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Nitrophenylacetonitriles as Versatile Nucleophiles in Enantioselective Organocatalytic Conjugate Additions

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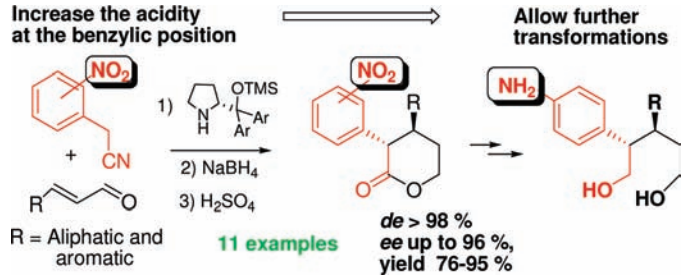
ABSTRACT



Arylacetonitriles are able to participate in organocatalytic Michael additions to α,β-unsaturated aldehydes by incorporating a nitro group at the phenyl ring, which acts as a temporary activating group in a remote position and allows further transformations. The sequential protocol Michael addition/$NaBH_4$ reduction/lactonization allows the synthesis of diastereomerically pure disubstituted lactones in high yield and optical purity.

Although asymmetric organocatalysis has proven to be a powerful tool for the efficient synthesis of complex molecules,[1] some challenges remain unsolved. With the exception of the nitroderivatives,[1f] the pro-nucleophilic species usually require the presence of two geminal electron-withdrawing groups to get the appropriate acidity of the methylenic protons for being able to intervene in organocatalytic processes.[2,3] As the second group is not usually required, it should be removed once it exerted its activating function, which reduces the scope of the process and produces epimerization, making the stereoselective formation of compounds bearing stereogenic centers at the nucleophilic carbon very difficult.

We reasoned that the incorporation of an appropriate electron-withdrawing group (EWG) to an aromatic ring could increase the acidity of the benzylic protons, allowing the use of any arylacetic acid derivative in organocatalytic processes. Elimination or transformation of the EWG group would not have any consequence on the possible chirality created at the nucleophilic center.[4]

In this paper, we report the first example of the use of arylacetonitriles bearing an EWG at the phenyl ring, as prochiral nucleophiles in their reactions with α,β-unsaturated

(1) For recent reviews on organocatalysis see, for example: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175. (b) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724. (c) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis—From Biomimetic Concepts to Powerful Methods for Asymmetric Synthesis*: WILEY-VCH: Weinheim, 2005. (d) Pellisier, H. *Tetrahedron* **2007**, *63*, 1733. (e) MacMillan, D. W. C. *Nature* **2008**, *455*, 304–308. (f) Dalko, P. I. *Enantioselective Organocatalysis: Reactions and Experimental Procedures*; WILEY-VCH: Weinheim, 2007.

(2) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218.

(3) For examples of nonprochiral monofunctionalized enolates, see: (a) Ricci, A.; Pettersen, D.; Bernardi, L.; Fini, F.; Fochi, M.; Pérez Herrera, R.; Sgarzani, V. *Adv. Synth. Catal.* **2007**, *349*, 1037. (b) Lubkoll, J.; Wennemers, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 6841.

(4) To our knowledge, the only paper related to the organocatalytic use of prochiral nucleophiles derived from monofunctionalized compounds deals with the reactions of trifluoroethyl thioesters derived from phenylacetic acid and was reported by Barbas III: Alonso, D. A.; Kitagaki, S.; Utsumi, N.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2008**, *47*, 4588.

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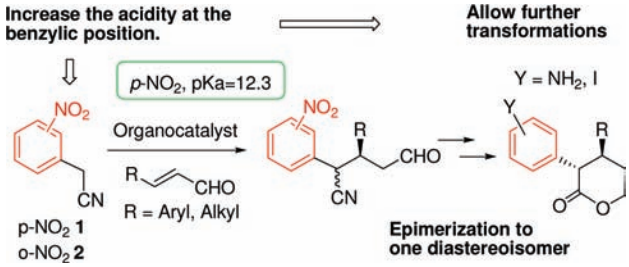
aldehydes catalyzed by prolinol ethers.[5,6] The nitro group at *para* (compound **1**) and *ortho* (compound **2**) have been chosen as EWGs because of its known influence for increasing the acidity at the benzylic position.[7] Moreover, **1** and **2** are both cheap and commercially available, have nucleophilicities similar to those of cyanoesters,[8] widely used in organocatalysis,[9] and have demonstrated a high synthetic versatility[10] (Scheme 1).

