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Diamine-Catalyzed Asymmetric Michael Additions of Aldehydes and Ketones to Nitrostyrene

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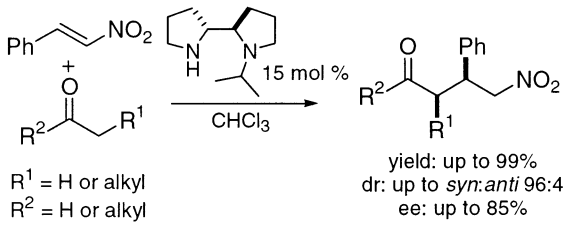
ABSTRACT



The direct Michael addition of aldehydes and ketones to nitrostyrene, catalyzed by *N-i*-Pr-2,2′-bipyrrolidine, is described. The desired 1,4-adducts are obtained in excellent yield with enantioselectivities up to 85% ee and dr up to 95:5 of the syn product.

The Michael addition is one of the most important C−C bond-forming reactions in organic chemistry.[1] Except for the reaction catalyzed by L-proline developed by Wiechert, Hajos, and Parrish,[2] the nonmetallic asymmetric catalysis was only reported very recently. L-Proline[3] is the most widely used catalytic organic system in asymmetric Michael addition, aldolization, Mannich-type reaction, and α-amination of ketones.

Other amines also seem to be potentially interesting organic catalysts, but only a few examples using amines in asymmetric catalysis have been reported.[4] Barbas has shown that reactions involving enamine intermediates can be catalyzed by pyrrolidine-type amines.[5] He has reported asymmetric Michael addition of ketones to alkylidene malonates[6] and of aldehydes to nitrostyrene[7] catalyzed by diamines containing a pyrrolidine moiety.

Recently, we have reported a new, asymmetric synthesis of 2,2′-bipyrrolidine[8] **1**, which could be an interesting catalyst for Michael reactions. Herein we report the addition of aldehydes and ketones to nitrostyrene[9] catalyzed by chiral diamines. This reaction leads to interesting functionalized compounds that could be converted into substituted pyrrolidines or γ-amino acids.

(1) Perlmutter, P. *Conjugate Addition Reaction in Organic Synthesis*; Tetrahedron Organic Chemistry Series 9; Pergamon Press: Oxford, 1992.
(2) (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *83*, 492. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.
(3) For recent examples of proline-catalyzed reactions, see: (a) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423. (b) Enders, D.; Seki, A. *Synlett* **2002**, 26. (c) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bogevig, A.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254. (d) Cordova, A.; Watanabe, S.-i.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866. (e) Cordova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842. (f) Córdova, A.; Notz, W.; Barbas, C. F., III. *J. Org. Chem.* **2002**, *67*, 301. (g) Thayumanavan, R.; Dhevalapally, B.; Sakthivel, K.; Tanaka, F.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 3817. (h) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc* **2002**, *124*, 827. (i) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc* **2001**, *123*, 5260. (j) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975. (k) List, B. *J. Am. Chem. Soc* **2000**, *122*, 9336. (l) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (m) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (n) List, B.; Lerner, R. A.; Barbas, C. F., III. *Org. Lett.* **1999**, *1*, 59.
(4) (a) Saito, S.; Nakadai, M.; Yamamoto, H. *Synlett* **2001**, 1245. (b) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097.
(5) Bui, T.; Barbas, C. F., III. *Tetrahedron Lett.* **2000**, *41*, 6951. For our part, we have confirmed the implication of enamine in the addition of 3,3-dimethylbutyraldehyde catalyzed by pyrrolidine, which showed the presence of the corresponding enamine by GC-MS.
(6) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 4441.
(7) Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737.
(8) Alexakis, A.; Tomassini, A.; Chouillet, C.; Roland, S.; Mangeney, P.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4093.

