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Highly enantioselective aza-Henry reaction promoted by amine-functionalized tridentate sulfinyl ligands

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ABSTRACT

Diastereomerically pure tridentate heteroorganic ligands containing hydroxyl, sulfinyl, and amino moieties as nucleophilic centers, capable of binding various organometallic reagents, have proven to be highly efficient catalysts in enantioselective aza-Henry reactions to give the desired products in very high yields (up to 98%) and with ees of up to 95%. The influence of the stereogenic centers, located on the sulfinyl sulfur atom and in the amino moiety on the stereochemical course of the reaction is also discussed.

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1. Introduction

The asymmetric aza-Henry (or nitro-Mannich) reaction constitutes as an attractive approach to access optically active precursors of a broad range of various chiral building blocks.[1,2] It consists of a nucleophilic addition of nitroalkanes to imines and is a fundamental C–C bond forming reaction in organic synthesis.[2,3] The importance of this transformation is illustrated by the considerable development of the asymmetric version of the aza-Henry reaction.[1–6] Some time ago, we elaborated upon the chemoenzymatic synthesis of chiral tridentate ligands, bearing hydroxyl, sulfinyl, and amine moieties with two stereogenic centers, one located on the sulfinyl sulfur atom and the other on the carbon atom in the amine moiety.[7] These ligands proved to be very efficient catalysts for various enantioselective reactions for asymmetric carbon–carbon bond formation. Thus, the ligands bearing chiral acyclic amine moieties turned out to be particularly useful for the stereoselective nitroaldol (Henry) reaction,[8] while those bearing chiral aziridinyl substituents were useful for the enantioselective diethylzinc and phenylethynylzinc addition to aldehydes[9,10] and enantioselective conjugate addition of diethylzinc to enones.[11] More-over, it was possible to obtain each enantiomer of the products of the aforementioned reactions using easily available, and enantiopure, diastereomeric ligands.

With this in mind, we decided to broaden the applicability of our tridentate ligands by using them as catalysts for the enantioselective addition of nitromethane to imines, known as the aza-Henry reaction.

2. Results and discussion

2.1. Screening of the ligands

Seven chiral tridentate ligands containing aziridines **1a–d**, (−)-(*S*)- and (+)-(*R*)-1-phenylethylamine **1e** and **1f** and (−)-(*S*)-1-(1′-naphthyl)-ethylamine **1g** were applied, because the former had given the best results in organozinc additions to various carbonyl compounds and the latter in the Henry additions, which are closely related to the reaction being investigated herein (Scheme 1).

To check the ability of these ligands to catalyze the enantioselective aza-Henry reaction, we chose the addition of nitromethane to benzaldehyde *N*-(*tert*-butoxycarbonyl)imine **2a** as a reference transformation. The reactions were performed under standard conditions, but were different from those used for the Henry reaction due to lack of a metal catalyst (Scheme 2). The results are shown in Table 1.

Inspection of Table 1 reveals that the stereogenic sulfinyl group exerts a moderate asymmetric induction. This is visible in the case of catalyst **1a** bearing an achiral aziridine moiety (entry 1), in which the sulfinyl group is the only source of chirality. Ligands bearing chiral acyclic amines **1e–g** proved to be much more efficient catalysts (entries 5–7) than those obtained from chiral aziridines **1b,c** (entries 2 and 3). It should be noted that a similar relationship was found in the Henry reaction.[8] Moreover, the reactions catalyzed by two sets of diastereomeric catalysts **1b** and **1c**, which were constructed from the opposite enantiomers of 2-isopropylaziridine, and **1e** and **1f**, constructed from opposite enantiomers of 1-phenylethylamine, led to the formation of the opposite enantiomers of product **3**. This means that the stereogenic center located in the amine moiety exerts a crucial influence on the stereochemistry of the reaction and hence on the absolute

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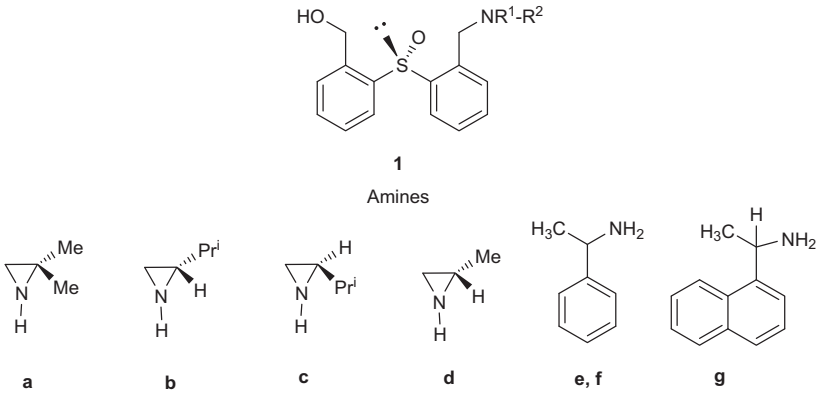


