Organocatalysis

DOI: 10.1002/anie.200802532

Organocatalytic Asymmetric Domino Reactions: A Cascade Consisting of a Michael Addition and an Aldehyde α-Alkylation**

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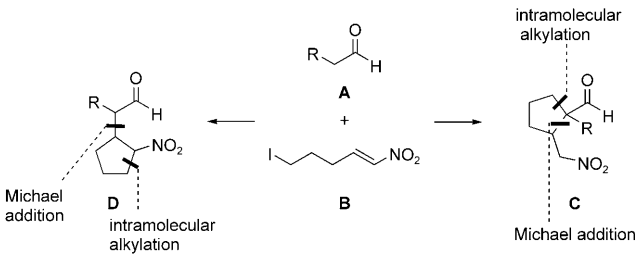
Dedicated to Professor Manfred T. Reetz on the occasion of his 65th birthday

The development of asymmetric reactions using small organic molecules as catalysts, which are often nontoxic, environmentally friendly, and stable under aerobic and aqueous reaction conditions, has attracted much attention in recent years.[1] Domino reactions provide an efficient means to construct complex molecules in a single process, while minimizing the number of manual operations and the generation of chemical waste and easing purification.[2] Organocatalytic domino reactions can combine these advantages, and many interesting reactions have been developed during the past few years.[3,4]

The asymmetric secondary-amine-catalyzed Michael addition of aldehydes and ketones to nitroalkenes is a direct entry to γ-nitroaldehydes and -ketones,[5,6] which has been applied by our group in organocatalytic triple-cascade reactions.[4d,h,w] In 2004, List and Vignola reported the first catalytic asymmetric intramolecular α-alkylation of aldehydes.[7] Asymmetric organocatalytic domino reactions consisting of a Michael addition and an alkylation have been recently developed to form enantioenriched and highly functionalized cyclopropane and cyclopentane derivatives.[4r–t] These reactions involve iminium–enamine activation and utilize α,β-unsaturated aldehydes and bromomalonates or bromo-β-ketoesters. We envisaged aldehydes **A** and the ω-iodonitroalkene **B** as potential substrates for a domino reaction made up of Michael addition and intramolecular alkylation, leading to either the cyclopentanecarbaldehydes **C** or the classical Michael-initiated ring-closure (MIRC) products **D** (Scheme 1). While the MIRC compounds **D** are not observed, the cyclic γ-nitro-substituted aldehydes **C** are synthetically useful compounds, which may be converted into cyclic γ-amino acids containing an all-carbon-substituted quaternary stereogenic center considered as a challenging task.[8,9]



Scheme 1. Secondary-amine-catalyzed domino reaction consisting of a Michael addition and an intramolecular alkylation proceeding by tandem enamine–enamine activation.

γ-Aminobutyric acid (GABA) is an important inhibitory neurotransmitter in the central nervous system of mammals,[10] and many of its derivatives show biological activity.[11] For example, Gabapentin,[12] Pregabalin,[13] and Vigabatrin[14] have been commercialized as drugs to treat neurological disorders. Thus, the efficient stereoselective synthesis of γ-amino acids is of great interest, and many asymmeric auxiliary-based and metal-catalyzed methods have been developed.[15] Recently, organocatalytic asymmetric syntheses of acyclic γ-amino acids have been reported.[6j,k,16]

Herein we report an organocatalytic domino Michael addition/alkylation reaction between aliphatic aldehydes and (*E*)-5-iodo-1-nitropent-1-ene (**B**) involving enamine–enamine activation.[17] The process is highly stereoselective and leads to the γ-nitroaldehydes **C**, which contain an all-carbon-substituted quaternary stereogenic center. Furthermore, a novel cyclic γ-amino acid was easily synthesized from the domino product in two steps.

Diphenylprolinol silyl ether **1**[18] shows good catalytic activity and gives excellent levels of asymmetric induction in the Michael addition of aldehydes to nitroalkenes.[6f] Therefore, we initially investigated its use as a catalyst in the reaction between propanal (**4a**) and nitroolefins bearing different leaving groups in the ω position (OMs, Br, I; Ms = mesyl). In the case of the bromo and mesylate derivatives, the initial Michael addition occurred in good yield (70–80%); however, the desired cyclopentane product **6a** was not formed. Using the ω-iodonitroalkene **5** the domino reaction occurred and cyclopentane **6a** was obtained in a low yield of 20% (entry 1, Table 1). Although the diastereoselectivity was only moderate (d.r. 70:30), the enantiomeric excess was excellent (*trans*: 94% *ee*, *cis*: 95% *ee*). Encouraged by this initial result, we undertook a detailed optimization study.

