

# Conjugate Addition of Nitroalkanes to an Acrylate Equivalent. Stereocontrol at C- $\alpha$ of the Nitro Group through Double Catalytic Activation

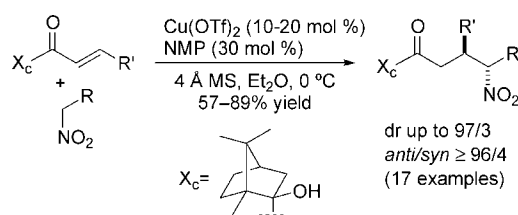
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Received June 16, 2009

## ABSTRACT



An unprecedented highly selective direct conjugate addition of prochiral nitroalkanes ( $R \neq H$ ) to acrylate equivalents is described. The method employs a unique Lewis acid/Brønsted base/MS ternary catalytic system and affords products with dr up to 97/3. With  $\beta$ -substituted ( $R' \neq H$ ) acceptors unprecedented levels of *anti/syn* selectivity ( $\geq 96/4$ ) are attained. Adducts can be transformed into enantioenriched  $\gamma$ -amino acids and derivatives, including aldehydes, ketones, lactams, and peptides, through simple protocols with full recovery of camphor auxiliary, the source of chiral information.

Conjugate addition of a nitroalkane to an electron-deficient olefin is one of the most powerful C–C bond-forming reactions and implies remote functionalization of a substrate acceptor. Upon proper functional group manipulation in the resulting adducts, a series of difunctional compounds become rapidly accessible. In particular, if an acrylate equivalent is used as the acceptor component,

reduction of the nitro group to the amine affords  $\gamma$ -amino acid ( $\gamma$ -AA) derivatives, an important class of building blocks in chemistry, biology, and materials sciences.<sup>1,2</sup> To date considerable efforts have been devoted to the control of the stereochemistry during the conjugate addition of nitro compounds to Michael acceptors.<sup>3</sup> However, while there is a number of methods to control absolute configuration at the resulting  $C\beta$  stereocenter ( $R' \neq H$ , Scheme 1), most known methods fail in controlling the configuration of the  $C\gamma$  stereocenter ( $R \neq H$ ). Thus, virtually all reported catalytic enantioselective conjugate additions<sup>4</sup> of prochiral nitroalkanes to unsaturated acyl equivalents<sup>5,6</sup> deal with  $\beta$ -substituted

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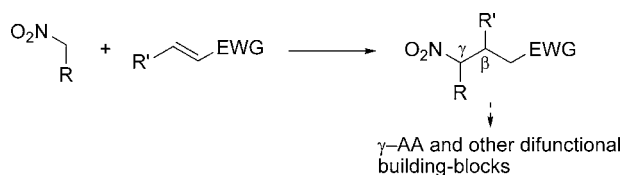
<sup>§</sup> Universidade da Coruña (X-ray analysis).

<sup>‡</sup> Universidad Pública de Navarra.

(1) For their relevance in peptide science, see: (a) Hanessian, S.; Luo, X.; Schaum, R.; Michnick, S. *J. Am. Chem. Soc.* **1998**, *120*, 8569–8570. (b) Hintermann, T.; Gademann, K.; Jaun, B.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 983–1002. (c) Seebach, D.; Brenner, M.; Rueping, M.; Jaun, B. *Chem.—Eur. J.* **2002**, *8*, 573–584.

(2) For a review on the stereoselective synthesis of  $\gamma$ -AAs, see: Ordoñez, M.; Cativiela, C. *Tetrahedron: Asymmetry* **2007**, *18*, 3–99.

