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Activation of nitroaldol reactions by diethylzinc and amino alcohols or diamines as promoters

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Abstract—Henry reactions of nitroalkanes can be initiated with diethylzinc in the presence of catalytic amounts of 1,2-aminoethanol or 1,2-diaminoethane.

The nitroaldol reaction (Henry reaction) is one of the classical C–C bond forming reactions, which has been of great interest due to the possibility of chemo- and regioselective chain elongation in natural products synthesis with tuneable functionalities.

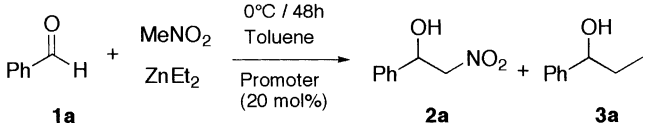
The most commonly applied protocols to form 2-nitroalcohols from nitroalkanes and carbonyl derivatives require the use of a base like KOH, NaOH, $Al(OR)_3$, CO_3^{2-}, HCO_3^-, F^-, TBAF, amines and Al_2O_3, etc.[1]

Until recently, the only protocol which made use of Lewis acid catalysts was developed by Shibasaki[2] with the introduction of bimetallic lanthanum catalysts, thereby opening the way to enantioselective nitroaldol reactions.

In a preliminary disclosure[3] we described that the use of Et_2Zn in the presence of diamines or amino alcohols as promoters, a well known protocol for the alkylation of aldehydes,[4] can be applied to nitroaldol reactions. The very recent reports of the Trost group,[5] introducing in a spectacular and most elegant way a bimetallic zinc catalyst for enantioselective nitroaldol reactions now prompts us to fully disclose our results.

Taking the substrate mixture of benzaldehyde, nitromethane and diethylzinc as our model system, we investigated the influence of several bifunctional promoters on the course of the reaction (Table 1). In principle, the formation of the nitroaldol adduct **2**, as well as the addition adduct of diethylzinc to benzaldehyde **3** could occur. Indeed, great differences in reactivity due to the structure of the promoter were observed. First, it was verified that in the absence of any promoter benzaldehyde neither underwent a reaction with diethylzinc nor with nitromethane (entry 1). Also, ethyleneglycol as an additive (entry 2) does not initiate any reaction. Amino alcohols were able to activate the reaction mixture, although—depending on their structure—in quite a different way. While *N*,*N*-dimethyl-1,2-aminoethanol gave rise to a 1:1 mixture of **2a** and **3a** (entry 3), 1,2-aminoethanol itself promoted exclusively the nitroaldol reaction, giving rise to **2a** in 88% yield

Table 1. Nitroaldol reactions in the presence of promoters



1a **2a** **3a**

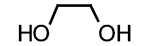
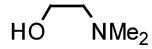
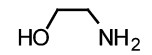
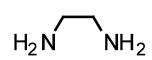
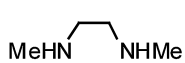
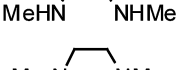
Entry	Promoter	Ratio **2a**/**3a**	**2a** Yield (%)
1	None	–	0
2		–	0
3		50:50	26
4		100:0	88
5		100:0	83
6		100:0	78
7		85:15	62

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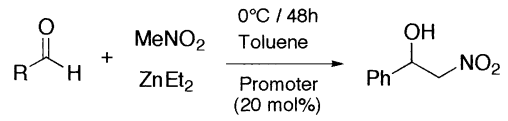
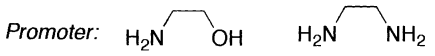
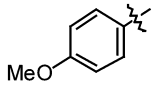
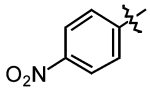
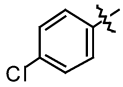
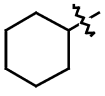
Table 2. Nitroaldol reactions with aromatic or aliphatic aldehydes in the presence of promoters **4** or **5**



1 **2**



4 **5**

Entry	R in **1**	Promoter	Yield (%) of **2**
1	Ph	**4**	88
2		**5**	83
3		**4**	78
4		**5**	83
5		**4**	56
6		**5**	64
7		**4**	51
8		**5**	57
9		**4**	50
10		**5**	52
11	Et	**4**	49
12		**5**	67
13	*n*-Bu	**4**	58
14		**5**	91
15	*n*-Hex	**4**	49
16		**5**	56
17		**4**	63
18		**5**	76

(entry 4).[6] Likewise, with 1,2-aminoethane and *N*,*N*′-dimethyl-1,2-diaminoethane only **2a** was formed, although in slightly diminished yields (entries 5 and 6). *N*,*N*′-Tetramethyl-1,2-diamine still favors the nitroaldol reaction, but alkylation of benzaldehyde to **3a** also occurred to a significant extent (entry 7).

