Henry Reaction

Enantioselective Henry Reactions under Dual Lewis Acid/Amine Catalysis Using Chiral Amino Alcohol Ligands**

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There is increasing interest in developing catalytic asymmetric C–C bond-forming processes.[1] In this endeavor the Henry reaction[2] is prominent because of the versatile chemistry of the nitro group.[3] Remarkably, however, while this reaction is closely related to the aldol addition reaction, it has been much less developed than the latter and only a few examples of efficient catalytic enantioselective Henry reactions are known to date.[4] The most outstanding examples include the use of metal-based bifunctional chiral catalysts, as reported by the groups of Shibasaki,[5] Trost,[6] and Evans,[7] which rely on concurrent activation of the aldehyde and the nitroalkane.[8,9] This concurrent activation in Henry reactions has also been

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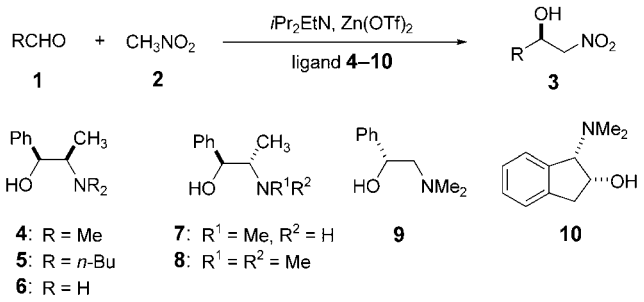
realized by the combined use of discrete Lewis acids and Brønsted bases as structurally independent entities.[10] While this approach allows the straightforward scrutiny of a wide range of Lewis acids and Brønsted bases during the optimization of the catalyst system, it is apparently troublesome because of the chemical incompatibility of Lewis acids and Brønsted bases[11] and the occurrence of a nonselective, base-initiated Henry side reaction.[12] Herein, we report that highly enantioselective direct Henry reactions can be triggered by a combination of a simple Zn^{II} salt, an amine base, and a chiral amino alcohol ligand.

On the basis of precedents in the literature, the combination of a metal triflate salt, a tertiary amine base, and a chiral amino alcohol ligand was initially selected.[13,14] Accordingly, the Henry reaction of nitromethane **2** with hydrocinnamaldehyde **1a** and benzaldehyde **1i** (see Table 3), as representative aliphatic and aromatic aldehydes, respectively, was examined in the presence of stoichiometric quantities of $Zn(OTf)_2$, diisopropylethylamine, and a series of commercially available chiral amino alcohol ligands[15,16] (**4**–**10**; Scheme 1). As the data collected in Table 1 show, (+)-*N*-methylephedrine ((+)-NME; **4**) was prominent in providing both nitroaldol products **3a** and **3i** in good yields and, most importantly, with 90% and 70% *ee*, respectively. When **5**, **8**, or **10** were employed as the ligand, the efficiency of the reaction was maintained although a decrease in enantioselectivity was observed, whereas the reactions of the two aldehydes in the presence of the related amino alcohol ligands **6**, **7**, and **9** were sluggish.

In subsequent experiments, it was found that substoichiometric quantities of the promoter system sufficed for the reaction between nitromethane (**2**) and **1a** (Table 2).[17] The



Scheme 1. Henry reaction of nitromethane (**2**) and an aldehyde **1** promoted by zinc triflate, iPr_2EtN, and a chiral amino alcohol ligand (**4**–**10**).

Table 1: Effect of the structure of the amino alcohol ligand on the efficiency of the Henry reaction between nitromethane (**2**) and either hydrocinnamaldehyde (**1a**) or benzaldehyde (**1i**) under stoichiometric conditions.[a]

	Product **3a** (R = $PhCH_2CH_2$)		Product **3i** (R = Ph)	
Ligand	Conv. [%][b]	*ee* [%][c]	Conv. [%][b]	*ee* [%][c]
4	>99	90	>99	70
5	>99	40	>99	20
6	0	–	20	8
7	37	24	60	40
8	>99	0	85	0
9	35	0	0	–
10	>99	8	90	20

[a] Reactions conducted on a 1-mmol scale (**1**) using nitromethane as solvent (1 mL). 1:1:1:1.5 molar ratio of aldehyde/$Zn(OTf)_2$/iPr_2EtN/(+)-NME. [b] Determined by ^1H NMR spectroscopy (500 MHz) after 15–16 h reaction at −20°C. [c] Determined by HPLC. See Supporting Information for further details.