**Scheme 1.** Conjugate Addition of Nitroalkanes to Michael Acceptors As a Route to Remote Functionalization

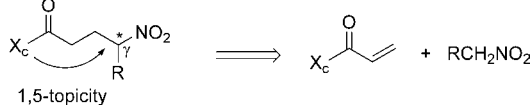


acceptors and usually provide mixtures of *syn/anti* isomers in nearly 1:1 ratio, epimeric at C $\gamma$ .<sup>5,7</sup> On the other hand, the alternative approach, which relies on chiral acryloyl systems covalently bound to the corresponding auxiliary, tends to provide unsatisfactory levels of stereocontrol as a consequence of the distance (4 chemical bonds away) between the chiral inductor and the newly formed stereocenter.<sup>8,9</sup>

Here we describe the first realization of highly stereoselective conjugate addition of unmodified prochiral nitroalkanes to acrylate systems based on an intriguing double catalytic activation of substrates.

It was argued that in order to get satisfactory levels of remote stereocontrol in the approach depicted in Scheme 2,

**Scheme 2.** Challenging Remote Stereocontrol in Conjugate Addition of Nitroalkanes to Chiral Acrylates



auxiliary groups (X<sub>c</sub>) displaying strong steric shielding would be required. Given the high level of asymmetric induction

(3) For a review on conjugate additions of nitrocompounds, see: Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933–971.

(4) For reviews on asymmetric conjugate additions covering metal catalysis, see: (a) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033–8061. Covering organocatalysis: (b) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701–1716. (c) Almasi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron Asymmetry* **2007**, *18*, 299–365. (d) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, 2065–2092.

(5) Iminium ion mediated additions to enals: (a) Zu, L.; Xie, H.; Li, H.; Wang, J.; Wang, W. *Adv. Synth. Catal.* **2007**, *349*, 2660–2664. (b) Gotoh, H.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 5397–5309. (c) Hojabri, L.; Hartikka, A.; Moghaddam, F. M.; Arvidsson, P. I. *Adv. Synth. Catal.* **2007**, *349*, 740–748. (d) Wang, Y.; Li, P.; Liang, X.; Zhang, T. Y.; Ye, J. *Chem. Commun.* **2008**, 1232–1234. Bifunctional thiourea-catalyzed additions to unsaturated N-acyl pyrroles: (e) Vakulya, B.; Varga, S.; Soós, T. J. *Org. Chem.* **2008**, *73*, 3475–3480. Diphenylprolinol-catalyzed cross-conjugate additions between nitroalkenes and enals: (f) Zhong, C.; Chen, Y.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. *Angew. Chem., Int. Ed.* **2009**, *48*, 1279–1282. Iminium ion mediated additions to enones: (g) Dong, L.-t.; Lu, R.-j.; Du, Q.-s.; Zhang, J.-m.; Liu, S.-p.; Xuan, Y.-n.; Yan, M. *Tetrahedron* **2009**, *65*, 4124–4129. For methods involving  $\beta$ -unsubstituted vinyl ketones that provide from poor to moderate ee, see the following. Al-catalyzed addition of nitroesters: (h) Keller, E.; Veldman, N.; Spek, A. L.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *8*, 3403–3413. Peptide-catalyzed additions of  $\alpha$ -nitroketones: (i) Linton, B. R.; Reutershand, R. H.; Aderman, C. M.; Richardson, E. A.; Brownell, K. R.; Ashley, C. W.; Evans, C. A.; Miller, S. J. *Tetrahedron Lett.* **2007**, *48*, 1993–1997.

imparted by acrylate equivalent **1** in other transformations<sup>10</sup> and stimulated by the simplicity of the approach, the present investigation was initiated by studying the behavior of **1** during conjugate addition of nitroethane.