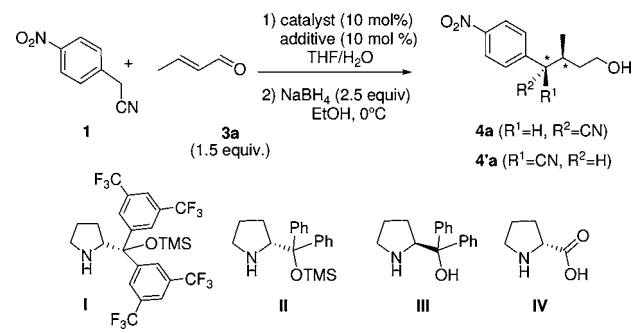
Scheme 1. Nitrophenylacetonitriles as Versatile Nucleophiles in Organocatalytic Michael Additions



Additionally, the high acidity transferred by the nitro group to the benzylic position has been exploited to epimerize the center to the most stable diastereoisomer by cyclization into lactones. These lactones can be obtained in a highly enantio- and diastereoselective manner. Once the temporary activating group has exerted its function, it can be transformed into other fuctional groups without affecting the integrity of the created stereogenic centers (Scheme 1).

Crotonaldehyde (**3a**) was chosen as a starting aldehyde for optimizing reactions with compound **1** (Table 1). The use of the Jørgensen−Hayashi catalyst **I**[11] allowed us to obtain a 59:41 diastereomeric mixture of Michael adducts in 90% yield under standard conditions, using benzoic acid as additive and THF/H_2O as solvent[12] (entry 1). The easy decomposition of these aldehydes in the HPLC columns

Table 1. Screening for the Addition of *p*-Nitrophenylacetonitrile **1** to Crotonaldehyde



entry	cat.	additive	*t* (h)	yield[a] (%)	de[b], ref 12 **4a**:**4′a**	ee (%) **4a**	ee (%) **4′a**
1	**I**	$PhCO_2H$	40	90	59:41	90	89
2	**I**	AcOLi	20	95	63:37	90	89
3	**I**	AcONa	24	63	60:40	84	88
4	**I**	DABCO	24	65	63:37	84	88
5	**I**	TMAF	40	60	61:39	64	78
6	**I**[c]	AcOLi	40	93	63:37	91	90
7	**II**	AcOLi	24	84[e]	60:40	86	70
8	**III**	AcOLi	24	82[e]	60:40	−50[d]	−62[d]
9	**IV**	AcOLi	24	54[e]	61:39	15	16

[a] After flash chromatography. [b] By HPLC. [c] Reaction at 0 °C. [d] The other enantiomer was obtained with catalyst **III**. [e] Conversion.

made necessary their transformation into alcohols (**4a** and **4′a**) before determining their optical purity. $NaBH_4$ reduction on the reaction crude of the Michael addition,[13] once the solvent (THF and H_2O) was eliminated under vacuum, allowed us to determine by HPLC an ee next to 90% for both alcohols (entry 1).

In the absence of additive, the reaction did not take place. The use of nonacidic additives reduced the reaction times (entries 2−5), with AcOLi providing the best results (entry 2).[14] Different additives, solvents,[12] or a decrease in the temperature did not produce any significant improvement in the ee (entry 6). The use of other catalysts like **II**−**IV** provided lower yields and enantiomeric excesses (entries 7−9).

To control the configuration at the benzylic carbon, we took advantage of its intrinsic acidity to epimerize it to the most stable isomer in a cyclic substrate.[15] To our delight, when the epimeric mixture of alcohols **4a** and **4′a** was treated with H_2SO_4 in AcOH,[16] diastereomerically pure lactone **6a**

(5) For a review of iminium catalysis, see: Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416.

(6) Review articles about organocatalytic Michael addition, see: (a) Almasi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (b) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (c) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, *14*, 2065.

(7) 12.3 is the pK_a value of *p*-nitrophenylacetonitrile in DMSO. See: Bordwell, F. G.; Cheng, J.-P.; Bausch, M. J.; Bares, J. E. *J. Phys. Org. Chem.* **1988**, *1*, 209.

(8) Kaumanns, O.; Appel, R.; Lemek, T.; Seeliger, F.; Mayr, H. *J. Org. Chem.* **2009**, *74*, 75–81.

(9) (a) Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120. (b) López-Cantarero, J.; Cid, M. B.; Poulsen, T. B.; Bella, M.; García Ruano, J. L.; Jørgensen, K. A. *J. Org. Chem.* **2007**, *72*, 7062.

(10) (a) Gaudemer, A.; Nguyen-Van-Duong, K.; Shahkarami, N.; Achi, S. S.; Frostin-Rio, M.; Pujol, D. *Tetrahedron* **1985**, *41*, 4095. (b) Sheppeck, J. E., II; Gilmore, J. L.; Tebben, A.; Xue, C.-B.; Liu, R.-Q.; Decicco, C. P.; Duan, J. J.-W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2769. (c) Boedeker, J.; Fieblinger, D.; Koeppel, H.; Radeglia, R. *Z. Chem.* **1988**, 183. (d) Allen, C. F. H. *J. Am. Chem. Soc.* **1925**, *47*, 1733.

