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Asymmetric Synthesis of γ-Nitroesters by an Organocatalytic One-Pot Strategy

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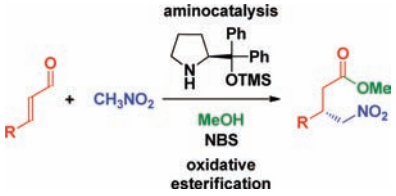
ABSTRACT



An enantioselective synthesis of γ-nitroesters by a one-pot asymmetric Michael addition/oxidative esterification of α,β-unsaturated aldehydes is presented. The procedure is based on merging the enantioselective organocatalytic nitroalkane addition with an *N*-bromosuccinimide-based oxidation. The γ-nitroesters are obtained in good yields and enantioselectivities, and the method provides an attractive entry to optically active γ-aminoesters, 2-piperidones, and 2-pyrrolidones.

The catalytic Michael reaction is an important and well-studied process for stereoselective carbon−carbon bond formations in organic synthesis.[1] In recent years, the field of asymmetric organocatalytic Michael reactions has received widespread attention.[2] Among the reactions studied, the conjugate addition of nitroalkanes to α,β-unsaturated systems is of great interest, because the products obtained are direct precursors to important structural moieties, such as γ-aminocarbonyls, aminoalkanes, 2-pyrrolidones, and 2-piperidones.[3] Several methods have been developed for the conjugate addition of nitroalkanes to enones[4] and enals;[5] however, notably, no direct asymmetric addition to conjugate esters[6] has been reported to date, which is surprising given the broad applicability of these compounds in the fields of organic, pharmaceutical, and material chemistry (Figure 1).[7]

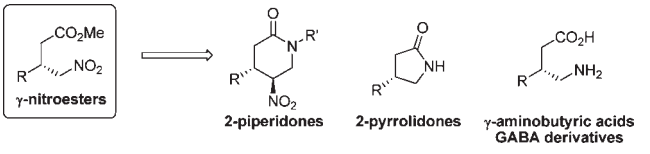


Figure 1. Application of γ-nitroesters in synthesis.

Traditionally, esters are prepared from the free carboxylic acid, which most often needs activation prior to

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(1) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, U.K., 1992.

(2) For recent reviews on asymmetric organocatalytic Michael reactions, see: (a) Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (b) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701.

(3) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933.

(4) (a) Yamaguchi, M.; Shiraishi, T.; Igarashi, Y.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 8233. (b) Yamaguchi, M.; Igarashi, Y.; Reddy, R. S.; Shiraishi, T.; Hirama, M. *Tetrahedron* **1997**, *53*, 11223. (c) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975. (d) Halland, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331. (e) Tsogoeva, S. B.; Jagtap, S. B. *Synlett* **2004**, 2624. (f) Prieto, A.; Halland, N.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 3897. (g) Mitchell, C. E. T.; Brenner, S. E.; Ley, S. V. *Chem. Commun.* **2005**, 5346. (h) Mitchell, C. E. T.; Brenner, S. E.; Garcia-Fortanet, J.; Ley, S. V. *Org. Biomol. Chem.* **2006**, *4*, 2039. (i) Hanessian, S.; Shao, Z.; Warrier, J. S. *Org. Lett.* **2006**, *8*, 4787.

(5) (a) Palomo, C.; Landa, A.; Mielgo, A.; Oiarbide, M.; Puente, Á.; Vera, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 8431. (b) Gotoh, H.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 5307. (c) Zu, L.; Xie, H.; Li, H.; Wang, J.; Wang, W. *Adv. Synth. Catal.* **2007**, *349*, 2660. (d) Wang, Y.; Li, P.; Liang, X.; Zhang, T. Y.; Ye, J. *Chem. Commun.* **2008**, 1232.

(6) For an intramolecular Michael addition to conjugated esters, see: Nodes, W. J.; Nutt, D. R.; Chippindale, A. M.; Cobb, A. J. A. *J. Am. Chem. Soc.* 2009, *131*, 16016.

(7) (a) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243. (b) Otera, J. *Esterification: Methods, Reactions and Applications*; Wiley: New York, 2003.

