Letter

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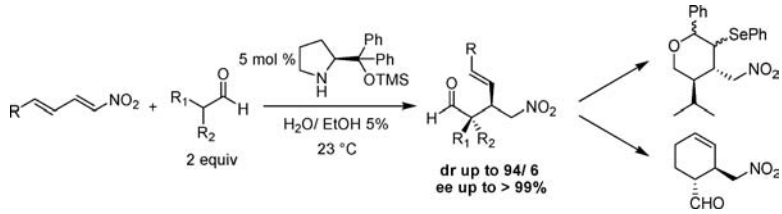

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Enantioselective Organocatalytic Conjugate Addition of Aldehydes to Nitrodienes

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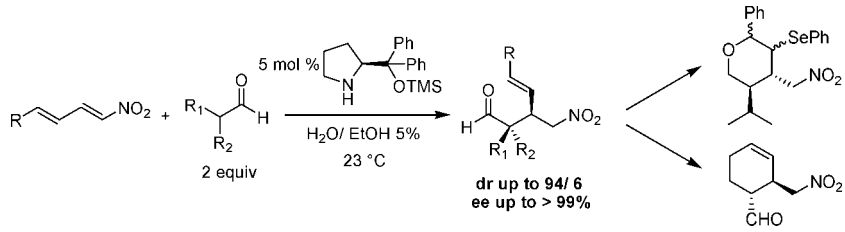
ABSTRACT



The asymmetric organocatalyzed Michael addition of aldehydes to α,*β*-*γ*,*δ*-unsaturated nitro compounds has been accomplished using only 5 mol % of (*S*)-diphenylprolinol silyl ether and 2 equiv of aldehyde in a mixture of ethanol and water (5% v/v). The Michael adducts were obtained in good yields, diastereoselectivities up to 94/6, and ee's up to 99%. This process provides synthetically useful compounds which can easily lead to more complex molecules, as exemplified with substituted tetrahydropyran or cyclohexene.

More than 30 years after the first organocatalyzed intramolecular asymmetric aldol reaction, known as the Hajos−Parish−Wiechert reaction,[1] proline was rediscovered as an efficient enantioselective catalyst for intermolecular aldolisation.[2] This enabled intensive growth especially in asymmetric enamine catalysis, and many research teams developed over the recent years their own pyrrolidine-based organocatalyst for a large scope of reactions.[3] Among them, asymmetric conjugate addition of aldehydes to *β*-nitrostyrene catalyzed by a pyrrolidine derivative appeared to be a useful synthetic method for the synthesis of *γ*-nitrocarbonyl compounds.[4,5] Nevertheless, the main drawback in enamine catalysis remains to be the high catalytic loading of amine (generally around 15 mol %) and the quantity of aldehyde (up to 10 equiv). Palomo and co-workers were the first to use only 5 mol % of a new designed organocatalyst and a slight excess

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(1) (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed* **1971**, *10*, 496. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.

(2) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395.

(3) (a) Bressy, C.; Dalko, P. I. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S. *Chem. Rev.* **2007**, *107*, 5471.

(4) For general reviews on organocatalytic asymmetric conjugate addition, see: (a) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (b) Almasi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (c) Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123.

(5) For selected references, see:(a) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423. (b) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., III *Tetrahedron Lett.* **2001**, *42*, 4441. (c) Betancort, J. M.; Barbas, C. F., III *Org. Lett.* **2001**, *3*, 3737. (d) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611. (e) Enders, D.; Seki, A. *Synlett* **2002**, 26. (f) Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147. (g) Mitchell, C. E. T.; Cobb, A. J. A.; Ley, S. V. *Synlett* **2005**, 611. (h) Hayashi, Y.; Gotoh, H.; Hayashi, H. T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (i) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 4966. (j) Mossé, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559.

