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Organocatalytic Synthesis of Multiple Substituted Bicyclo[4.4.0]Decalin System

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ABSTRACT

An efficient and unprecedented organocatalytic reaction of γ-nitroketones with α,β-unsaturated aldehydes to give polyfunctionalized [4.4.0] bicyclic skeletons was developed. The diphenylprolinol silyl ether mediated nitro-Michael/Aldol reaction afforded the hexa-substituted decalin carboaldehydes with excellent diastereo- and enantioselectivity (up to >99:1 dr and >99% ee) via a formal [4 + 2] carbocyclization process.

Polyfunctional cyclic carbon frameworks are typical structural features of many diterpenoid natural products and pharmaceutical drugs.[1] Chiral bicyclic decalin structures are important intermediates for the synthesis of biologically active compounds.[2] Over the past decade, organocatalysis has emerged as a powerful alternative for the synthesis of functionalized monocyclic[3] (five[3a−e] and six[3f−m] membered), bicyclic,[4] tricyclic,[5] and spirocyclic[6] systems under metal-free conditions. The development of facile routes to nontrivial core structures via a cascade sequence continues to challenge the synthetic community.[7]

Following the discovery of the Hajos−Parrish−Eder−Sauer−Wiechert reaction in the 1970s,[8] proline and its derivatives have now been found to catalyze the intra-/inter-aldolization process for the synthesis of many chiral

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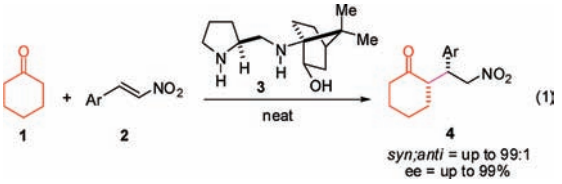
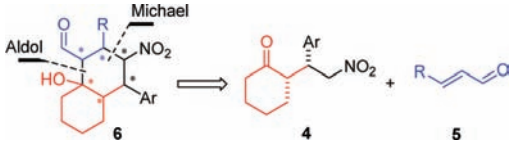
products.[9] While achievements have been made in the synthesis of decalin scaffolds via Diels–Alder,[10] oxy-Cope-ene,[11] and oxidative dearomatization approaches,[12] the efficient synthesis of important multisubstitutent scaffolds with excellent optical purity remains elusive. In continuation of our research interest in organocatalytic reactions,[13] a unique annulation strategy involving a domino reaction to obtain [4.4.0] bicyclic decalin derivatives was embarked upon. We envisioned that the preparation of chiral [4.4.0] bicyclic structures **6** with multiple functionalities could be achieved via a domino nitro-Michael/Aldol reaction using γ-nitroketone **4** and α,β-unsaturated aldehyde **5** in the presence of an efficient organocatalyst.

Recently we reported an efficient protocol for the preparation of γ-nitroketones **4** in the presence of the pyrrolidinyl-camphor based bifunctional organocatalyst **3** (HOMO-raising activation mode).[13g,h] The corresponding Michael adducts, i.e. γ-nitroketones **4**, were obtained in high chemical yields (up to 95%) and exceptionally high diastereo- and enantioselectivity (up to 99:1 dr and 99% ee) under solvent-free conditions (eq 1).[13h]



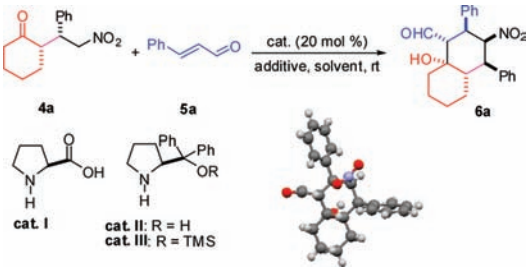
We speculated that these γ-nitroketones **4** could act as potential synthons for the synthesis of chiral [4.4.0] bicycles via an iminium-enamine activation mode. Although the fundamental understanding of iminium-enamine chemistry has been well developed and explored,[14] never have γ-nitroketones been used as precursors for the preparation of chiral [4.4.0] bicyclic skeletons with α,β-unsaturated aldehydes (Scheme 1).