Having identified 1,2-aminoethanol and 1,2-diaminoethane as the most active promoters in combination with diethylzinc, we explored these protocols for a variety of aliphatic and aromatic aldehydes in their reaction with nitromethane (Table 2).

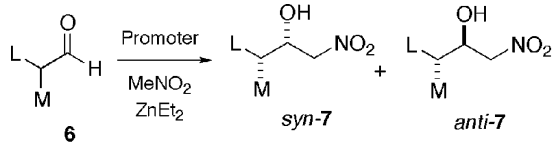
In no case any alkylation products were observed, and good yields of the nitroalcohols **2** were obtained. Aromatic aldehydes reacted in the presence of both promoters **4** or **5** with approximately the same results (entries 1–10). However, it was somewhat surprising to note that electron donors in the arene (entries 3 and 4) proved to be advantageous compared to electron acceptors (entries 5–10) for the reactivity with nitromethane. For aliphatic aldehydes, 1,2-diaminoethane seems to be advantageous over 1,2-aminoethanol (cf. entries 11–18).

Nitroaldol reactions with α-chiral aldehydes (Table 3) yielded in all cases the Felkin–Anh adducts[7] as the major diastereomers (75:25 to 85:15). This was especially true with α-amino and α-alkoxyaldehydes, indicating that no chelation between the amino or alkoxy group, the aldehyde group and zinc occurs in contrast to proposals for diethylzinc additions with *N*,*N*-dibenzylaminoaldehydes.[8] Moreover, no change in the diastereoselectivity with regard to the promoter employed was observed.

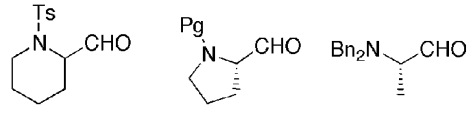
Finally, other nitroalkanes can be applied in this protocol as well, although the reactivity in such reactions is decreased and higher amounts of the promoter are necessary. The products **8** are formed as a 1:1 mixture of diastereomers in all cases (Table 4).

Since there are a great number of chiral 1,2-amino alcohols and 1,2-diamines available, the protocol ade-

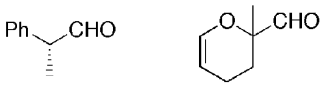
Table 3. Nitroaldol reaction with α-chiral aldehydes in the presence of promoters **4** or **5**



6 Felkin-Anh Anti-Felkin-Anh/ Cram-Chelat



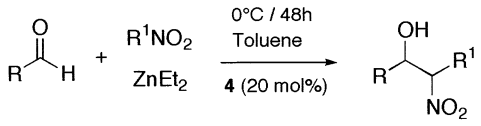
6a **6b**: Pg = Ts **6c**: Pg = CO_2Me **6d**



6e **6f**

Entry	Aldehyde	Promoter	Ratio *syn*/*anti*	Yield (%)
1	**6a**	**4**	80:20	75
2	**6a**	**5**	80:20	75
3	**6b**	**4**	80:20	72
4	**6b**	**5**	80:20	71
5	**6c**	**4**	80:20	73
6	**6d**	**5**	85:15	67
7	**6e**	**4**	73:27	77
8	**6f**	**4**	75:25	68

Table 4. Nitroaldol reaction with nitroalkanes in the presence of 1,2-aminoethanol (**4**)



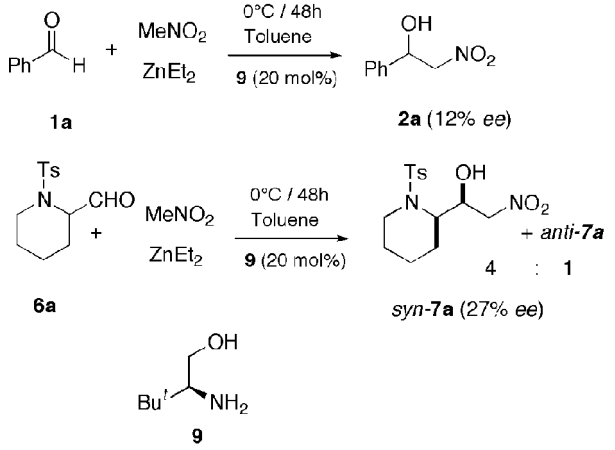
1 **8**

Entry	Aldehyde R	Nitroalkane R^1	Yield (%)
1		Et	52[a]
2		Et	43
3		Pr	40

[a] 50 mol% of **4** were employed.