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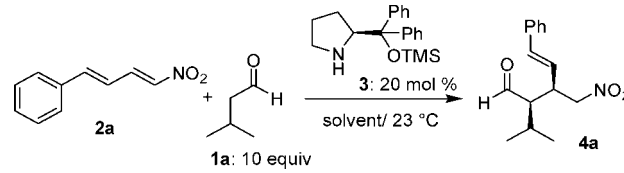
of the aldehyde substrate for the addition to β-nitrostyrene.[6] Then, the group of Wennemers described a tripeptide as a very efficient organocatalyst for this reaction (1 mol %).[7] Finally (a more simple molecule) diphenylprolinol silyl ether (0.5−2 mol %), turned out to be highly effective in water.[8] Among all nitroolefins, β-nitrostyrenes are the most widely used because of their possible conversion into useful compounds such as substituted pyrrolidines[5a,g] or γ-butyrolactones.[6] Nevertheless, other nitroolefins have also been used in synthesis, for instance (−)-Botryodiplodin[9] and potent H_3 agonist Sch50917.[10] Moreover, fonctionalized nitroolefins such as β-nitroacroleine dimethyl acetal[11] and 3-nitroacrylate[8] have also been tested in asymmetric organocatalyzed conjugate addition. Herein, we report the organocatalyzed conjugate addition of aldehydes **1** to nitrodienes **2**. The Michael addition of 10 equiv of isovaleraldehyde **1a** to phenylnitrodiene **2a** in the presence of 20 mol % of organocatalyst was selected as the model reaction. Thus, (*S*)-diphenylprolinol silyl ether **3** appeared to be the best organocatalyst in terms of diastereo- and enantioselectivities (see Supporting Information).

Surprisingly, no trace of 1,6-addition adduct has ever been observed during the preliminary optimization study. Only 1,4-addition occurred with perfect control of the regioselectivity for the adduct **4a**. Furthermore, the water and ethanol 5% v/v system was proved to be the most suitable solvent for our mode reaction (Table 1, entry 5). Beer also gave the same results with a diastereoselectivity of 92/8 in favor of the *syn* adduct and a perfect enantioselectivity (Table 1, entry 6). Dichloromethane gave similar results, but the reaction time was longer (Table 1, entry 2). Choloroform and neat conditions led also to excellent enantioselectivity but lower diastereoselectivity (Table 1, entry 1 and 3). A decrease of both diastereo- and enantioselectivities has also been observed when beer was replaced by wine to increase the alcohol proof (Table 1, entry 6). Subsequently, moderate results were obtained when the reaction was performed in ethanol as the solvent (Table 1, entry 8), whereas water showed to be as suitable as the water and ethanol 5% v/v system, though isolated yields are slightly lower (Table 1, entry 7). Moreover, a slight amount of ethanol appeared to be useful in some cases to solubilize the starting materials. Further studies showed also that it was possible to decrease both the quantity of aldehyde **1a** (2 equiv) and the amount of (*S*)-diphenylprolinol silyl ether **3** (5 mol %) (see Supporting Information). No changes in term of reaction time or enantioselectivity were observed, only a slight improvement for the diastereoselectivity, since these conditions afforded the expected product within the same reaction time, the same enantioselectivity, and a slight improvement of diastereoselectivity (Table 2, entry 1). With these new optimized conditions in hand, we investigated the scope and limitations of this reaction by testing phenylnitrodiene **2a** with a variety of aldehydes **1a**−**f** (Table 2).

Thus, unbranched aldehydes such as propionaldehyde **1b**, pentanal **1c**, and penten-4-al **1d** underwent the 1,4-addition in excellent yield and excellent enantioselectivities (Table 2, entries 2−4). On the other hand, α-branched aldehydes, isobutyraldehyde **1e**, and 2-phenylpropanal **1f** led to good isolated yield but moderate enantiocontrol (Table 2, entries 5 and 6). It is also interesting to notice that among unbranched aldehydes, only penten-4-al **1d** gave no diastereoselectivity (Table 2, entry 4). We then continued to evaluate the scope of the reaction by testing the Michael addition of isovaleraldehyde **1a** to various nitrodienes **2a**−**e**

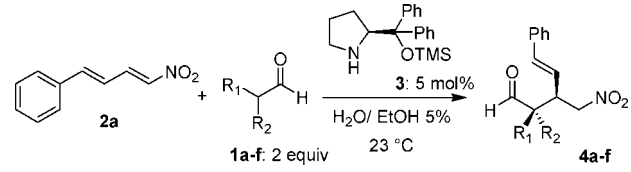
Table 1. Solvent's Optimization



entry	solvent	time	yield[a]	dr[b] (syn/ anti)	ee[c]
1	$CHCl_3$	24 h	91	88/12	>99
2	CH_2Cl_2	24 h	95	92/8	>99
3	neat	2 days	87	87/13	99
4	beer[d]	14 h	89	92/8	>99
5	H_2O/EtOH 5% v/v	14 h	97	92/8	>99
6	wine[e]	20 h	78	80/20	97
7	H_2O	14 h	88	92/8	98
8	EtOH	50 h	87	65/35	88