Scheme 1. Domino Nitro-Michael/Aldol Condensation Approach to the [4.4.0] Bicyclic Skeleton



Thus, our investigations began by the reaction of γ-nitroketone **4a** with *trans*-cinnamaldehyde **5a** in the presence of L-proline (**cat. I**). This resulted in the recovery of starting material even after stirring for 7 days (Table 1, entry 1). Conducting the reaction in the presence of α,α-diphenyl prolinol catalyst (**cat. II**) gave very little product

Table 1. Screening of Catalysts and Optimization of the Domino Nitro-Michael/Aldol Reaction[a]



Entry	cat.	Additive	Solvent	t [h]	Yield [%][b]	dr[c]	ee [%][e]
1	I	-	MeOH	7 d	-	-	-
2	II	-	Toluene	96	<5	n.d.	-
3	III	-	Toluene	15	33	88:12	99
4	III	BA	Toluene	48	38	90:10	99
5[d]	III	BA	Toluene	48	-	-	-
6	III	2-FBA	THF	48	35	93:7	98
7	III	AA	Toluene	48	40	95:5	99
8	III	TEA	Toluene	11	80	82:16	87
9[f]	III	NaOAc	Toluene	15	62	92:8	90
10	III	DIPEA	Toluene	24	70	91:9	90
11[g]	**III**	**AA/DIPEA**	**Toluene**	**24**	**76**	**95:5**	**>99**
12[h]	-	DIPEA	Toluene	5 d	<10	78:22	65

[a] Unless otherwise mentioned, all reactions were performed using **4a** (0.2 mmol), **5a** (0.4 mmol), catalyst (20 mol %), and additive (20 mol %) in toluene (0.4 mL) at ambient temperature for the required time. [b] Isolated yield. [c] By ^{1}H NMR analysis of crude reaction mixtures. [d] The reaction was carried out at 0 °C. [e] By chiral HPLC analysis on a chiral column. [f] The reaction was carried out using 0.5 equiv of additive. [g] The reaction was carried out using AA (20 mol %) and DIPEA (25 mol %). [h] The reaction was carried out using 1.0 equiv of DIPEA. BA: benzoic acid; 2-FBA: 2-fluorobenzoic acid; AA: acetic acid; DIPEA: *N,N*-Diisopropylethylamine.

with most of the starting materials remaining intact (Table 1, entry 2). Recently, diarylprolinol silyl ethers were recognized as one of most promising catalysts for carbonyl compound activation in organocatalysis.[15] We were thus pleased to find that the use of α,α-diphenylprolinol silyl ether catalyst (**cat. III**) led to the formation of a highly functionalized [4.4.0] bicyclic skeleton encompassing a total of six stereocenters (Table 1, entry 3). The product

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(14) For discussion see:(a) List, B. *Chem. Commun.* **2006**, 819. (b) MacMillan, D. W. C. *Nature* **2008**, *455*, 304.

(15) For selected references for the use of α,α-diarylprolinol silyl ethers catalysis, see: (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (b) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (c) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (d) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (e) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167.

6a was obtained with a moderate chemical yield (33%) and fairly good dr selectivity of 88:12.

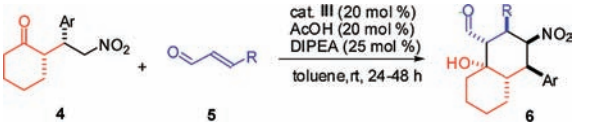
In exploratory efforts directed at improvement of the diastereoselective ratio and chemical yield of this domino reaction, various acidic/basic additivies were evaluated (Table 1, entries 4−11). Attempts to increase the diastereoselectivity of the cascade process by carrying out the reaction at 0 °C led mainly to the recovery of the starting substrate (Table 1, entry 5). Screening of three acidic additives (BA, 2-FBA, AA) revealed that moderate chemical yields were obtained with high diastereoselectivity and excellent enantioselectivity over 48 h (Table 1, entries 4, 6, and 7).