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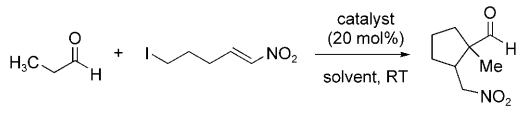
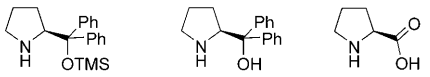
[**] This work was supported by the Deutsche Forschungsgemeinschaft (priority program Organocatalysis) and the Fonds der Chemischen Industrie.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200802532.

Table 1: Catalyst and solvent screening for the enantioselective domino reaction.[a]



4a 5 6a



1 2 3

Entry	Cat.	Solv.	*t* [d]	Yield [%][b]	d.r.[c] *trans*/*cis*	*ee* [%][d] *trans*, *cis*
1	**1**	MeCN	1	20	70:30	94, 95
2	**1**	THF	1	traces[c]	71:29	n.d.[e]
3	**1**	CH_2Cl_2	1	0	–	–
4	**1**	DMF	1	27	74:26	93, 93
5	**1**	DMSO	5	55	67:33	88, 95
6	**2**	DMSO	1	traces[c]	–	–
7	**3**	DMSO	1	59	70:30	55, −11

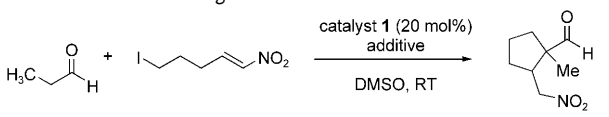
[a] Reaction conditions: 2 mmol **5**, 5 equiv propanal (**4a**), and 20 mol% catalyst **1** (TMS = trimethylsilyl), **2**, or **3** at RT in 4.0 mL solvent. [b] Combined yield of separable diastereomers obtained after flash chromatography. [c] Determined by GC analysis. [d] Determined by HPLC analysis on a chiral stationary phase. [e] Not determined.

Various solvents were screened and it was found that the polarity of the solvent had a significant effect on the outcome of the reaction. In less polar solvents, such as dichloromethane and tetrahydrofuran, only the Michael adduct was obtained (entries 2 and 3, Table 1). In polar solvents, the yield of domino product **6a** could be increased: DMF gave a slightly better yield (27%) with a similar diastereoselectivity (74:26) and enantioselectivity (*trans*: 93% *ee*, *cis*: 93% *ee*), in the case of DMSO the yield increased to a synthetically useful level (55%). Importantly, the enantioselectivity of the process remained high (≥88% *ee*) with a similar diastereoselectivity (67:33) (entries 4 and 5, Table 1). Next, two additional enantiopure secondary amine catalysts were evaluated in the domino reaction. (*S*)-Diphenylprolinol (**2**) afforded only the Michael addition product (entry 6, Table 1). (*S*)-Proline (**3**) was highly active giving the cyclopentane **6a** in a similar yield (59%) and diastereoselectivity (70:30); however, the enantioselectivity of the reaction was low (55%, −11%) (entry 7, Table 1).

In order to shorten the reaction time, various additives were screened. The reaction was complete within 12 h using several basic co-catalysts, but this led to a decrease in yield or enantioselectivity (entries 1–3, Table 2). With benzoic acid as an additive the reaction rate increased and the yield and enantioselectivity improved (entries 4 and 5, Table 2). When the reaction was carried out at 40°C, the time could be shortened to one day with an improved yield but with slightly lower stereoselectivity (entry 6, Table 2).