(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 a review of chiral diarylprolinol ether catalysis, see: Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876.

(12) For more details see the Supporting Information.

(13) $NaBH_4$ reduction of the diastereomerically pure aldehydes, separated from the crude by flash chromatography, produce epimerization into their thermodinamic mixture of **4a**/**4′a**.

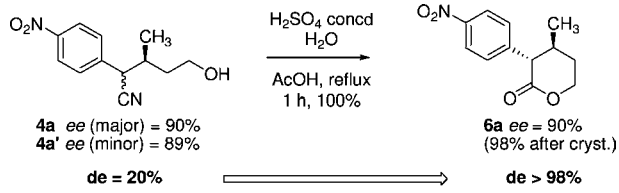
(14) For other examples where AcOLi has been used, see: (a) Wang, Y.; Li, P.; Liang, X.; Zhang, Y.; Ye, J. *Chem. Commun.* **2008**, 1232. (b) García Ruano, J. L.; Marcos, V.; Alemán, J. *Chem. Commun.* **2009**, 4435.

(15) This strategy has been previously used. See, for example: (a) García Ruano, J. L.; de Haro, T.; Singh, R.; Cid, M. B. *J. Org. Chem.* **2008**, *73*, 1150. (b) Brandau, S.; Landa, A.; Franzen, J.; Marigo, M.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4305. (c) Valero, G.; Schimer, J.; Cisarova, I.; Vesely, J.; Moyano, A.; Rios, R. *Tetrahedron Lett.* **2009**, 1943.

(16) Corrie, J. E. T.; Munasinghe, V. R. N. *J. Labelled Compd. Radiopharm.* **2005**, *48*, 231.

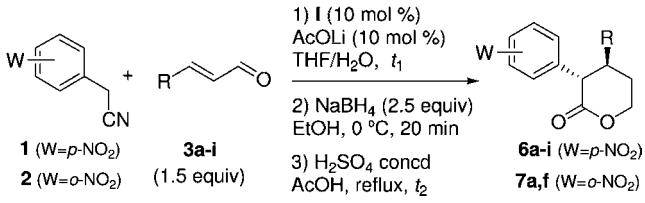
was obtained in quantitative yield, without erosion of the enantiomeric purity (90% ee, Scheme 2).

Scheme 2. Formation of Diastereomerically Pure Lactone **6a**



We then searched a sequential procedure Michael addition/reduction/lactonization, to afford the direct synthesis of lactone **6a** from compounds **1** and **3a** without isolation of the intermediates. It required the elimination of the solvents under vacuum after the first step (see above) and the filtration through a short pad of silica gel after the reduction. Under these conditions, **6a** could be obtained as only one diastereoisomer (de > 98%) in 95% yield and 90% ee (entry 1, Table 2). The enantiomeric excess could be increased until 98% ee by simple crystallization, and the reaction was scaled up until 1 g of product.

Table 2. Scope for the Addition of *p*-Nitrophenylacetonitriles **1** and **2**



entry[a]	R	t_1[b] (h)	t_2[c] (h)	product	overall yield (%)	ee[d] (%)
1	**3a** (Me)	20	1	**6a**[e]	95	90
2	**3b** (Et)	24	1	**6b**[e]	89	92
3	**3c** (*n*-Pr)	48	1	**6c**[e]	92	92
4	**3d** (*n*-Bu)	48	1	**6d**[e]	89	90
5	**3e** (iPr)	120	3	**6e**[e]	90	96
6	**3f** (Ph)	48	8	**6f**[e]	79	80
7	**3g** (*p*-OMe-C_6H_4)	72	30	**6g**[e]	82	30
8	**3h** (*p*-NO_2-C_6H_4)	48	48	**6h**[e]	86	85[g]
9	**3i** (*p*-Br-C_6H_4)	72	3.5	**6i**[e]	84	70
10	**3a** (Me)	24	8	**7a**[f]	78	84
11	**3f** (Ph)	40	25	**7f**[f,h]	76	50

[a] Reactions performed on 1 mmol scale. [b] Michael addition. [c] Cyclization. [d] Determined by HPLC. [e] **1** was used as starting material. [f] **2** was used as starting material. [g] Estimated from the ee of the mixture of alcohols.[12] [h] Obtained as a 94:6 mixture of epimers.

