Organocatalysis

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Catalytic Asymmetric Michael Reactions of Acetaldehyde**

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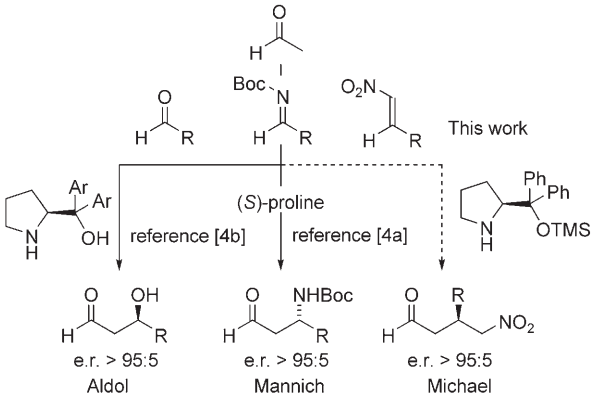
Enamine catalysis recently emerged as a powerful method for the direct use of ketones and aldehydes as nucleophiles in asymmetric catalysis.[1] The scope of this chemistry is growing and a large number of electrophiles, including carbonyl compounds, imines, Michael acceptors, and many other useful reagents, have been employed. Even reactions that had been considered impossible, such as aldehyde cross aldolizations[2] and α-alkylations,[3] became a reality by using this approach. Whereas all types of ketones and aldehydes, including branched, unbranched, cyclic and acyclic, as well as aliphatic and aromatic ones, have found utility as nucleophiles, acetaldehyde, the "simplest" of all enolizable carbonyl compounds, was only very recently added to this list (Scheme 1).[4,5]

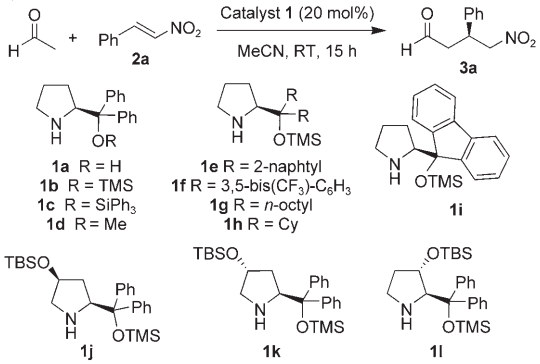


Scheme 1. Acetaldehyde as a nucleophile in enamine catalysis. TMS = trimethylsilyl.

We have developed proline-catalyzed Mannich reactions of acetaldehyde with N-Boc imines that furnish the corresponding β-amino aldehydes with exceptionally high enantioselectivities.[4a] Independently, Hayashi et al. reported analogous aldol reactions of acetaldehyde with aromatic aldehydes as electrophiles.[4b] Despite the significant progress, the corresponding Michael reactions are, at least to our knowledge, completely unknown, even in a nonenantioselective fashion. Herein we report a practical solution to this problem; we found that acetaldehyde reacts with both aromatic and aliphatic nitroolefins in the presence of a silyl prolinol catalyst to give the corresponding Michael products in good yields and excellent enantioselectivities.[6]

The Michael addition of acetaldehyde to β-nitrostyrene (**2a**) was selected as a model reaction. Preliminary experiments identified prolinol silyl ethers such as **1b**, first used by Jørgensen and co-workers and by Hayashi and co-workers,[6d,7] as suitable catalysts. In contrast, proline and prolinol **1a** gave the product in low yields (as expected) and lead to the formation of significant amounts of byproducts (Table 1, entries 1–3). We found that the byproduct formation was significantly suppressed and that good conversions into Michael adduct **3a** were realized by slow addition of a solution of acetaldehyde, in acetonitrile, to the reaction mixture. Conditions involving addition of an acetaldehyde

Table 1: Catalyst screening for the Michael addition of acetaldehyde to β-nitrostyrene.



Entry	Catalyst	Yield [%][a]	e.r.[b,c]
1	(*S*)-proline	10	65:35
2	**1a**	no conv.	–
3	**1b**	55	94:6
4[d]	**1b**	51	96:4
5	**1c**	46	94:6
6	**1d**	44	95:5
7	**1e**	23	94:6
8	**1f**	25	95:5
9	**1g**	44	90:10
10	**1h**	27	92:8
11	**1i**	5	92:8
12	**1j**	41	94:6
13	**1k**	38	96:4
14	**1l**	6	53:47

[a] Yields from ^{1}H NMR analysis of the crude reaction mixture by using 1,3,5-trimethoxybenzene as an internal standard. [b] Determined from chiral GC analysis. [c] Absolute configuration determined from known optical rotation.[8b] [d] Reaction performed at 0 °C for 64 h.

