A Dinuclear Zn Catalyst for the Asymmetric Nitroaldol (Henry) Reaction**

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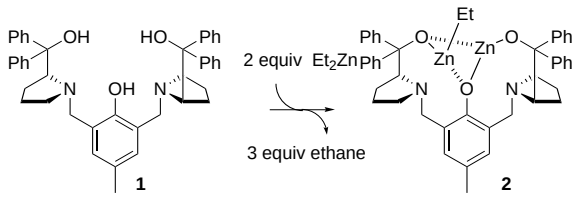
The nitroaldol (Henry) reaction is a fundamental synthetic tool for the construction of C–C bonds.[1] The diversity of the transformations of the adducts, such as reduction to amines or Nef reaction to carbonyl compounds, provides numerous applications of this process. Like the aldol reaction, it may be highly atom economic.[2] In spite of the many applications, the catalytic enantioselective variant of the nitroaldol reaction is relatively under-developed compared to its aldol reaction counterpart. Shibasaki and co-workers have reported a series of heterobimetallic catalysts that proved to be effective for asymmetric Henry reactions.[3] We have recently reported the development of a novel type of asymmetric catalyst (**2**, see Equation (1)) which involves a dinuclear zinc complex center with a chiral semi-azacrown ligand. This catalyst has been successfully applied in enantioselective, direct aldol reactions involving various ketone nucleophiles and aldehyde electrophiles.[4] To the best of our knowledge, zinc catalysts and/or mediators have not been employed for the Henry reaction. Herein we explore the applicability of **2** in catalytic enantioselective Henry reactions.

The catalyst is prepared by treating phenol **1** with two equivalents of diethylzinc wherein three equivalents of ethane [Eq. (1)] evolve. The solution of this complex is then added



(1)

directly into the reaction solution containing nitromethane and the aldehyde substrate. The nitroaldol reaction between nitromethane and cyclohexylcarboxaldehyde [Eq. (2), R = cyclohexyl] was explored to determine the optimal conditions. Table 1 summarizes the results of the initial studies. The data clearly demonstrates the superiority of THF as solvent in

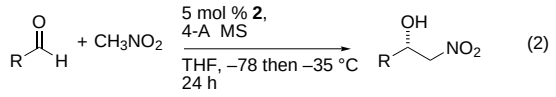


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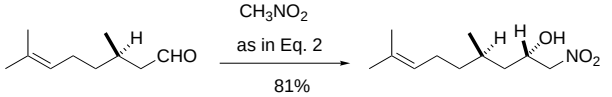
Table 1. Optimization of the nitroaldol reaction between nitromethane and cyclohexanecarboxaldehyde.[a]

Entry	CH_3NO_2 [Equiv]	Catalyst [mol %]	T [°C]	Solvent	Yield [%]/ *ee* [%][b]
1	10	5	5	THF	69/78
2	10	5	–20	THF	68/85
3	10	5	–20	toluene	68/57
4	10	5	–20	CH_2Cl_2	75/51
5	2	5	–20	Et_2O	20/55
6	2	5	–20	THF:dioxane 4:1	17/86
7	10	5	–78 then –20	THF	75/85
8	10	2.5	–78 then –20	THF	44/85
9	6	5	–78 then –20	THF	70/86

[a] All reactions were run on 1 mmol scale at 0.33 m in aldehyde in the presence of 100 mg of 4-Å MS. [b] Enantiomeric excess determined by chiral HPLC using chiralcel OD column.

terms of yield and *ee* values (entries 1 and 2) compared to other solvents (entries 3–6). The minimum amount of nitromethane and catalyst that could be used to obtain a reasonable yield of the product within a 24 h time frame were five equivalents and 5 mol %, respectively. In the cases where yields were low (entries 5, 6, and 8), the aldehyde was recovered unchanged. Temperature played a significant effect on the *ee* value of the product. Lowering the temperature of the reaction from 5 to –20 °C (entry 1 versus 2) significantly increased the *ee* value. Furthermore, pre-cooling the reaction to –78 °C during the addition of the catalyst insures consistent *ee* values for each individual run.[5] The addition of 4-Å molecular sieves (100 mg per 1 mmol of aldehyde) was employed in all reactions. The use of additives[4] such as Ph_3PS or CF_3CH_2OH proved not to be beneficial in terms of either yield or *ee* value.