Compound **1** is readily accessible in gram quantities from camphor, one of the cheapest chiral raw materials available in bulk, and has been shown to be activated by added acid, either Brønsted acid,<sup>10a</sup> Lewis acid,<sup>10b</sup> or combined Lewis acid–molecular sieves (MS).<sup>10c</sup> However, none of these conditions was effective for the target reaction (Table 1,

**Table 1.** Catalyst Screening for the 1,4-Addition of Nitroethane (**2a**, R = CH<sub>3</sub>) to **1**<sup>a</sup>

entry	acid	base	additive	t (h)	dr	conv. (%)
1	TfOH			24		0
2	Cu(OTf) <sub>2</sub>			24		0
3	Cu(OTf) <sub>2</sub>		4 Å MS	24		0 <sup>b</sup>
4	Mg(OTf) <sub>2</sub>		4 Å MS	18		0
5		<i>i</i> -Pr <sub>2</sub> NEt		24	59/41	98
6		NMP		24	52/48	>99 <sup>b</sup>
7	Cu(OTf) <sub>2</sub>	<i>i</i> -Pr <sub>2</sub> NEt		24	55/45	50
8	Cu(OTf) <sub>2</sub>	<i>i</i> -Pr <sub>2</sub> NEt	4 Å MS	4	80/20	>99
9	Cu(OTf) <sub>2</sub>	Et <sub>3</sub> N	4 Å MS	1	88/12	>99
10	<b>Cu(OTf)<sub>2</sub></b>	<b>NMP</b>	<b>4 Å MS</b>	<b>1</b>	<b>97/3</b>	<b>&gt;99</b>
11	Cu(OTf) <sub>2</sub>	NMP	4 Å MS	1	90/10	>99 <sup>b</sup>
12		NMP	4 Å MS	120	60/40	90 <sup>b</sup>
13	Cu(OTf) <sub>2</sub>	NMP		18	50/50	>99 <sup>b</sup>

<sup>a</sup> Ratio of **1/2a/acid/base** = 1:5:0.2:0.4 as applicable; loading of powdered 4 Å MS = 100 mg/mmol of **1**. <sup>b</sup> Reaction run at rt. NMP = *N*-methylpiperidine.

entries 1–4). It was then found that base-promoted activation of the pronucleophilic nitroalkane was effective, although the reaction to afford **3a** was totally unselective with all tertiary amines tested (entries 5 and 6). These results suggest once again that for full realization of the stereodiscriminating power of reagent **1**, conformational restriction of the ketol

(6) Conjugate additions of prochiral nitroalkanes to non-carbonyl Michael acceptors promoted by bifunctional thiourea organocatalysts. To nitroalkenes: (a) Rabalakos, C.; Wulff, W. J. *Am. Chem. Soc.* **2008**, *130*, 13524–13525. (b) Dong, X.-Q.; Teng, H.-L.; Wang, C.-J. *Org. Lett.* **2009**, *11*, 1265–1268. To vinyl sulfones: (c) Zhu, Q.; Lu, Y. *Org. Lett.* **2009**, *11*, 1721–1724.

(7) For exceptions using preformed silyl nitronates, see: (a) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 9022–9023. (b) Ooi, T.; Fujioka, S.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 11790–11791.

(8) For a review on remote stereocontrol, see: Mikami, K.; Shimizu, M.; Zhang, H.-C.; Maryanoff, B. E. *Tetrahedron* **2001**, *57*, 2917–2951.

(9) For conjugate addition of prochiral nitroalkanes (R  $\neq$  H) to selected chiral acrylate systems, leading to 70:30 or lower dr, see: Ballini, R.; Fiorini, D.; Palmieri, A.; Petrini, M. *Lett. Org. Chem.* **2004**, *1*, 335–339.

(10) (a) Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Lecumberri, A.; Linden, A. *J. Am. Chem. Soc.* **2002**, *124*, 10288–10289. (b) Palomo, C.; Oiarbide, M.; Arceo, E.; García, J. M.; López, R.; González, A.; Linden, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6187–6190. (c) Palomo, C.; Oiarbide, M.; García, J. M.; Bañuelos, P.; Odriozola, J. M.; Razkin, J.; Linden, A. *Org. Lett.* **2008**, *10*, 2637–2640.