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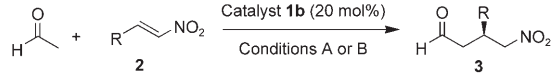
solution, by syringe pump, to a solution of β-nitrostyrene (**2a**) and the catalyst were used to screen prolinol ethers **1b–1l** (Table 1). Catalyst **1b** gave product **3a** in reasonable yield (51%) and high enantioselectivity (96:4 e.r.) when the reaction was conducted at 0°C (Table 1, entry 4). Changing the trimethylsilyl group into either a triphenylsilyl group (**1c**, Table 1, entry 5) or a methyl group (**1d**, Table 1, entry 6) did not significantly influence the outcome of the reaction. Catalysts **1e** and **1f**, bearing bulky aryl groups, led to lower conversions and lower yields, whereas the enantioselectivity remained similar to that observed with catalyst **1b** (Table 1, entries 7 and 8). A significant decrease in the conversion was observed with a less flexible catalyst (**1i**, Table 1, entry 11). Dialkylprolinol silyl ethers, both with linear (**1g**, Table 1, entry 9) and branched alkyl groups (**1h**, Table 1, entry 10) provided lower enantioselectivities. We continued the screening by testing diphenylprolinol silyl ethers bearing an OTBS (TBS = *tert*-butyldimethylsilyl) group at different positions of the pyrrolidine ring. The results show that neither *cis* (**1j**, Table 1, entry 12) nor *trans* substitution (**1k**, Table 1, entry 13) at the 4-position significantly affects the enantioselectivity of the reaction. However, the e.r. value was poor with *trans* 3-OTBS-substituted catalyst **1l** (Table 1, entry 14).

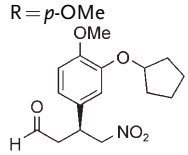
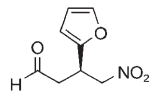
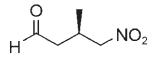
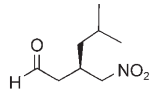
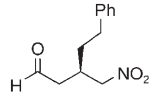
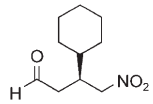
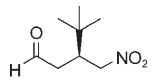
On the basis of these studies the scope of the reaction was evaluated by using catalyst **1b** (Table 2). Indeed, several nitrostyrenes and related compounds underwent the Michael reaction with acetaldehyde in reasonable yields and excellent enantioselectivities (Table 2, entries 1–8). Nitrostyrenes substituted with both electron-poor and electron-rich arenes, and one heteroarene, gave products in good yields and high enantioselectivities (Table 2, entries 1–8). In addition, all possible monosubstituted substrates (*o*, *m*, or *p*) are well tolerated. Gratifyingly, after significantly varying the reaction conditions we were able to use aliphatic nitroolefins in the reaction (Table 2, entries 9–13). Unbranched (Table 2, entries 9–11), branched (Table 2, entry 12), and tertiary (Table 2, entry 13) alkyl substituents on the nitroolefin were well tolerated, and gave the corresponding products in very good enantioselectivities and in reasonable yields.

Nitroaldehydes **3** are versatile synthetic intermediates as demonstrated previously (Scheme 2);[8] for example, the corresponding γ-amino acids can be synthesized in a simple two-step procedure. Accordingly, compounds **3c** and **3j** have been converted into baclofen, a $GABA_B$ receptor antagonist, and into pregabalin, an anticonvulsant drug, respectively.[8b] Additionally, nitroaldehyde **3g** has recently been used by Palomo et al. in the synthesis of the antidepressant rolipram.[8a] We reasoned that aldehydes **3** should be readily converted into the corresponding 3-monosubstituted pyrrolidines, although this has not previously been demonstrated.[9] Indeed, hydrogenation of aldehyde **3a** in the presence of $Pd(OH)_2$ furnished the desired pyrrolidine in good yield. The combination of an amine catalyzed Michael reaction of acetaldehyde with a nitroolefin and subsequent reductive amination should be a highly attractive approach to other 3-monosubstituted pyrrolidines.