Table 2 and Equation (2) summarize the results for a number of examples. α-Branched aldehydes gave nitroaldol products in high yields and high *ee* values (entries 3 and 4). Aldehydes with no α branch were generally more challenging substrates. However, reasonable yields were obtained by using 15 equivalents of nitomethane instead of 10, and by using more concentrated solutions in the reaction (entries 6 and 7). The *ee* value of product **8** (entry 6) could be increased to 96 % by one recrystallization. The product **9** (entry 7) is a useful bifunctional molecule that could serve as a starting material for the rapid access to an unusual GABOB amino acid.[6] Aromatic and heterocyclic aldehydes also gave nitroaldol products in good yields and good *ee* value as well (entries 8–11). The product **12** (entry 10) may be used as the starting material for the synthesis of arbutamine.[7] The use of (*R*)-**14** and (*S*)-**15** (citronellal) [Eqs. (3) and (4)] deals with the



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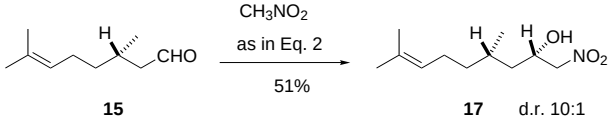

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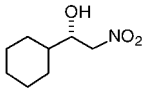
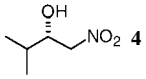
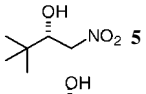
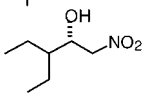
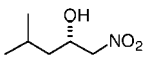
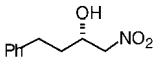
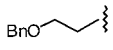
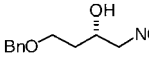
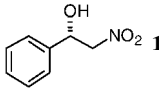
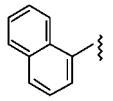
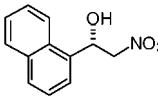
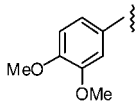
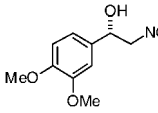
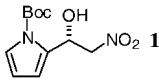
Table 2. Enantioselective nitroaldol reaction with CH_3NO_2.[a]

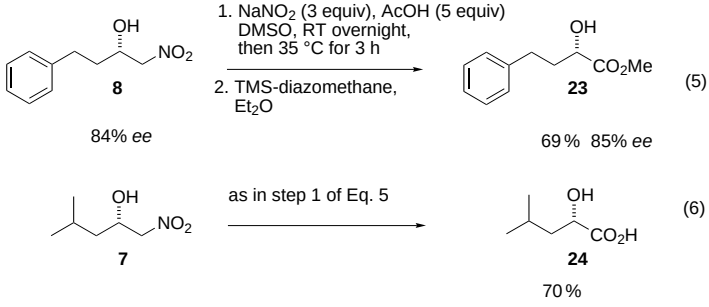
Entry	R	Product	Yield [°C]	*ee* [%][b]
1		 **3**	75	85
2[c]		 **4**	58	88
3[c]		 **5**	88	93
4		 **6**	90	92
5		 **7**	84	87
6 **a**[d]		 **8**[f]	56	85
6 **b**[e]			59	84
7[d]		 **9**	56	86
8		 **10**	75	91
9		 **11**	71	93
10		 **12**	69	78
11		 **13**[11]	79	90

[a] All reactions were carried out on a 1-mmol scale using 5 mol% catalyst, 10 equiv CH_3NO_2 in 0.33 M THF solution at $-35\,^{\circ}C$ for 24 h unless noted otherwise. [b] Determined by chiral HPLC. See Supporting information for details. [c] Reaction performed using 5 equiv CH_3NO_2 at $-60\,^{\circ}C$. [d] Reaction performed using 15 equiv CH_3NO_2 and 5 mol% catalyst in 0.66 M THF solution at $-35\,^{\circ}C$ for 2 days. [e] Same as [a], except using 10 mol% catalyst in 0.33 M THF solution. [f] The product had 96% *ee* after one recrystallization from Et_2O:hexane.