The scope of the reaction was evaluated under the optimized conditions (Table 3). Variation of the aldehyde structure was possible, and in all cases the major diastereomer was formed in excellent enantiomeric excess (93–97% *ee*). The diastereoselectivity ranged from moderate to excellent

Table 2: Additive screening for the enantioselective domino reaction.[a]

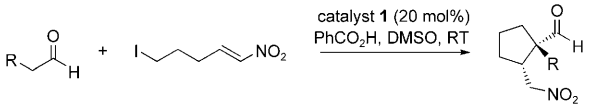


4a 5 6a

Entry	Add.	mol%	*t* [d]	Yield [%][b]	d.r.[c] *trans*/*cis*	*ee* [%][d] *trans*, *cis*
1	K_2CO_3	20	0.5	25	n.d.[e]	87, n.d.
2	NEt_3	20	0.5	40	61:39	89, 66
3	NaOAc	20	0.5	35	62:38	89, 92
4	$PhCO_2H$	20	4	59	66:34	92, 95
5	$PhCO_2H$	100	2	62	66:34	94, 96
6[f]	$PhCO_2H$	100	1	65	63:37	91, 92

[a] Reaction conditions: 2 mmol **5**, 5 equiv propanal (**4a**), 20 mol% catalyst **1**, and the additive indicated (20 mol% or 100 mol%) at RT in 4.0 mL DMSO. [b] Combined yield of separable diastereomers obtained after flash chromatography. [c] Determined by GC analysis. [d] Determined by HPLC analysis on a chiral stationary phase. [e] Not determined. [f] Carried out at 40°C.

Table 3: Organocatalytic domino reaction of aldehydes **4a–e** and (*E*)-5-iodo-1-nitropent-1-ene (**5**).[a]



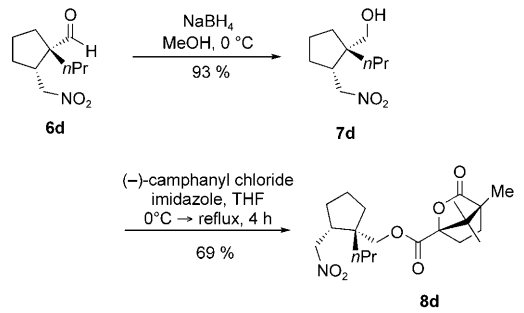
4a-e 5 6a-e

Prod.	R	*t* [d]	Yield [%][b]	d.r.[c] *trans*/*cis*	*ee* [%][d] *trans*, *cis*
6a	Me	2	62	66:34	94, 96
6b	Et	4	59	13:87	60, 97
6c	*i*Pr	7	40	1:99	–, 93
6d	*n*Pr	4	45	10:90	59, 97
6e	*n*Bu	4	41[e]	11:89	–, 97[f]

[a] Reaction conditions: 2 mmol **5**, 5 equiv aldehyde, 20 mol% catalyst **1**, and 100 mol% $PhCO_2H$ at RT in 4.0 mL DMSO. [b] Combined yield of separable diastereomers. [c] Determined by GC analysis. [d] Determined by HPLC analysis on a chiral stationary phase on the corresponding aldehyde **6** except **6e**. [e] Yield after reduction of the aldehyde to the alcohol ($NaBH_4$, MeOH, 0°C). [f] Determined by HPLC analysis of alcohol **6e** on a chiral stationary phase.

(d.r. 66:34–99:1), and the diastereomers were readily separable by flash chromatography. The corresponding nitroalcohol **7** could be obtained by chemoselective reduction with sodium borohydride. Reaction of the primary alcohol with camphanyl chloride gave the crystalline ester **8** (Scheme 2). The absolute configuration of the major diastereomer **6d** was determined to be *S*,*R* by X-ray structure analysis of its camphanyl derivative **8d** (Figure 1).

A plausible catalytic cycle is described below (Scheme 3). The reaction starts with enamine activation of the aldehyde by the chiral amine. Assuming that the bulky catalyst diphenylsiloxymethyl group shields the *Re* face at Cα of the enamine intermediate **9**, the Michael addition occurs at its more accessible *Si* face in an acyclic synclinal transition state to give the Michael adduct **10**.[20] Next, a second enamine intermediate **11** is formed when the intermediate **10** undergoes a proton shift temporarily destroying the α-carbon



Scheme 2. Synthesis of the alcohol and a the corresponding crystalline camphanyl derivative.