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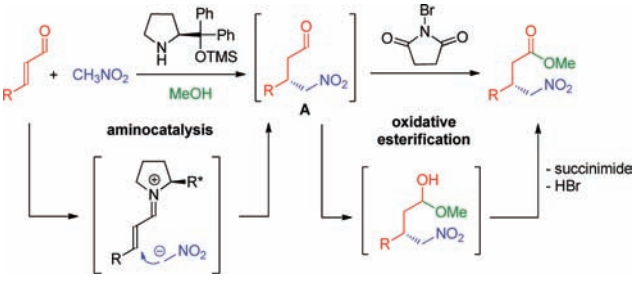
the esterification step. The direct formation of esters from aldehydes, also known as one-pot oxidative esterification, combines oxidation and C–O bond formation into a single step. This approach has become an economically attractive alternative, because it utilizes readily available materials and avoids isolation of the free carboxylic acid intermediates. These obvious advantages have inspired numerous investigations of the direct conversion of aldehydes into esters.[8] We envisioned that a one-pot enantioselective synthesis of γ-nitroesters[9] could be accomplished by merging the organocatalytic Michael addition of nitroalkanes to α,β-unsaturated aldehydes with a suitable oxidative esterification process (Scheme 1).

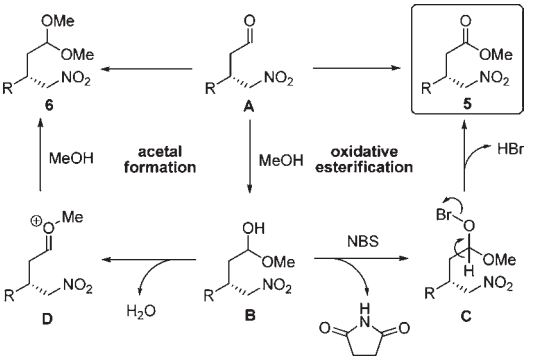
Scheme 1. Synthetic Outline for the Formation of γ-Nitroesters



Previous studies have demonstrated that bromine, iodine, or *N*-iodosuccinimide in alkaline alcoholic solutions can function as mild oxidants for this transformation.[10] However, a major complication of this reaction design is the fact that the intermediate aldehyde products readily undergo 1,2-intermolecular addition of nitromethane *via* the Henry reaction under basic conditions. Therefore, in order to achieve a successful oxidation, the use of a basic oxidation medium should be avoided. Furthermore, the oxidant should not react with the substrate in an enamine-based reaction, thereby functionalizing the α-position. Herein, we present a simple and straightforward asymmetric synthesis of γ-nitroesters from readily available α,β-unsaturated aldehydes, nitromethane, and MeOH (Scheme 1). The reaction takes place under mild conditions, and the products are formed in good yields and enantioselectivities in a one-pot process.

We started our studies by performing the initial Michael reaction[5] between cinnamaldehyde **1a** and nitromethane **2a** (3 equiv) applying 10 mol % of (*S*)-2-(diphenyl(trimethylsilyloxy)methyl)pyrrolidine[11] **3** as the catalyst[12] in MeOH at room temperature. Under these conditions, full and clean conversion to the Michael adduct **A** was observed. The anticipated oxidative esterification was then attempted, and, gratifyingly, the addition of 1.5 equiv of *N*-bromosuccinimide **4** (NBS) gave full conversion to the desired product **5a**, by incorporation of the solvent, MeOH. The product was obtained in 58% yield and 94% ee, along with a minor amount of the dimethyl acetal **6**, which could be separated from the product by column chromatography. It should be noted that no α-bromination of the aldehyde was observed.[13] The appearance of **6** as a byproduct can be explained by the mechanistic proposal presented in Scheme 2.

Scheme 2. Mechanistic Proposal for the Oxidative Esterification Process



The intermediate hemiacetal **B** is assumed to react with NBS to form the corresponding hemiacetal hypobromite species **C**. Subsequent elimination of HBr furnishes the oxidized product **5** (Scheme 2).[10] Notably, the acid formed can function as a catalyst for the formation of the acetal byproduct. In order to avoid the formation of **6**, a screening of weakly basic additives was attempted. These conditions resulted in low conversions/yields and substantial amounts of the Henry condensation product. Application of less than 1.5 equiv of NBS resulted in a reduced product to acetal ratio, whereas increased amounts gave no improvement.

With the obtained conditions in hand, the scope of the one-pot formation of γ-nitroesters **5** was examined for a series of α,β-unsaturated aldehydes as demonstrated in Scheme 3.

In general, all the reactions evaluated gave full conversion to the desired products **5a**–**n** with good yields ranging

(8) For a recent review on one-pot oxidative esterifications, see: (a) Ekoue-Kovi, K.; Wolf, C. *Chem.—Eur. J.* **2008**, *14*, 6302. For carbene-based oxidations, see e.g.: (b) Maki, B. E.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 4331. (c) Giun, J.; Sarkar, S. D.; Grimme, S.; Studer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8727. (d) Sarkar, S. D.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2010**, *132*, 1190.

