychotropic constituent) is a representative canabinoid. CBD, the drug brand name as Nabidiolex, does not cause marijuana-like effects and has been shown to possess a plethora of pharmacological effects and have some therapeutic applications, such as in treatment of type-1 diabetes, anti-emetic and antinausea effects, anti-epileptic, anti-anxiety, inhibition of neurodegeneration in Parkinson's disease, anti-arthritic, cancer therapy, and cerebral ischemia. See: Mechoulam, R.; Parker, L. A.; Gallily, R. *J. Clin. Pharmacol.* **2002**, *42*, 11S–19S.

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