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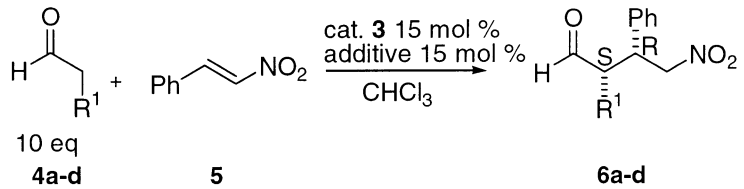
Table 1. Conjugate Addition of Aldehydes **4a**−**d** to Nitrostyrene **5** Catalyzed by **3** in Chloroform to Afford γ-−tro Aldehydes **6a**−**d**

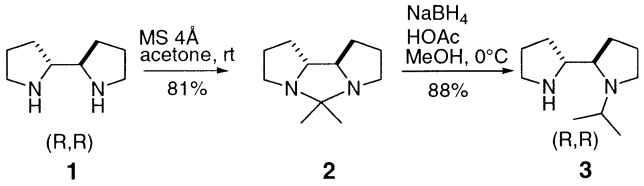


entry	aldehyde	R^1	additive	conditions	yield[a] (%)	dr[b] (syn:anti)	ee[c] (syn)	product
1	**4a**	Me	none	rt, 1 h and 30 min	99	75:25	66	**6a**
2			none	−25 °C, 2 days	71	95:5	83	**6a**
3			HCl[d]	rt, 3 h	86	85:15	79	**6a**
4			HCl[d]	0 °C, 2 days	83	94:6	85	**6a**
5	**4b**	Et	none	−25 °C, 4 days	70	90:10	70	**6b**
6			HCl[d]	0 °C, 2 days	82	88:12	68	**6b**
7	**4c**	Pr	none	rt, 15 h	99	72:28	62	**6c**
8			none	−25 °C, 4 days	98	96:4	73	**6c**
9			HCl[d]	rt, 15 h	99	85:15	67	**6c**
10			HCl[d]	0 °C, 2 days	82	96:4	72	**6c**
11	**4d**	*i*-Pr	none	rt, 2 days	99	87:13	61	**6d**
12			HCl[d]	rt, 5 days	95	95:5	68	**6d**

[a] Isolated yield after column chromatography. [b] Determined by ^{1}H NMR of crude product. [c] Determined by GC or SFC employing chiral phases: Hydrodex B-3P, Chiralcel OD-H. [d] Diamine hydrochloride was formed using a solution of HCl in MeOH and recrystallized prior to use.

As described above, pyrrolidine-type catalysts seem to be very efficient in Michael addition and other reactions involving an enamine intermediate as the nucleophile. However, first attempts of asymmetric addition of ketones or aldehydes to Michael acceptors catalyzed by 2,2′-bipyrrolidine **1** gave no adduct. The catalyst was not recovered at all, but the corresponding aminals could be isolated. Nevertheless, these aminals were reduced by sodiumborohydride to give the mono-N-alkylated 2,2′-bipyrrolidine. Thus, a wide range of new diamines were synthesized starting from 2,2′-bipyrrolidine and a variety of ketones and aldehydes to give Me, Et, *i*-Pr **3** (Scheme 1),

Scheme 1. Synthesis of Catalyst **3**



CH_2t-Bu, Bn, CH_2Mes, CH_2FeCp_2, and *c*Hex N-alkylated derivatives.

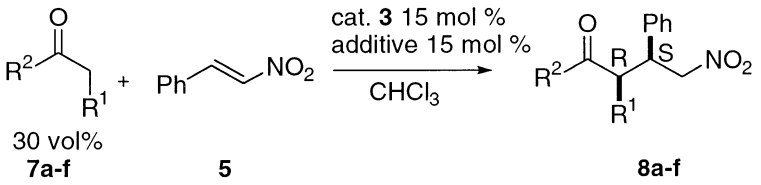
These new diamines were first tested in the asymmetric addition of valeraldehyde **4c** to β-nitrostyrene **5** in a 3:1 THF/DMF mixture at room temperature using 0.15 equiv of diamine.

Preliminary results have shown that N-*i*-Pr **3** (54% ee) and N-*c*Hex (52% ee) are the superior diamines for this reaction. We then focused our attention on the N-*i*-Pr derivative and tested other solvents in an attempt to optimize the conditions. No conversion was observed in THF, and lower ees were observed in MeOH and lower drs in a 3:1 THF/$CHCl_3$ mixture; finally, the best results were obtained in $CHCl_3$ (62% ee), which also gave the fastest reaction. Then, with the optimal catalyst and solvent, we examined a series of aldehydes. The results are summarized in Table 1.