(9) For other procedures for the synthesis of optically active γ-nitroesters, see e.g.: Baschieri, A.; Bernardi, L.; Ricci, A.; Suresh, S.; Adamo, M. F. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9342.

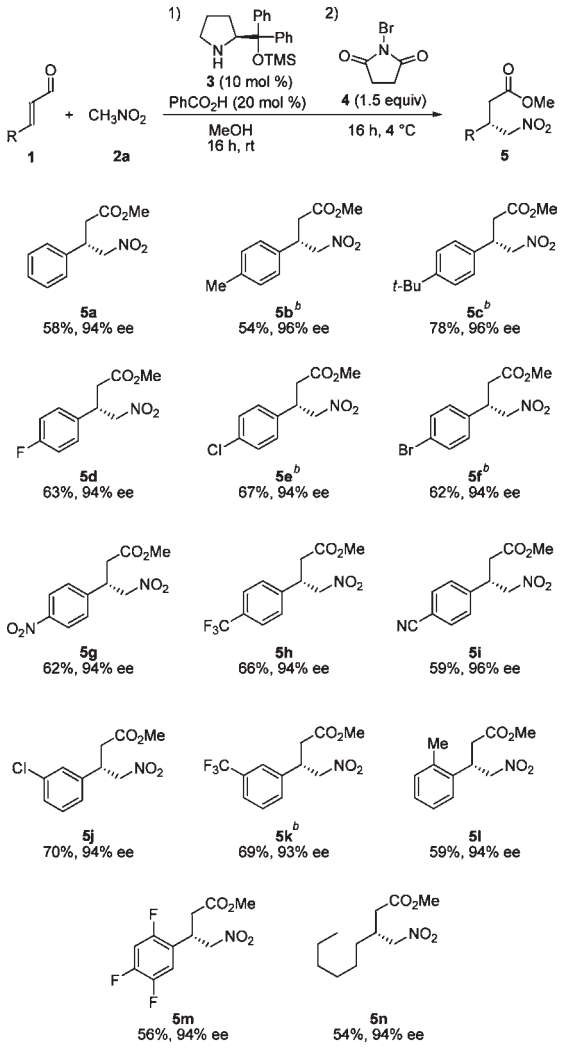
(10) For an example with bromine as oxidant, see: (a) Williams, D. R.; Klingler, F. D.; Allen, E. E.; Lichtenthaler, F. W. *Tetrahedron Lett.* **1988**, *29*, 5087. For an example with *N*-iodosuccinimide as oxidant, see: (b) McDonald, C.; Holcomb, H.; Kennedy, K.; Kirkpatrick, E.; Leathers, T.; Vanemon, P. *J. Org. Chem.* **1989**, *54*, 1213.

(11) (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. For general and comprehensive reviews on applications of the diarylprolinol silylether catalysts, see: (c) Palomo, C.; Mielgo, A. *Chem.—Asian J.* **2008**, *3*, 922. (d) Xu, L.-W.; Li, L.; Shi, Z.-H. *Adv. Synth. Catal.* **2010**, *352*, 243. (e) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248.

(12) Other related catalysts were less effective.

(13) Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jørgensen, K. A. *Chem. Commun.* **2005**, 4821.

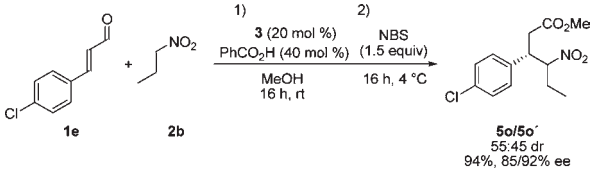
Scheme 3. Scope of the One-Pot Process for the Formation of γ-Nitroesters[a]



[a] For reaction conditions, see Supporting Information. [b] 3.0 equiv of NBS employed.

from 54 to 78% and high enantioselectivities (93 to 96% ee). The scope of the 4-substituted cinnamaldehyde derivatives was first examined, demonstrating that the electronic nature of the substituent had little effect on the outcome of the reaction. Electron-rich substituents, illustrated by a methyl and *tert*-butyl group, gave the products **5b** and **5c** in good yields (54 and 78%) with an enantioselectivity of 96% ee. Electron-poor substituents were also tolerated affording the products **5d**–**i** in good yields (59 to 67%) and enantioselectivities (94 to 96% ee). To further test the developed reaction concept, different substitution patterns of the aldehyde were explored. Aldehydes with chloro- and trifluoromethyl-substituents in the *meta*-position were successfully applied, affording the products **5j** and **5k** in good yields and enantioselectivities (70 and 69% with 94 and 93% ee, respectively). It was also demonstrated that *ortho*-methyl and 2,4,5-trifluoro-substituted aldehydes were tolerated, affording the γ-nitroesters **5l** and **5m** in good yields (59 and 56%) and 94% ee. Finally, the reaction concept was extended to aliphatic aldehydes by application of non-2-enal **1n**, which furnished the desired product **5n** in 54% yield and 94% ee. It should be noted that substantial amounts of the acetal **6** was formed in the reactions of aldehydes **1b**,**c**,**e**,**f**,**k** when 1.5 equiv of NBS was employed. The problem was successfully addressed by employing 3.0 equiv of NBS.