[a] Yield of isolated product after flash column chromatography on SiO_2. [b] Determined by ^1H NMR or chiral SFC of crude product. [c] Determined by chiral SFC on the *syn* adduct. [d] Heineken. [e] White wine of Jura, France.

Table 2. Scope of the Reaction: Aldehydes **1a**−**f**



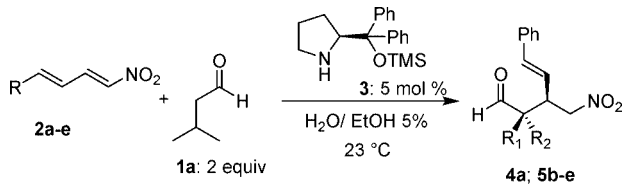
entry	R_1	R_2	time	yield[a] (%)	dr[b] (*syn/anti*)	ee[c] (%)
1	*i*Pr	H	14 h	**4a**: 91	94/6	>99
2	Me	H	10 h	**4b**: 81	80/20	96
3	*n*Pr	H	10 h	**4c**: 91	93/7	99
4	allyl	H	36 h	**4d**: 84	52/48	93
5[d]	Me	Me	5 days	**4e**: 72	−	68
6	Me	Ph	4 days	**4f**: 78	95/5	16

[a] Yield of isolated product after flash column chromatography on SiO_2. [b] Determined by ^1H NMR or chiral SFC of crude product. [c] Determined by chiral SFC on the *syn* adduct. [d] 10 mol % of catalyst.

(6) Palomo, C.; Vera, S.; Mielgo, A.; Gomez-Bengoa, E. *Angew. Chem., Int. Ed* **2006**, *45*, 5984.
(7) Wiesner, M.; Revell, J. F.; Wennemers, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1871.
(8) Zhu, S.; Yu, S.; Ma, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 545.
(9) Andrey, O.; Vidonne, A.; Alexakis, A. *Tetrahedron Lett.* **2003**, *44*, 7901.
(10) Aslanian, R.; Lee, G.; Iyer, R. V.; Shih, N.-Y.; Piwinski, J. J.; Draper, R. W.; McPhail, A. T. *Tetrahedron: Asymmetry* **2000**, *11*, 3867.
(11) Reyes, E.; Vicario, J. L.; Badía, D.; Carillo, L. *Org. Lett.* **2006**, *8*, 6135.

in the presence of 5 mol % of organocatalyst in a mixture of water and ethanol 5% v/v (Table 3).

Table 3. Scope of the Reaction: Nitrodienes **2a**−**e**



entry	R	time	yield[a] (%)	dr[b] (*syn*/*anti*)	ee[c][c] (%)
1	Ph (**2a**)	14 h	**4a**: 91	94/6	>99
2	*p*MeO-Ph (**2b**)	2 days	**5b**: 94	66/34	89
3[d]	*p*MeO-Ph (**2b**)	4 days	**5b**: 94	72/28	98
4	*p*Cl-Ph (**2c**)	36 h	**5c**: 93	92/8	98
5	Et (**2d**)	8 h	**5d**: 81	90/10	85
6[d]	Et (**2d**)	10 days	**5d**: 78	88/12	82
7	*c*-Hex (**2e**)	2 days	**5e**: 62	94/6	95

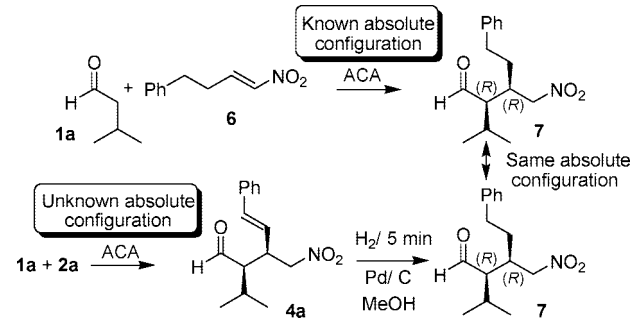
[a] Yield of isolated product after flash column chromatography on SiO_2. [b] Determined by ^1H NMR or chiral SFC of crude product. [c] Determined by chiral SFC on the *syn* adduct. [d] The reaction was carried out in chloroform.