The highest rate of reaction was observed for propionaldehyde **4a**, even at −25 °C (Entry 2), the reaction went to completion in a reasonable length of time. Decreasing the temperature had a drastic effect on enantioselectivity and diastereoselectivity, which increased from 66% ee and 75:25 dr (entry 1) to 83% ee and 95:5 dr (Entry 2) for propionaldehyde **4a**. Butyraldehyde **4b** and valeraldehyde **4c** also reacted at −25 °C with good enantioselectivities, 70 (entry 5) and 73% ees (entry 8), respectively, but the reaction took twice as long as that with propionaldehyde **4a**. Isobutyraldehyde **4d**, however, reacted only at room temperature and yielded products with a modest enantioselectivity (61% ee) (entry 11). We were then interested in optimizing the reaction conditions further by using an additive. Reaction in the presence of *p*TSA (0.15 equiv) gave higher drs but lower ees. Addition of hydrochloric acid (0.15 equiv) was then carried out using the hydrochloride of the free diamine which was recrystallized prior to use. At room temperature, the enantioselectivity and diastereoselectivity were significatively higher than for the free diamines. Unfortunately, the reactions with hydrochloride derivatives were slower, and it was not possible to carry out the reaction below 0 °C. Therefore, only the enantioselectivities obtained with propionaldehyde at 0 °C (entry 4) and for isobutyraldehyde (entry 13) were enhanced with respect to the free diamine

(9) For a review on asymmetric Michael additions to nitroalkenes, see: Berner, B. J.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877.

Table 2. Conjugate Addition of Ketones **7a**−**f** to Nitrostyrene **5** Catalyzed by **3** in Chloroform to Afford γ-−tro Ketones **8a**−**f**



entry	ketone	R^1	R^2	additive	conditions	yield[a] (%)	rr[b]	dr[c] (syn:anti)	ee[d] (syn)	product
1[e]	**7a**	H	Me	none	rt, 15 h	29(15)[g]			29	**8a**
2[e]				*p*TSA	rt, 15 h	74(0)[g]			23	**8a**
3[e]				HCl[f]	rt, 15 h	82(9)[g]			25	**8a**
4	**7b**	Me	Me	none	rt, 3 days	61	43:57(70)[h]	85:15	32	**8b**
5				*p*TSA	rt, 4 days	99	70:30(56)[h]	82:18	48	**8b**
6				HCl[f]	rt, 6 days	55	74:26(49)[h]	80:20	51	**8b**
7	**7c**	Et	Me	none	rt, 6 days	46	33:67(53)[h]	78:22	37	**8c**
8				*p*TSA	rt, 6 days	trace	nd	nd	nd	**8c**
9				*p*TSA	60 °C, 7 days	81	40:60(40)[h]	70:30	36	**8c**
10				HCl[f]	rt, 6 days	trace	nd	nd	nd	**8c**
11				HCl[f]	60 °C, 7 days	95	33:67(38)[h]	68:32	34	**8c**
12	**7d**	Me	Et	HCl[f]	rt, 6 days	8		nd	76	**8d**
13				HCl[f]	60 °C, 7 days	65		84:16	67	**8d**
14	**7e**	-$(CH_2)_4$-	HCl[f]	rt, 15 h	74			95:5	74	**8e**
15	**7f**	-$(CH_2)_3$-	HCl[f]	rt, 6 days	6			69:31	50	**8f**

[a] Isolated yield after column chromatography. [b] Regioisomeric ratio determined by ^{1}H NMR or GC. [c] Determined by ^{1}H NMR of crude product. [d] Determined by GC or SFC employing chiral phases: Lipodex E, Chiralcel OB-H, Chiralpak AD. [e] Using only acetone as a solvent. [f] Diamine hydrochloride was formed using a solution of HCl in MeOH and recrystallized prior to use. [g] Yield of double addition product on acetone. [h] Enantiomeric excess of terminal regioisomer.

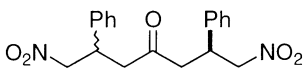
3. Having observed good selectivities for aldehydes, we then tested the asymmetric addition of ketones to nitrostyrene **5** using diamine **3**. Results are summarized in Table 2. The reactions with acetone, catalyzed by **3**, gave a nonnegligible quantity of dinitro adduct[10] (entry 1). A catalytic amount of *p*TSA completely eliminated the formation of this byproduct and also caused an increase in the reaction rate (entry 2). Diamine **3** hydrochloride gave adduct **8a** in good yield and moderate ee (25% ee)[11] (entry 3) but also with a small amount of byproduct.