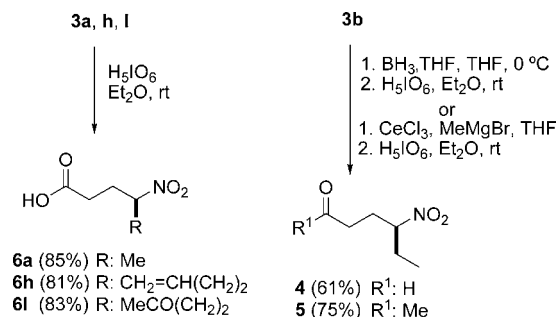
unit through 1,4-metal or 1,4-proton binding in the transition state is crucial. Guided by this idea, a concurrent activation of the nucleophile and the electrophile components by combined Lewis acid–Brønsted base system was pursued.<sup>11</sup> Experiments were carried out in both the presence and absence of molecular sieves (MS), which demonstrated that sieves are an important additive for the reaction to proceed efficiently. Thus, while no improvement was observed in the absence of MS (entry 7), in their presence the reaction proceeded to afford **3a** with increasing level of diastereoselectivity (entries 8–10). Of the amines studied, *N*-methyl piperidine was the most effective<sup>12</sup> and after 1 h of reaction at 0 °C gave a remarkable 97/3 dr value. The reaction temperature was important, since the same reaction run at rt led to 90/10 dr.<sup>13</sup> As data from entries 12 and 13 show, reactions carried out in the absence of either the Lewis acid or the MS were completely unselective. To the best of our knowledge, the present system represents one of the most intriguing demonstrations of MS-dependent reaction stereoselectivity.<sup>14</sup> Subsequently, we observed that lowering the reaction temperature from 0 to –20 °C did not lead to better results, while changing the solvent from CH<sub>2</sub>Cl<sub>2</sub> to Et<sub>2</sub>O led to higher isolated yields.

The scope of the method is shown in Table 2. In general, reactions proceeded with diastereoselectivities from very

ketones, or ethers were well tolerated, with the alcohol group in **2m** being the one exception due to the competing oxa-Michael reaction (15% of isolated product). Of practical interest, reactions could be run at 10 mmol scale without compromising selectivity or yield.

The potential of the present methodology is illustrated by elaboration of adduct **3** into the corresponding  $\gamma$ -nitro carboxylic acids, aldehydes, and ketones using simple protocols that tolerate the nitro group. For instance, Scheme 3, treatment of adducts **3a,h,i** with periodic acid afforded

**Scheme 3.** Removal of the Auxiliary Leading to Carboxylic Acids, Aldehydes, and Ketones



**Table 2.** Scope of the Catalytic Addition of Nitroalkanes **2** to **1**<sup>a</sup>

$1 + \text{RCH}_2\text{NO}_2 \xrightarrow[4 \text{ \AA MS, Et}_2\text{O, 0 } ^\circ\text{C}]{\text{Cu}(\text{OTf})_2 \text{ 10 mol \%}, \text{NMP 30 mol \%}} 3$			
compd	R	dr <sup>b</sup> ( <b>3</b> )	yield (%) <sup>c</sup> ( <b>3</b> )
<b>a</b>	CH <sub>3</sub>	97/3	79 <sup>d</sup>
<b>b</b>	CH <sub>3</sub> CH <sub>2</sub>	97/3	74
<b>c</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub>	97/3	74
<b>d</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub>	97/3	77
<b>e</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub>	97/3	79
<b>f</b>	(CH <sub>3</sub> ) <sub>2</sub> CH	97/3	62 <sup>e</sup>
<b>g</b>	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub>	97/3	75
<b>h</b>	CH <sub>2</sub> =CH(CH <sub>2</sub> ) <sub>2</sub>	96/4	77
<b>i</b>	PhCH <sub>2</sub>	93/7	79
<b>j</b>	2-Me-Furyl-CH <sub>2</sub>	92/8	57 <sup>d</sup>
<b>k</b>	MeO <sub>2</sub> C(CH <sub>2</sub> ) <sub>2</sub>	96/4	89
<b>l</b>	MeCO(CH <sub>2</sub> ) <sub>2</sub>	96/4	86
<b>m</b>	HOCH <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub>	96/4	50 <sup>d,f</sup>
<b>n</b>	BnOCH <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub>	94/6	60 <sup>d</sup>