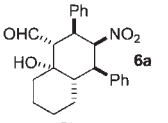
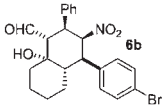
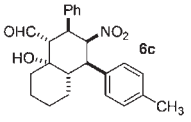
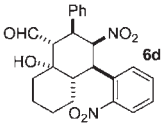
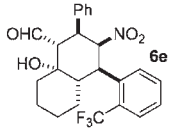
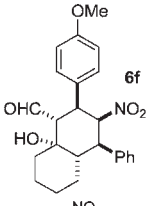
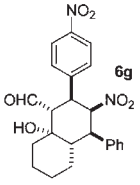
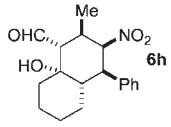
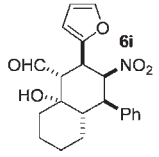
Reactivity was enhanced, at the expense of the enantioselectivity, by the use of a basic additive. Therefore, the addition of TEA afforded **6a** with a better chemical yield but a drop in enantioselectivity (87% ee) (Table 1, entry 8). A similar observation was found upon the addition of NaOAc (0.5 equiv) and DIPEA for the domino product **6a** (Table 1, entries 9 and 10). To better balance the chemical and stereochemical outcomes of the reaction, an acid/base dual activation process was developed and the optimum reaction conditions were realized. Toward this end, to the starting γ-nitroketone **4a** and cinnamaldehyde **5a** in toluene was added acetic acid at ambient temperature. This was followed by the addition of the sterically hindered diisopropylethylamine (DIPEA) after 30 min. To our satisfaction, the reaction led to isolation of the desired product with an appealing chemical yield and excellent diastereo- and enantioselectivity (95:5 dr and >99% ee) (Table 1, entry 11).

The structure of the product was fully characterized by IR, ^{1}H,^{13}C NMR, HRMS spectroscopic analysis, and the absolute configuration was unambiguously determined as (1*R*, 2*S*, 3*S*, 4*R*, 4a*S*, 8a*S*) by single-crystal X-ray analysis.[16] To the best of our knowledge, this is the first report of the synthesis of the [4.4.0] bicyclic skeleton with multiple stereocenters using a cyclohexanone derived γ-nitroketone and an α,β-unsaturated aldehyde through a formal [4 + 2] intermolecular carbocyclization reaction.[17]

An understanding of the chirality transfer of the organocatalytic protocol in organic reactions is important. Barbas and co-workers reported an efficient Michael/Henry synthesis of carbohydrate derivatives and the stereochemistry of the latter reaction was found to be substrate controlled.[18] We speculated that the high selectivity of this domino nitro-Michael/Aldol product could possibly be controlled by chirality from the Michael donor **4a**, the electrophilic iminium ion, or both. To confirm this hypothesis, we carried out a control experiment using DIPEA in the absence of an organocatalyst (Table 1, entry 12). No reaction was observed when the reaction was conducted for 48 h. When continued for 5 days, the reaction resulted in a less than 10% isolated chemical yield.

Table 2. Subsrate Scope for Nitro-Michael/Aldol Reaction[a]



Entry	Product	*t* [h]	Yield [%][b]	dr[c]	ee [%][d]
1	 **6a**	24	76	95:5	>99
2	 **6b**	24	75	95:5	>99
3	 **6c**	24	73	98:2	>99
4	 **6d**	48	68	93:7	>99
5	 **6e**	48	71	98:2	>99
6	 **6f**	24	75	89:11	>99
7	 **6g**	24	74	88:12	>99
8	 **6h**	48	69	>99:1	>99
9	 **6i**	48	83	82:18	>99

[a] Unless otherwise mentioned, all reactions were performed using **4** (0.2 mmol) and **5** (0.4 mmol) in toluene (0.4 mL) in the presence of **catalyst III** (20 mol %), AA (20 mol %), and DIPEA (25 mol %) at ambient temperature. [b] Isolated yield. [c] By ^{1}H NMR analysis of the crude reaction mixtures. [d] By chiral HPLC analysis.

(16) Detailed X-ray crystallographic data are available from CCDC, 12 Union Road, Cambridge CB2, 1EZ, UK for products **6a** (CCDC 806842) and **6g** (CCDC 805805).