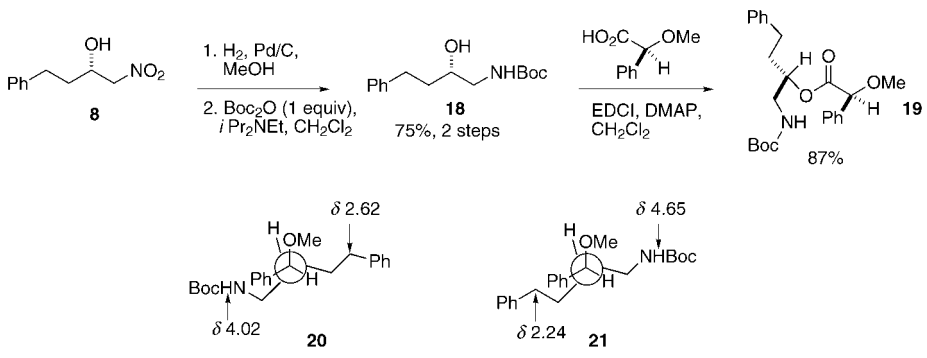
issue of controlling the diastereoselectivity. The catalyst indeed controls the facial selectivity. Interestingly, the selectivity in forming the *anti* diastereomer **16** is higher than forming the *syn* diastereomer **17**, but in both cases, the major epimer of the alcohol has the *S* configuration. This difference is understandable on the basis of the enhanced steric strain associated with the *syn* isomer compared to the *anti* isomer.

The absolute configuration of the nitroaldol adducts **3** was assigned by comparison to literature compounds.[3a] Additional analysis were made on the nitro alcohols **4, 8**, and **16** by the *O*-methyl mandelate method.[8] For example, enantiomerically enriched **8** was converted into the corresponding (*S*)-*O*-methyl mandelate **19** as shown in Scheme 1.[9] Racemic **8** was converted into a diastereomeric mixture of mandelates, shown in extended Newman projections **20** and **21**. The absolute configuration of the newly generated stereogenic center of the nitroaldol products using the (*S*,*S*)-ligand **1** could be assigned from ^1H NMR correlation results as "*S*" (as depicted). It is likely that the absolute configuration of the remaining examples are the same.

The nitroaldol products could also be further elaborated into chiral α-hydroxy acids by sodium nitrite in acetic acid and dimethyl sulfoxide (DMSO)[10] without epimerization of the stereogenic center [Eqs. (5) and (6); TMS = trimethylsilyl].



The dinuclear zinc complexes of ligand **1** (namely, **2**) are indeed effective for the addition of nitromethane to aldehydes. The facial selectivity is the same as that observed in the aldol reaction. The lack of structural information on the catalytic active species makes the development of a model to understand this selectivity difficult. Nevertheless, a catalytic cycle as depicted in Scheme 2 may be envisioned, and accounts for the observations. This new catalyst system provides a ready entry to this important building block, which has been used for the asymmetric synthesis of β-hydroxyamines as well as α-hydroxycarboxylic acids. While further work to define the source of the asymmetric induction and scope of the reaction with substituted systems is planned, the current version involving nitromethane has already proven to be useful, and has been shown to be effective for the broadest array of aldehydes examined to date.



Scheme 1. Determination of the absolute configuration of nitro alcohol **8**. Boc = *tert*-butoxycarbonyl, EDCI = 3-(3-dimethylaminopropyl-1-ethylcarbodiimide, DMAP = 4-dimethylaminopyridine.