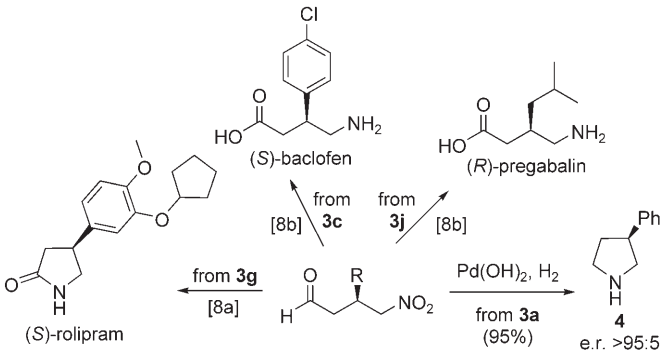
In summary, we have developed a highly enantioselective Michael reaction of acetaldehyde with nitroolefins. Whereas the yields are typically around 50%, the enantioselectivities

Table 2: Catalytic asymmetric Michael reaction of acetaldehyde with nitroalkenes.



Entry	Product	3	Conditions	Yield [%][a]	e.r.[b]
1	R = H	**3a**	A	51	96:4
2	R = *p*-Br	**3b**	A	53	95:5
3	R = *p*-Cl	**3c**	A	58	96:4
4	R = *m*-Cl	**3d**	A	51	96:4
5	R = *o*-Cl	**3e**	A	57	95:5
6	R = *p*-OMe	**3f**	A	44	96:4
7[c,d]		**3g**	A	50	94:6
8		**3h**	A	49	95:5
9		**3i**	B	38	94:6
10		**3j**	B	52	97:3
11		**3k**	B	56	96:4
12		**3l**	B	61	96:4
13		**3m**	B	41	97:3

[a] Conditions A: MeCN, 0°C, 62–93 h; Conditions B: DMF, 10 equiv *i*PrOH, RT, 24–40 h. [b] Determined by chiral GC analysis. [c] Reaction performed at RT for 23 h. [d] The e.r. values were determined by chiral HPLC after conversion of the aldehyde into the corresponding methyl ester.



Scheme 2. Synthetic applications of γ-nitroaldehydes.

are excellent in almost all cases studied, including those with aromatic and aliphatic nitroolefins. The utility of the reaction is illustrated in the formal synthesis of three pharmaceuticals and in the synthesis of an enantiopure 3-monosubstituted pyrrolidine. Our reaction nicely complements a related approach to the same products that has recently been reported, involving the Michael addition of nitromethane to α,β-unsaturated aldehydes.[8] The synthetic utility of acetaldehyde as a nucleophile in organic synthesis is additionally expanded with this work, and more applications will be forthcoming.

Experimental Section

Typical procedure, conditions A (Table 2, entry 1): 250 μL of a 0.8 M solution of catalyst **1b** in dry MeCN was added to nitroolefin **2a** (149 mg, 1 mmol) in a vial under argon at 0 °C. Then 1 mL of a 5 M solution of acetaldehyde in anhydrous MeCN, prepared at 0 °C from freshly distilled acetaldehyde, was added at 12 μL min^{-1} (tad = 83.3 min). After stirring for 64 h, the reaction mixture was treated with 1N HCl and extracted twice with ethyl acetate. The organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (hexane/ethyl acetate = 3:1) gave nitroaldehyde **3a** (99 mg, 0.51 mmol) in 51 % yield and with an e.r. value of 96:4.

Typical procedure, conditions B (Table 2, entry 11): 500 μL of DMF, 760 μL of 2-propanol and 250 μL of a 0.8 M solution of catalyst **1b** in dry DMF were successively added to nitroolefin **2l** (155 mg, 1 mmol) contained in a vial under argon at room temperature. Then 500 μL of a 10 M solution of acetaldehyde in anhydrous DMF, prepared at 0 °C from freshly distilled acetaldehyde, was added at 12 μL min^{-1} (tad = 41.6 min). After stirring for 23 h, the reaction mixture was quenched with 1N HCl and extracted twice with ethyl acetate. The organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (pentane/diethyl ether = 9:1) gave nitroaldehyde **3l** (122 mg, 0.61 mmol) in 61 % yield and with an e.r. value of 96:4.

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