Scheme 4. Application of Nitropropane in the One-Pot Procedure



The developed one-pot procedure also proved suitable for other nitroalkanes as illustrated in Scheme 4.

Accordingly, the Michael addition of nitropropane **2b** to 4-chlorocinnamaldehyde **1e** proceeded smoothly, when applying 20 mol % of catalyst **3**. The subsequent oxidative esterification with NBS afforded two diastereomeric products **5o** and **5o′** in a combined yield of 94%. The isomers were obtained in good enantioselectivities (85 and 92% ee) and a diastereoselectivity of 55:45.

In order to demonstrate the synthetic value of the formed γ-nitroesters **5**, a series of transformations were performed (Scheme 5). A reductive cyclization of the *para*-chloro-substituted product **5e** was easily achieved by hydrogenation using $NiCl_2/NaBH_4$ affording the 2-pyrrolidone **7** in 88% yield. The lactam **7** can then be hydrolyzed using 6 M HCl to afford the hydrochloride salt of Baclofen,[14] which is a therapeutically important $GABA_B$ receptor agonist.[15] The products also provide access to 2-piperidones, which are key intermediates for the preparation of pharmaceutically important drug candidates.[16] The synthesis was accomplished by a one carbon homologation *via* a nitro-Mannich reaction. In practice, the reaction was carried out by treating product *ent*-**5d** with benzylamine and formaldehyde in an *i*-PrOH/H_2O mixture. After 4 h the 2-piperidone product **8** was obtained as a 3:1 diastereomeric mixture and the major *trans*-diastereomer was isolated in 48% yield and 94% ee. The obtained product could potentially be applied for the synthesis of (3*S*,4*R*)-paroxetine, which is a selective serotonin reuptake inhibitor used in the treatment of depression.[17]

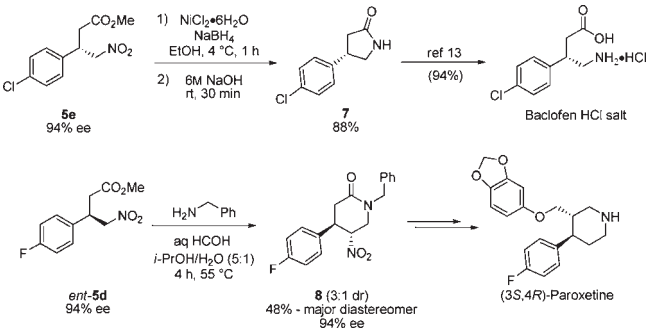
(14) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.

(15) For information on Baclofen, see: Felluga, F.; Gombac, V.; Pitacco, G.; Valentin, E. *Tetrahedron: Asymmetry* **2005**, *16*, 1341 and references therein.

(16) Xu, F.; Corley, E.; Murry, J. A.; Tschaen, D. M. *Org. Lett.* **2007**, *9*, 2669 and references therein.

(17) Barnes, R. D.; Wood-Kaczmar, M. W.; Curzons, A. D.; Lynch, I. R.; Richardson, J. E.; Buxton, P. C. U.S. Patent 24721723, 1986.

Scheme 5. Synthetic Transformations of the Formed γ-Nitroesters



In conclusion, we have designed a one-pot procedure, classified as a Type A-2-1C2X reaction,[18] for the synthesis of γ-nitroesters in good yields and enantioselectivities. The method is based on a one-pot asymmetric aminocatalyzed addition of nitroalkanes to α,β-unsaturated aldehydes followed by an oxidative esterification using NBS as the oxidant. The system displays great tolerance toward a number of aromatic as well as aliphatic aldehydes. The synthetic usefulness of the products was demonstrated by the synthesis of 2-pyrrolidones and 2-piperidones, which can be utilized in the synthesis of pharmaceutically important compounds.

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Supporting Information Available. Detailed experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8492.

The authors declare no competing financial interest.