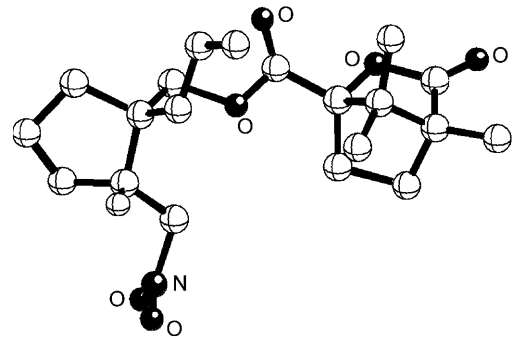
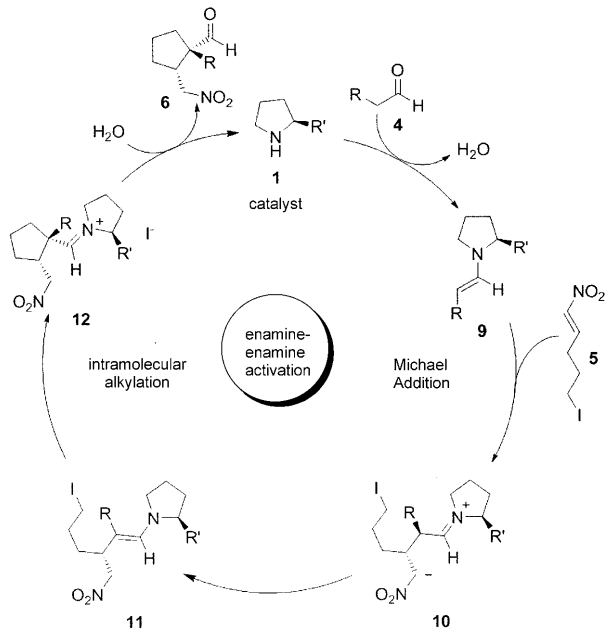


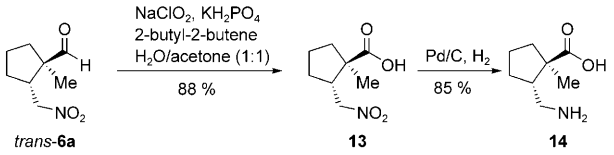
Figure 1. X-ray crystal structure of **8d**.



Scheme 3. Proposed catalytic cycle of the domino reaction. R′ = C-(OTMS)Ph_2.

stereogenic center. In the next step, an intramolecular nucleophilic substitution reaction occurs resulting in ring closure.[7] To account for the *cis*-selective formation of the *S*,*R*-cyclopentane products, the intramolecular alkylation reaction likely occurs from the *Si* face at Cα of enamine **11**. Finally, the product is released and the catalyst regenerated following a hydrolysis reaction of the intermediate **12**. In the case of cyclopentane **6a**, the reaction was *trans*-selective. Presumably the intramolecular alkylation occurs at the diastereotopic *Re* face at Cα in this case.

As an illustration of the utility of this method, the domino product *trans*-**6a** could be readily converted into a novel cyclic γ-amino acid. To achieve this, the diastereomerically pure cyclopentane **6a** was subjected to a Pinnick oxidation to give the γ-nitro acid **13** followed by reduction with Pd/C, H_2 affording the γ-amino acid **14** in good overall yield (75%; Scheme 4).



Scheme 4. Two-step synthesis of the cyclic γ-amino acid **14** from the domino product *trans*-**6a**.

In summary we have developed a diastereo- and enantioselective organocatalytic domino reaction between aliphatic aldehydes and (*E*)-5-iodo-1-nitropent-1-ene under diphenylprolinol silyl ether catalysis following an enamine–enamine mechanism. This method provides access to cyclic γ-nitroaldehydes of the cyclopentane type containing an all-carbon-substituted quaternary stereogenic center. Furthermore a novel cyclic γ-amino acid of potential pharmaceutical relevance could be synthesized from the domino product in two steps.

Experimental Section

Catalyst **1** (130 mg, 0.4 mmol) was added to a solution of benzoic acid (244 mg, 2 mmol), propanal (**4a**) (0.75 mL, 10 mmol), and (*E*)-5-iodo-1-nitropent-1-en (**5**) (482 mg, 2 mmol) in DMSO (4 mL) at room temperature. The reaction mixture was stirred for 2 d, quenched with saturated NH_4Cl (5 mL), and extracted three times with ether. The combined organic phases were washed successively with saturated $NaHCO_3$ and brine, and dried over Na_2SO_4, concentrated, and purified by preparative TLC (pentane/ether 12:1) to afford the product (212 mg, 62%) as a yellow oil.

Received: May 30, 2008
Published online: August 27, 2008

Keywords: alkylation · amino acids · domino reactions · organocatalysis · quaternary stereocenters

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