(17) For substituted cyclohexene ring formation using acyclic γ-nitroketone, see: Enders, D.; Narine, A. A.; Benninghaus, T. R.; Raabe, G. *Synlett* **2007**, 1667.

(18) (a) Uehara, H.; Imashiro, R.; Hernandez-Torres, G.; Barbas, C. F., III. *Org. Lett.* **2010**, *12*, 5250. (b) Uehara, H.; Imashiro, R.; Hernandez-Torres, G.; Barbas, C. F., III. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20672.

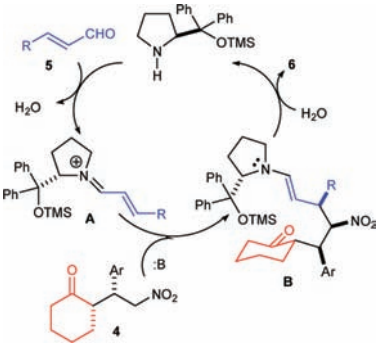
A low dr selectivity of 78:22 and a low enantioselectivity (65% ee) was observed. This clearly indicated the significant role played by the organocatalyst. The diphenylprolinol silyl ether catalyst **III** enhanced the reactivity by forming an iminium ion as well as controlling the stereoselectivity. The domino reaction proceeded smoothly with the creation of four contiguous stereogenic centers, one of which is a quaternary carbon center.

With the optimized reaction conditions identified, we next explored the substrate scope for the domino nitro-Michael/Aldol reaction. Various γ-nitroketones and α,β-unsaturated aldehydes were used for the preparation of densely functionalized [4.4.0] bicyclic derivatives under the optimum reaction conditions (Table 2, entries 1−9). Various functional groups appeared to be well tolerated in the α,β-unsaturated aldehyde **5** as well as in γ-nitroketones **4** under the optimized conditions. The employment of electron-donating groups at the *para*-position of the phenyl substituent hardly had any effect on this reaction in terms of chemical yield or selectivity (Table 2, entries 2 and 3). By way of contrast, an electron-withdrawing substituent at the *ortho*-position decreased the overall reactivity and required 48 h to complete the reaction (Table 2, entries 4−5). A decrease in diastereoselectivity was observed with a phenyl *para*-substituent on the Michael acceptor of the α,β-unsaturated aldehyde **5** (Table 2, entries 6 and 7). To our surprise, an aliphatic α,β-unsaturated aldehyde such as methyl acrolein was an excellent substrate for this reaction and gave the product with excellent diastereo- and enantioselectivity (Table 2, entry 8). The use of a heterocyclic α,β-unsaturated aldehyde also gave good results in the [4.4.0] bicyclic structure formation (Table 2, entry 9).

The asymmetric domino organocatalytic nitro-Michael/Aldol reaction for the multiple functional derivative **6** can be explained by the mechanism shown in Scheme 2. The γ-nitroketone first reacts with the in situ formed iminium species (**A**) to give keto-enamine **B**. The intramolecular aldol reaction then proceeds from the enamine to the ketone *re* face to cyclize the decalin ring system. Hydrolysis generates the product with concomitant release of the organocatalyst for the next catalytic cycle.

In conclusion, we have developed a viable catalyzed cascade nitro-Michael/Aldol strategy for the facile construction of densely functionalized [4.4.0] bicyclic structures containing multiple stereocenters. The reactions proceed with high to excellent diastereo- and enantioselectivity (up to >99:1 dr and $>99\%$ ee). The accessibility of the starting γ-nitro ketones and the easy manipulation of the organocatalytic system make this system attractive. The sequential nitro-Michael/Aldol reaction constitutes the first organocatalytic stereoselective construction of functionalized [4.4.0] bicyclic carbon frameworks through a formal [4 + 2] carbocyclization strategy. Further exploration is in progress.

Scheme 2. Proposed Catalytic Cycle



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Supporting Information Available. Experimental procedures and copies of ^{1}H NMR and ^{13}C NMR spectra for all new products as well as X-ray crystallographic data for compounds **6a** and **6g** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.