Table 2: Effect of the quantities of metal triflate, amine base, and amino alcohol ligand on the reaction between hydrocinnamaldehyde (**1a**, R = $PhCH_2CH_2$) and nitromethane (**2**).[a]

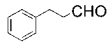
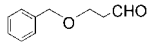
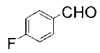
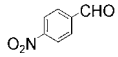
Entry	$Zn(OTf)_2$ [%][b]	iPr_2EtN [%][b]	(+)-NME [%][b]	Conv. [%][c]	*ee* [%][d]
1	30	30	30	>99	80
2	30	30	45	90	90
3	30	20	45	48	50
4	30	0	45	≤14	≤12
5	30	0	75	88	64
6	20	20	45	>99	84
7	10	10	45	>99	70
8	0	0	135	70	0

[a] Reactions conducted on a 1-mmol scale (**1**) in nitromethane (1 mL) for 15–16 h at −20°C. [b] Percentage values refer to the mole percentage (% mol) of the catalyst constituents with respect to the aldehyde. [c] Percentage conversion of the reaction. [d] Determined by HPLC.

threshold loading for satisfactory results was set at 30 mol% of metal salt, relative to the aldehyde, with lower loadings usually accompanied by a diminished selectivity (entries 6 and 7).[18] The optimum result (90% yield, 90% *ee*) was obtained by using $Zn(OTf)_2$, iPr_2EtN, and (+)-NME (**4**) in a percentage mole ratio of 30:30:45 (entry 2). Lowering the loading of (+)-NME to 30 mol% slightly diminished the selectivity (entry 1), whereas increasing the ligand loading above 45 mol% did not improve the result. The quantity of iPr_2EtN was crucial too. Lower loading or absence of iPr_2EtN (entries 3 and 4) led to diminished yields and *ee* values. Interestingly, the absence of iPr_2EtN could be partially compensated by increasing the quantity of the ligand (Table 2, entry 5) which is consistent with the amino alcohol ligand playing the double role of chiral inductor and base. Also, while a stoichiometric quantity of (+)-NME (**4**) alone promoted the reaction (entry 8), the product was obtained as a racemic mixture. Amongst the solvents examined, namely methylene chloride, toluene, diethyl ether, and tetrahydrofuran, all worked similarly well and lead to high enantioselectivities except for THF.

A representative selection of aldehydes **1** were evaluated under the optimized conditions and the results obtained are summarized in Table 3. The enantioselectivities obtained were above 90% for essentially all the aliphatic aldehydes explored and even for the branched or sterically hindered aldehydes, which gave values of up to 98% *ee*. Aromatic aldehydes were also tolerated with equal chemical efficiency although the enantioselectivities were comparatively moderate. Typically, the reactions were carried out at −20°C, but lower temperatures (−40°C, or even −60°C under stoichio-

Table 3: Scope of the aldehyde **1** for the Henry reaction with nitromethane under substoichiometric conditions of $Zn(OTf)_2$/iPr_2EtN/(+)-NME.[a]

	Aldehyde	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1a		−20	16	90	90
1b		−20	16	83	92
		−40[d]	20	81	94
1c		−20	16	92	92
1d		−20	16	75	90
		−30	16	75	92
1e		−20	15	68	97
		−40[d]	17	78	98
1f		−20	16	72	90
		−40[d]	20	74	94
1g		−20	16	71	96
1h		−20	16	87	74
		−60[d]	16	82	87
1i		−60[d]	45	82 (91)	92
1j		−60[d]	45	68 (80)	89
1k		−60[d]	60	77	84

[a] Reactions conducted on the 1-mmol scale (**1**) in dry nitromethane (1 mL) using $Zn(OTf)_2$ (30 mol%), iPr_2EtN (30 mol%), and (+)-NME (45 mol%), otherwise stated. [b] Isolated yields after chromatography. The numbers in parentheses refer to the percentage conversion. If not specified, conversions are >99%. [c] Determined by HPLC. [d] Using a 1:1 (v/v) mixture of nitromethane and CH_2Cl_2 as solvent, and a ratio of 1:1:1:1.5 of aldehyde/$Zn(OTf)_2$/iPr_2EtN/ligand.

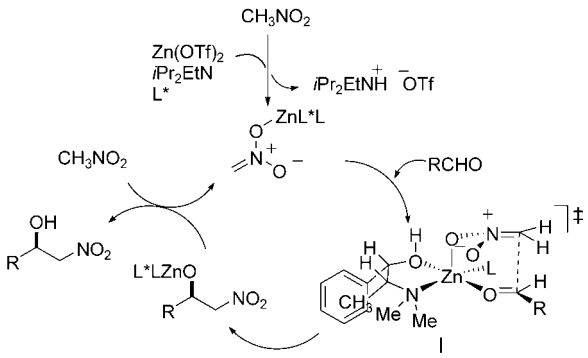


Figure 1. Proposed reaction pathway and transition state (I) for the catalytic Henry reaction. L* = (+)-NME (**4**).