Nitrodiene substituted with electron-rich arene **2b** gave the 1,4-adduct **5b** in moderate diastereoselectivity and good enantioselectivity in the mixture of water and ethanol 5% v/v (Table 3, entry 2). Selectivities could be improved by carrying out the reaction in chloroform instead, with however a longer reaction time (Table 3, entry 3). By testing the addition to nitrodiene substituted with electron-poor arene **2c**, we could observe excellent yield and selectivities for the adduct **5c** (Table 3, entry 4). Aliphatic nitrodienes gave products in good yield and good diastereoselectivities. In the case of cyclohexyl **2e**, excellent enantioselectivity could be achieved (Table 3, entry 7). With an ethyl group **2d**, the enantioselectivity was good, and we did not succeed in improving it by performing the reaction in chloroform. Moreover, the reaction became five times longer than the reaction in a water and ethanol 5% v/v mixture (Table 3, entries 5 and 6).

Furthermore, the absolute configuration of the adduct **4a** could be determined by a simple manner. By carrying out the synthesis of compound **7** through two differents pathways, SFC analyses revealed that both products presented the same absolute configuration (Scheme 1).

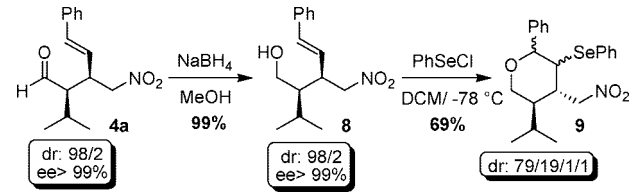
The first was the organocatalyzed conjugate addition of isovaleraldehyde **1a** to (*E*)-(4-nitrobut-3-enyl)benzene **6** leading to the 1,4-adduct **7** whose absolute configuration is known. Indeed, it has been well established that the addition of an aldehyde to a nitroolefin gives preferentially the *syn* adduct with the (*R*,*R*) configuration, thanks to Seebach's model.[12] The second way consisted of the selective hydrogenation of the C=C double bond of the adduct **4a**, whose absolute configuration has to be determined, in the presence of palladium on charcoal. This could be achieved in good yield by letting the reaction run under a hydrogen atmosphere for only 5 min. Through this way and thanks to SFC analysis, the absolute configuration of **7** could be compared and was found to be the same, i.e., (*R*,*R*).

Scheme 1. Determination of the Absolute Configuration of **4a**



The 1,4-adducts, thus obtained through our method, are interesting building blocks, which can be easily converted into other compounds by taking advantage of the C=C double bond. Therefore, we first envisaged to introduce a new access to tetrahydropyran **9**. Therefore, the 1,4-adduct **4a** was first converted into the corresponding alcohol **8** in the presence of $NaBH_4$ in methanol, with a nearly quantitative yield (Scheme 2). Then, the alcohol **8** was treated with PhSeCl at −78 °C to afford the expected tetrahydropyran **9** as a mixture of two major diastereoisomers (Scheme 2). Those might be converted to *C*-aryl glycosides, which constitute a family of natural products of interest.[13]

Scheme 2. Access to Tetrahydropyran **9**

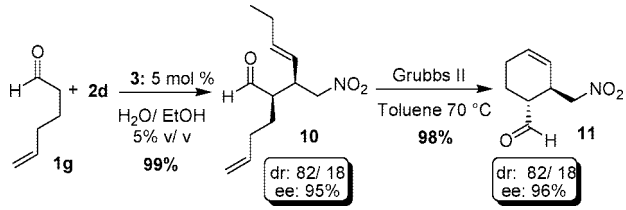


Second, we also considered metathesis to take advantage of our adducts (Scheme 3). As penten-4-al **1d** gave poor results in terms of diastereoselectivity (Table 1, entry 4), we decided to do the Michael addition with hexen-5-al **1g**. We performed the reaction of this aldehyde to the nitrodiene **2d** substituted by an ethyl group under the previously developed conditions. The expected adduct **10** was obtained in high isolated yield and with an excellent enantioselectivity of 95%. The diastereoselectivity was good in this case (Scheme 3).