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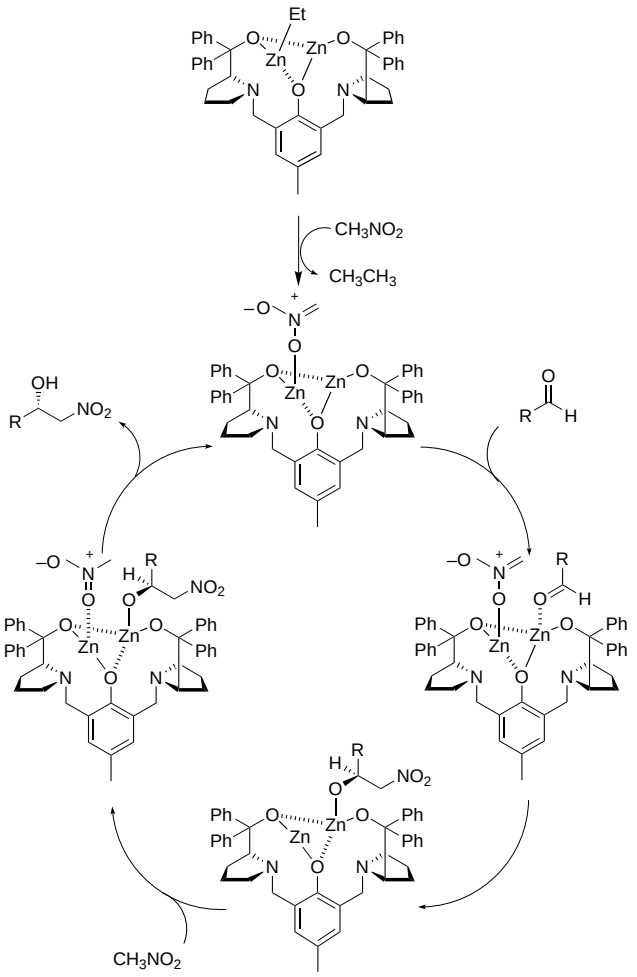

Scheme 2. Proposed catalytic cycle.

Experimental Section

Typical experimental procedure: A solution of diethylzinc (0.36 mL, 1.1 M in toluene, 0.4 mmol) was added to a stirred and cooled (0 °C) solution of **1** (0.128 g, 0.2 mmol) in THF (2 mL) under an argon atmosphere. After the addition, the cold bath was removed and the solution was stirred at room temperature for 30 min to form a solution of **2** (ca. 0.1 M).

A solution of the zinc catalyst **2** (0.5 mL, 0.1 M in THF, 0.05 mmol) was added dropwise to a stirred and cooled (−78 °C) suspension of powdered molecular sieves (4 Å; 100 mg, dried at 120 °C under vacuum overnight), cyclohexanecarboxaldehyde (0.112 g, 1 mmol), and CH_3NO_2 (0.32 mL, 6 mmol) in THF (3 mL) under an argon atmosphere. After the addition, the resulting mixture was transferred to a −20 °C cold bath and left stirring for 24 h. The reaction was quenched by adding aqueous HCl solution (3 mL, 0.5 M), and the resulting mixture was partitioned with Et_2O (10 mL). The organic phase was washed with water and brine, then dried ($MgSO_4$), and filtered. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (EtOAc:petroleum ether, 1:9) to afford the nitroaldol product **3**[3a] (0.12 g, 70 %) as a clear oil: $[\alpha]_D^{25} = +15.87$ ($c = 5.01$, $CHCl_3$) (86 % *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 1.0 – 1.34 (m, 5H), 1.40 – 1.54 (m, 1H), 1.61 – 1.85 (m, 5H), 2.58 (br s, 1H), 4.02 – 4.12 (m, 1H), 4.35 – 4.50 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta =$ 25.69, 25.82, 26.02, 27.89, 28.75, 41.37, 42.81, 79.28; $t_r = 16.81$ and 17.64 min (major; Chiralcel OD, $\lambda = 254$ nm, heptane:isopropanol 97:3, 1 mL min^{-1}).

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[5] See the Experimental Section for typical experimental procedures.

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[11] We thank Nadine Bremeyer for preparing compound **13**.

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