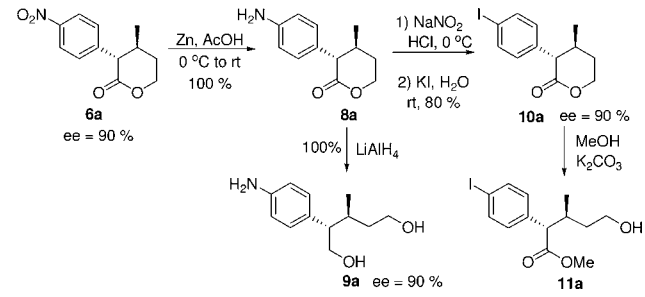
This sequential procedure (Table 2) was applied with similar efficiency for synthesizing the presumably most stable *trans*-lactones **6a**−**6e** with R = alkyl (entries 1−5). When R is aromatic, diastereoselectivity remains complete, but ee is lower (entries 6−9). It seems that electron-donating groups, like *p*-OMe, seriosly reduced the ee (entry 7), whereas it is slighly improved by electron withdrawing groups like *p*-NO_2 (entry 8).

ortho-Nitrophenylacetonitrile **2** also reacted with aldehydes **3a** (R = alkyl) and **3f** (R = aryl), under the same sequential procedure used for **1** (entries 10 and 11) affording **7a** and **7f**, respectively. Reaction times for cyclization (t_2) are longer than those required for **1**, and the ee is slightly lower (compare entries 1 and 10 or 6 and 11), probably due to the steric hindrance of the *ortho* substituent.

It is remarkable that *m*-nitrophenylacetonitrile did not react under the same conditions. As the pK_a for this compound is 18.1 in DMSO,[7] this lack of reactivity is in agreement with the requirements established for the nucleophile activation using amine organocatalysts, which fix the pK_a values below 17.[17]

To illustrate the versatility of these nucleophiles, several transformations have been carried out. The reduction of the NO_2 into the NH_2 group is fundamental for decreasing the acidity of the benzylic possition, thus minimizing its tendency to epimerize. It can be easily performed in quantitative yield by treatment of **6a** with Zn/AcOH.[18] The so-obtained **8a** was transformed into the acyclic diol **9a** without epimerization (Scheme 3). Analogously, iodide **10a**, a useful starting material for metal-catalyzed cross coupling reactions and easily obtained from **8a**,[19] can also be opened to the ester **11a** (Scheme 3).[12]

Scheme 3. Transformation of **6a** into Acyclic Compounds without Epimerization



As **9a** and **11a** can be considered as the optically enriched acyclic compounds which would result in an organocatalytic asymmetric Michael reaction with monoactivated benzylic

(17) Malonates with a pK_a of 16.4 are used in enantioselective organocatalysis with chiral amines. See: (a) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 661. (b) Wang, J.; Li, H.; Zu, L.; Jiang, W.; Xie, H.; Duan, W.; Wang, W. *J. Am. Chem. Soc.* **2006**, *128*, 12652. Nevertheless, ketones with a pK_a around 18 need activation via enamine, see also ref 4.

(18) Higuchi, K.; Sato, Y.; Tsuchimochi, M.; Sugiura, K.; Hatori, M.; Kawasaki, T. *Org. Lett.* **2009**, *11*, 197.

(19) Peretto, I.; Radaelli, S.; Parini, C.; Zandi, M.; Raveglia, L. F.; Dondio, G.; Fontanella, L.; Misiano, P.; Bigogno, C.; Rizzi, A.; Riccardi, B.; Biscaioli, M.; Marcello, M.; Marchetti, S.; Puccini, P.; Catinella, S.; Rondelli, I.; Cenacchi, V.; Bolzoni, P. T.; Caruso, P.; Villetti, G.; Facchinetti, F.; Del Giudice, E.; Moretto, N.; Imbimbo, B. P. *J. Med. Chem.* **2005**, *48*, 5705.

prochiral nucleophiles, we can consider our strategy as an indirect way for getting these transformations.

The absolute configuration of the lactone **10a** was unequivocally established as (3*S*, 4*S*) by X-ray diffraction studies (Figure 1). This configuration was assumed for the rest of the lactones **8a**, **6**, and **7**.[12]

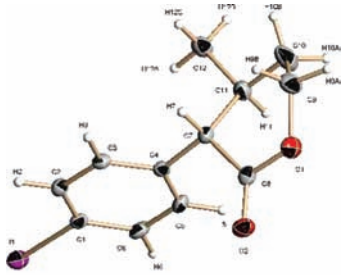


Figure 1. X-ray structure of **10a**.

In conclusion, we have demonstrated that the nitro group at an aromatic ring can be used as a temporary activating group of benzylic nucleophiles in organocatalytic processes. Particularly, the *para*-nitrophenylacetonitrile (cheap and commercially available) is able to react with *β*-alkyl-substituted acroleines in a highly enantioselective manner. Performing three sequential reactions (Michael/reduction/lactonization) affords diastereomerically pure lactones in a very high yield and optical purity (up to 96% ee) with minimal laboratory manipulation. These results open a new route to study the behavior of other benzylic versatile nucleophiles.

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Supporting Information Available: Experimental procedures, characterization, spectra, chiral HPLC conditions, and X-ray crystallographic data of **10a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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