(12) (a) Blarer, S. J.; Seebach, D. *Chem. Ber.* **1983**, *116*, 3086. (b) Häner, R.; Laube, T.; Seebach, D. *Chimia* **1984**, *38*, 255. (c) Seebach, D.; Beck, A. K.; Golinski, J.; Hay, J. N.; Laube, T. *Helv. Chim. Acta* **1981**, *64*, 1413. (d) Seebach, D.; Beck, A. K.; Golinski, J.; Hay, J. N.; Laube, T. *Helv. Chim. Acta* **1985**, *68*, 162.

(13) Hacksell, U.; Daves, G. D. *Prog. Med. Chem.* **1985**, *38*, 1280.

Scheme 3. Metathesis: Access to Substituted Cyclohexene **11**



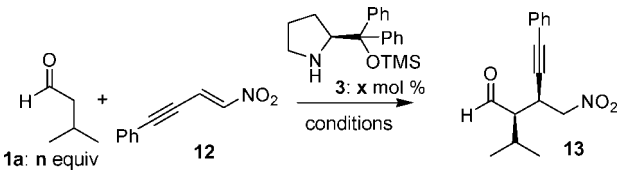
Then we treated the adduct **10** with Grubbs second generation[14] catalyst in toluene to obtain the corresponding substituted cyclohexene **11** in excellent yield and without any loss of enantioselectivity (Scheme 3).

Finally, to complete the study, we investigated the feasibility of our reaction, starting from nitro compounds bearing a triple bond. Therefore, we decided to start from phenylnitroeneyne **12** and to do the Michael addition of isovaleraldehyde **1a**. After optimization, we found two suitable methods. The first one has been successfully developed for the addition of aldehydes **1a**−**g** to nitrodienes **2a**−**e**: 2 equiv of aldehyde, 5 mol % of (*S*)-diphenylprolinol silyl ether **3** in a mixture of water and ethanol 5% v/v. This enabled us to obtain excellent enantioselectivity but moderate diastereoselectivity for the *syn*-adduct **13** (Table 4, entry 1). The second one is "usual" conditions in organocatalysis: 10 equiv of aldehyde **1a**, 10 mol % of catalyst in chloroform at −25 °C. By this way, excellent diastereoselectivity could be achieved with very good enantioselectivity (Table 4, entry 1). It should be noticed that as for nitrodienes 1,6-addition has never been observed.

In conclusion, we succeeded in developing the asymmetric organocatalyzed Michael addition of aldehydes to α,*β*-*γ*,*δ*-unsaturated nitro compounds. This has been accomplished using only 5 mol % of (*S*)-diphenylprolinol silyl ether and 2 equiv of aldehyde in a mixture of ethanol and water (5% v/v). The Michael adducts were obtained in good yields, diastereoselectivities up to 94/6, and up to 99% ee in the case of nitrodienes. This process provides synthetically useful compounds which can easily lead to both substituted tetrahydropyran and cyclohexene. Moreover, the Michael addition has also been developed for nitroeneyne where the triple bond of the corresponding adduct appeared to be interesting. In all cases, only 1,4-addition occurred without any trace of the 1,6-adduct.

(14) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.

Table 4. Organocatalyzed Conjugate Addition of Isovaleraldehyde **1a** to Phenylnitroeneyne **12**



entry	conditions	*n* equiv	*x* mol %	yield[a] **13** (%)	dr[b] (*syn*/*anti*)	ee[c] (%)
1	H_2O/EtOH 5% v/v; 23 °C	2	5	60	83/17	98
2	$CHCl_3$/−25 °C	10	10	83	94/6	94

[a] Yield of isolated product after flash column chromatography on SiO_2. [b] Determined by ^1H NMR or chiral SFC of crude product. [c] Determined by chiral SFC on the *syn* adduct.

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Supporting Information Available: Experimental procedures, ^1H and ^{13}C spectra, and chiral separations for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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