scribed here should open up the possibility to find new catalysts for asymmetric nitroaldol reactions. Indeed, initial investigations with chiral amino alcohols show that this process can be rendered asymmetric, although the selectivities obtained so far are not satisfactory (Scheme 1). Nevertheless, the results with *t*-butyl-leucin as promoter both, in nitroaldol reactions with a prochiral aldehyde **1a** as well as in a kinetic resolution of the racemic amino aldehdyde **6a** clearly show that the reaction takes place in a chiral environment.

Moreover, we had recently introduced bis(oxazoline) ligands **10** with hydroxymethylene side chains as efficient chiral promoters for the addition of diethylzinc to aldehydes[9] and concluded, that a bimetallic zinc



Scheme 1. Nitroaldol reactions with *t*-Bu-leucin as promoter.

intermediate of type **11** is decisive in the catalytic cycle for the high enantioselectivities obtained (Fig. 1). Consequently, this ligand was a promising choice for the nitroaldol protocol discussed here, especially in light of the ligands recently introduced by Trost,[5] which also coordinate to two zinc atoms as depicted in **12**.

Interestingly, in the reaction of nitromethane with benzaldehyde (**1a**) in the presence of **10**, the nitroaldol product **2a** and the alkylated product **3a** were obtained in a ratio of 1:1. While **2a** was obtained racemically, **3a** was isolated with 90–92% ee. Obviously, the arrangement of the substrates is very different in the nitroaldol and in the ethyl transfer to benzaldehyde.

In conclusion, we have demonstrated that 1,2-aminoethanol or 1,2-diaminoethane efficiently promote nitroaldol reactions with nitromethane.

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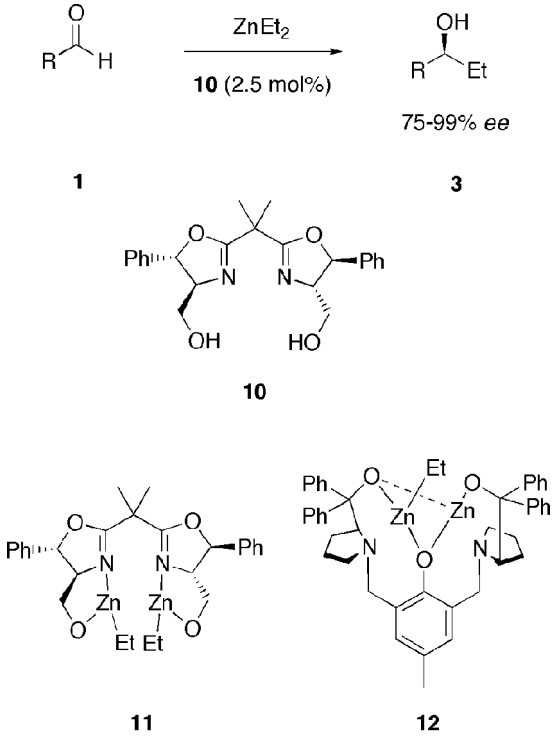

Figure 1. Bimetallic zinc complexes for diethylzinc additions (**11**) and nitroaldol reactions (**12**).

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6. *Typical procedure*: To a precooled (0°C) solution of nitromethane (4 mmol) and 2-aminoethanol (0.2 mmol) in dry toluene (4 ml) was added a Et_2Zn solution (3 mmol, 1 M hexane solution). After 30 min a solution of benzaldehyde (1 mmol) in toluene (1 ml) was added and stirring continued for 48 h. Aqueous ammoniumchloride solution was added, and the aqueous layer was extracted with dichloromethane (3 times 15 ml). The combined organic layers were dried and concentrated, and the crude product was purified on silica to yield 2-nitro-1-phenylethanol (88% yield).
7. For a review, see: Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, 1191–1223.
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