The catalytic Michael addition of nonsymmetrical ketones such as methylethyl ketone **7b** and methylpropyl ketone **7c** introduced the problem of regioselectivity. When the enamine was formed under kinetic conditions, the less hindered methyl group reacts preferentially, in a low regioisomer ratio (rr) for adduct **8b** (57:43) (entry 4) and modest regioisomer ratio for adduct **8c** (67:33) (entry 7). In the presence of *p*TSA (0.15 equiv) or the hydrochloride catalyst, the formation of the enamine under thermodynamic conditions inverted the regioselectivity for the adduct **8b** (entries 5, 6). Only traces of product were observed for adduct **8c** at room temperature after 7 days (entries 8, 10), but after 7 days at 60 °C, the reaction was complete (entries 9, 11). Nevertheless, the regioselectivity was not inverted. We assume that the enamine isomerization had occurred but that the thermodynamic enamine was too hindered to react quickly. Hence, the methyl adduct was the major product, but the reaction rate was very slow, due to the low concentration of kinetic enamine in solution. To avoid the problem of regioisomers, diethyl ketone **7d** was tested. It did not react at all, neither with diamine **3** nor with addition of *p*TSA. Surprisingly, only the reaction catalyzed by diamine **3** hydrochloride gave adduct **8d**. At room temperature, only 8% was isolated, after 6 days, with good enantioselectivity (76% ee) (entry 12). After 7 days at 60 °C, the reaction was complete and adduct **8d** was obtained in moderate yield (65%), good enantioselectivity (67% ee), and diastereoselectivity (84:16) (entry 13).

Cyclic ketones such as cyclohexanone **7e** and cyclopentanone **7f** were also used. As for diethyl ketone **7c**, addition of cyclohexanone was only catalyzed by diamine **3** hydrochloride. The adduct **8e** was obtained after 15 h in good yield (74%), good enantioselectivity (74% ee), and high diastereoselectivity (95:5) (entry 14).

The syn selectivity we observe is in accordance with Seebach's model.[12] It is explained by an acyclic synclinal model, in which there are favorable electrostatic interactions between the nitrogen of the enamine and the nitro group in the transition state. A model has been proposed to explain the inverted absolute configuration[13] between the aldehydes

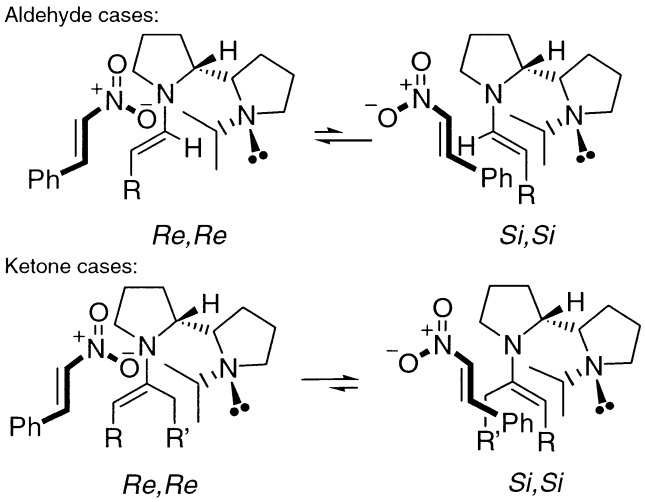
(10) Dinitro-adduct:



(11) The best enantioselectivity for addition of acetone to nitrostyrene was obtained with the more sterically hindered *N*-cyclohexyl-2,2′-bipyrrolidine in the presence of *p*TSA (0.15 equiv) (89%, 30% ee).

(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* **1985**, *68*, 162. (d) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413.

Scheme 2. Transition State Model Proposed for Enamine Additions to Nitrostyrene



and ketones (Scheme 2). Two factors are important for good enantioselection: first, one face of the enamine must be less accessible; second, the equilibrium between the enamine rotamers must be well displaced to one side. According to our results, the Re,Re approach is favored for aldehydes and the *Si*,*Si* approach for ketones. In conclusion, we have developed the asymmetric Michael addition of various aldehydes and ketones to nitrostyrene catalyzed by new chiral diamines. Enantioselectivity and diastereoselectivity remain modest for most of the ketones but excellent for aldehydes, up to 85% ee and 95:5 dr. Further development of new diamines and new applications in catalysis are currently underway in our laboratory.

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Supporting Information Available: Experimental procedures, characterization data of diamines and Michael adducts, determination of the absolute configuration, and chiral phase SFC and GC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For the determination of the absolute configuration, see Supporting Information.