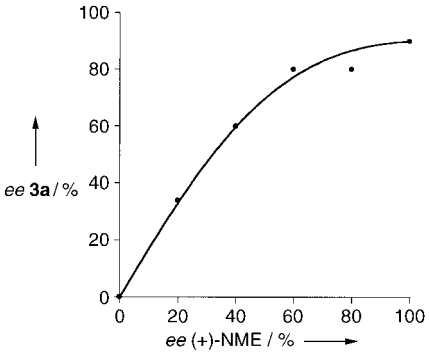


Figure 2. Positive nonlinear effect for the Henry reaction of nitromethane and hydrocinnamaldehyde under substoichiometric conditions.

metric conditions) could also be used effectively to enhance the enantioselectivity. Enals, however, constitute a limitation of the present Henry reaction as they were either recovered unconverted or led to a complex mixture of unidentifiable products. Of practical relevance, the source of chirality, (+)-NME (**4**), could be easily recovered in near-quantitative yield after the reaction by simple aqueous acid/base workup and reused (see Experimental Section).

While the present Henry reaction[19] is simple in execution and uses readily available reagents, the elucidation of its mechanism is appealing. The sense of the asymmetric induction imparted may be correctly predicted by transition model I (Figure 1), which is in accord with previously reported steric and electronic considerations.[7] However, the nonlinear effect observed for the substoichiometric reaction suggests a higher order molecularity of the catalytically active species. In this respect, the data collected in Figure 2 for the Henry reaction of nitromethane (**2**) with hydrocinnamaldehyde (**1a**) seem to fit well with Kagan's two-ligand model.[20] However, control experiments indicate that there is not an appreciable variation of the nonlinear magnitude measured at different values of catalyst loading, while the enantiomeric composition of the product remains essentially constant regardless of the level of conversion of the reaction.[21] Accordingly, it also appears that both the reservoir effect and the possible interaction of the catalytic species with the forming nitroaldol may be discarded as factors of the observed nonlinearity. Studies directed to clarify these mechanistic aspects as well as the extension of this Lewis acid–Brønsted base dual-activation strategy to other reactions is currently underway.

Experimental Section

In a typical procedure, diisopropylethylamine (1.04 mL, 6 mmol) was added to a suspension of $Zn(OTf)_2$ (2.18 g, 6 mmol) in CH_3NO_2 (**2**; 15 mL), and the slurry was stirred for 1 h at 25 °C. (1*S*,2*R*)-(+)-*N*-Methylephedrine (**4**; 1.61 g, 9 mmol) was then added, and the resulting yellow mixture was stirred for an additional 2 h at room temperature. After cooling the mixture to −20 °C a solution of trimethylacetaldehyde (**1g**; 2.17 mL, 20 mmol) in **2** (5 mL) was added by syringe, and the mixture was stirred at the same temperature for 17 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (20 mL), the mixture was extracted with Et_2O (3 × 20 mL), and the combined organic layer was washed with HCl (12 N; 2 × 10 mL) and saturated NH_4Cl (1 × 10 mL). The organic layer was dried with $MgSO_4$ and filtered, and the solvent was removed by evaporation. The crude product was purified by column chromatography to give (*R*)-3,3-dimethyl-1-nitrobutan-2-ol (**3g**) as the major product (2.3 g, 83% yield, 96% *ee*; Chiralcel OD, 98:2 hexane/*i*PrOH, 0.8 mL min^{-1}). *R* major t_r = 16.5 min, *S* minor t_r = 19 min; $[\alpha]_D^{25} = -37.2$ ($c = 1$, CH_2Cl_2).[22] To recover the chiral ligand from the aqueous phase, a solution of NaOH (20% w/v) was added dropwise to the aqueous phase, cooled in an ice bath, until pH 10. The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the organic layer was dried

over $MgSO_4$ and filtered, and the solvent was evaporated to afford chemically and optically pure (1*S*,2*R*)-*N*-methylephedrine (2.8 g, 97% recovered).

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[17] Other combinations of metal salts and Brønsted bases were also examined, with either inferior results or complete failure of the reaction observed. See Supporting Information for more details.
[18] Remarkably, the reaction between nitromethane (**2**) and pivalaldehyde (**1d**) under a low catalyst loading of $Zn(OTf)_2$/*i*Pr_2EtN/(+)-NME (10:10:15 mol% each) led to product **3d** in 75% yield and in 90% *ee*.
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[22] By using (1*R*,2*S*)-(−)-*N*-methylephedrine as the ligand under otherwise identical reaction conditions, the corresponding (*S*)-nitroaldol was obtained (80% yield, 96% *ee*). $[\alpha]_D^{25} = +36.8$ ($c = 1$, CH_2Cl_2) ($[\alpha]_D^{25} = +29.39$ ($c = 3.39$, CH_2Cl_2), 93% *ee*).[7]