<sup>a</sup> Reactions carried out at 1 mmol scale in Et<sub>2</sub>O (4 mL) in the presence of 4 Å MS (100 mg) at 0 °C. Molar ratio of 1:2:Cu(OTf)<sub>2</sub>/*N*-methylpiperidine = 1:5:0.1:0.3. <sup>b</sup> Determined by <sup>1</sup>H NMR. <sup>c</sup> Isolated yields after chromatography. <sup>d</sup> 20 mol % of Cu(OTf)<sub>2</sub> and 40 mol % of *N*-methylpiperidine employed. <sup>e</sup> Reaction run at room temperature. <sup>f</sup> 15% of O-addition product was obtained.

good to almost perfect for simple saturated and unsaturated nitroalkanes. In addition, functional groups such as esters,

(11) For the concept of, and inherent problems associated with, double activation of substrates in the context of enantioselective catalysis, see: Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394–13395.

acids **6** in high yields. Similarly, reduction or, alternatively, nucleophilic alkylation of the carbonyl prior to the oxidation step yielded the corresponding aldehyde, **4**, or ketone, **5**. Of special interest, the method can be integrated with a peptide coupling step (**3a** → **7** → **8**, Scheme 4) wherein camphor, the source of chiral information that is easy to recover and recycle, also functions as an efficient protecting group of the carboxy terminus.<sup>15</sup>

To further assess the generality of the method, the same catalytic conditions were applied to  $\beta$ -substituted enoyl

(12) Other cyclic amines led to comparable results (*N*-methyl pyrrolidine, dr = 97/3; *N*-methyl morpholine, dr = 95/5).

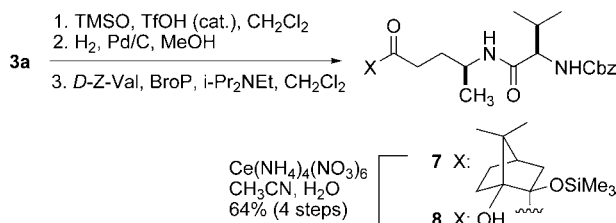
(13) Because of the acid character of the CH positioned  $\alpha$  to the nitro group, base-promoted epimerization of the product nitroalkane may be of concern. We carried out control experiments by stirring solutions of product **3b** (dr = 97/3) in Et<sub>2</sub>O in the presence of 20 mol % of various amine bases. With *i*-Pr<sub>2</sub>NEt, epimerization was below the limit of detection of <sup>13</sup>C NMR spectroscopy (50 MHz) after 24 h at rt. Under the same conditions but with NMP as base, dr diminished to 93/7. Finally, with DBU complete epimerization was observed after 24 h even at 0 °C. Therefore, and in agreement with the high dr values observed under our reaction conditions, we can conclude that epimerization of products would be a problem in the presence of strong bases (DBU) only, or eventually when weaker bases (NMP, *i*-Pr<sub>2</sub>NEt) are employed at temperatures above 0 °C.

(14) (a) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 5483–5488. (b) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466–468. (c) Steinhoff, B. A.; King, A. E.; Stahl, S. S. *J. Org. Chem.* **2006**, *71*, 1861–1868. (d) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 4016–4018. (e) Hasegawa, M.; Ono, F.; Kanemasa, S. *Tetrahedron Lett.* **2008**, *49*, 5220–5223.

(15) Usual carboxy-protecting groups fail with  $\gamma$ -amino acids because of their high tendency to lactamize spontaneously. See, for instance: (a) Pettit, G. R.; Singh, S. B.; Hogan, F.; Lloyd-Williams, P.; Herald, D. L.; Burkett, D. D.; Clewlow, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 5463–5465. (b) O'Connell, C. E.; Salvato, K. A.; Meng, Z.; Littlefield, B. A.; Schwartz, C. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1541–1546.

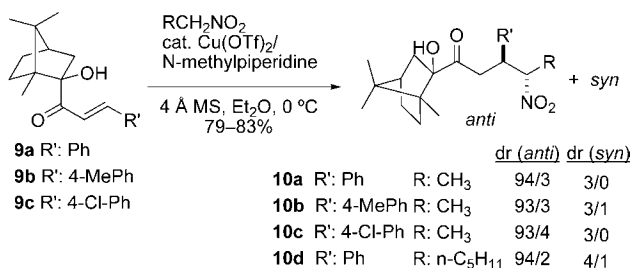
(16) In the case of  $\beta$ -substituted enones **9**, the reaction with nitroethane did not proceed at all in the absence of Cu(OTf)<sub>2</sub> (2 equiv of *N*-methylpiperidine, rt, 24 h, 0% conversion).

**Scheme 4.** Auxiliary Camphor-Derived Ketol Working As Carboxy Protecting Group in Peptide Coupling

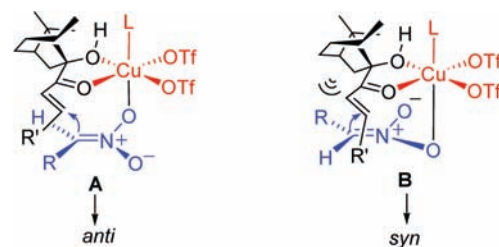


derivatives **9**. Gratifyingly, Scheme 5, the addition reaction of nitroalkanes to **9** also proceeded satisfactorily and stereoisomer *anti*-**10** was obtained as the major product out of the four possible isomers. As shown in Scheme 5, *anti/syn* ratios of up to 97:3 were obtained, which is the highest selectivity so far reported for this type of conjugate addition.<sup>5</sup>

**Scheme 5.** *anti*-Selective 1,4-Addition of Nitroalkanes to  $\beta$ -Substituted Enones **9**



While the precise role played at the molecular level by MS on the course of the present catalytic reactions is yet far from being understood, simplified stereomodels A and B might account for the preferable *re*-face attack of the evolving nitronate species. Accordingly, metal centered preassociation of both the in situ generated nitronate and



**Figure 1.** Stereomodels with both the acceptor hydroxy enone and donor nitronate coordinated to Cu displaying a (A) *re* and (B) *si* approach of nitronate.

hydroxy enone would be a key activation<sup>16</sup> and organizational element, and the camphor skeleton would sterically favor a *re-re* approach of the two prochiral carbon atoms.

In conclusion, we have developed a highly stereoselective direct conjugate addition of prochiral nitroalkanes to  $\beta$ -unsubstituted Michael acceptors. The method, which requires a unique ternary Lewis acid/Brønsted base/MS catalytic system, also tolerates  $\beta$ -substituted enoyl acceptors with unprecedented levels ( $\geq 96:4$ ) of *anti/syn* selectivity. Simple elaboration of adducts affords enantiopure difunctional building blocks, such as  $\gamma$ -AA and derivatives, camphor, the source of chiral information, being easy to recycle. Although the precise role played by each catalyst component is still unclear, the bases are set for the development of an enantioselective version, which is currently under study.

**Acknowledgment.** This work was financially supported by Universidad del País Vasco, Gobierno Vasco, and by Ministerio de Educación y Ciencia (Spain).

**Supporting Information Available:** Experimental procedures and characterization data of compounds **1** and **3–10**, including NMR spectra and HPLC chromatograms. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL901351K