a) 2,2`-dimethylaziridine

b) (-)-(*S*)-2-isopropylaziridine

c) (+)-(*R*)-2-isopropylaziridine

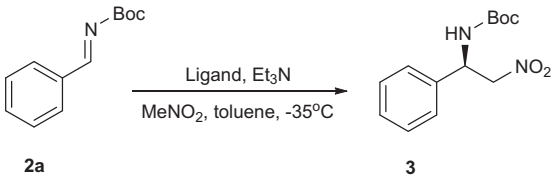
d) (-)-(*S*)-2-methylaziridine

e) (-)-(*S*)-1-phenylethylamine

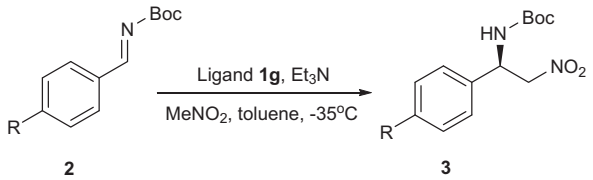
f) (+)-(*R*)-1-phenylethylamine

g) (-)-(*S*)-1-(1`-naphthyl)ethylamine

Scheme 1. Ligands for the asymmetric aza-Henry reaction.



Scheme 2. Screening of ligands **1**.



Scheme 3. The addition of nitromethane to various imines in the presence of ligand **1g**.

Table 1
Screening of ligands **1**

Entry	Ligand	Product **3**			
		Yield (%)	$[\alpha]_D$[a]	ee[b] (%)	Absolute configuration[c]
1	**1a**	52	−7.7	37	(*R*)
2	**1b**	84	−12.6	60	(*R*)
3	**1c**	86	+13.2	63	(*S*)
4	**1d**	76	−10.7	51	(*R*)
5	**1e**	93	−13.5	90	(*R*)
6	**1f**	91	+12.9	86	(*S*)
7	**1g**	97	−19.7	94	(*R*)

[a] In chloroform, $c = 1$.
[b] Determined using chiral HPLC.
[c] Taken from literature.[2]

Table 2
Addition of nitromethane to imines in the presence of **1g**

Entry	R	Product **3**				
		Symbol	Yield (%)	$[\alpha]_D$[a]	ee[b] (%)	Absolute configuration[c]
1	H	**a**	97	−19.7	94	(*R*)
2	Me	**b**	97	−35.0	96	(*R*)
3	MeO	**c**	98	−33.1	95	(*R*)
4	NO_2	**d**	91	−15.2	86	(*R*)
5	Br	**e**	95	−25.0	94	(*R*)

[a] In chloroform, $c = 1$.
[b] Determined using chiral HPLC.
[c] Taken from the literature.[2]

configuration of the addition product. The small differences in the ee values of the product may be explained in terms of 'match' and 'mismatch' interactions with the stereogenic sulfinyl center.

2.2. The addition of nitromethane to various imines in the presence of catalyst 1e

Having obtained the best results with ligand **1g**, we then decided to determine the scope of its activity. Thus ligand **1g** was used to catalyze the title transformation performed with a series of imines (Scheme 3). The results are collected in Table 2.

The results shown in Tables 1 and 2 clearly indicate that ligand **1g** as well as the two diastereomeric ligands **1e** and **1f** are very effective catalysts for the title reaction, all leading to the appropriate chiral β-nitroamine in high chemical yield with high enantiomeric excesses. As mentioned above, each diastereomeric ligand is easily accessible and leads to the formation of opposite enantiomer of the addition product. This means that the desired enantiomer of the product can be obtained by choosing the appropriate enantiomeric amine to synthesize a diastereomeric ligand starting from the same chiral precursor.[7]

3. Conclusions

The chiral tridentate ligands which contained two stereogenic centers, one located on the sulfinyl sulfur atom and the other on the carbon atom in the amine moiety, were found to be very

efficient catalysts for the enantioselective addition of nitromethane to N-protected imines (aza-Henry or nitro-Mannich reaction). The stereogenic centers located in the amine moieties exerted a decisive influence on the stereochemistry of the reaction and the absolute configuration of the products. Each enantiomer of the product may be obtained by using easily available diastereomeric ligands.

4. Experimental

4.1. General

Unless otherwise specified, all reagents were purchased from commercial suppliers and used without further purification. Tetrahydrofuran and toluene were distilled from sodium benzophenone ketyl radical. NMR spectra were recorded on a Bruker instrument at 600 MHz with $CDCl_3$ as solvent and relative to TMS as internal standard. Data are reported as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter with a sodium lamp at room temperature (*c* 1). Melting points were measured on MELTEMP apparatus and were uncorrected. Column chromatography was carried out using Merck 60 Silica Gel. TLC was performed on Merck 60 F_{254} silica gel plates. Visualization was accomplished with UV light. The enantiomeric excess (ee) values were determined by chiral HPLC (Knauer, Chiralcel OD). Chiral tridentate ligands were obtained using the procedure described previously.[7] Imines **2a**–**e** were synthesized according to the protocols described in the literature.[12,13]

4.2. General procedure for the asymmetric aza-Henry reaction[2]

A round-bottomed flask was charged with catalyst **1** (0.2 mmol) and imine **2** (1 mmol). The solids were dissolved in dry toluene (4 mL) and the mixture was cooled to −35 °C. Nitromethane (10 mmol, 0.52 mL) was added and the mixture was stirred at this temperature for 5 min. After this time, Et_3N (0.4 mmol, 0.056 mL) was added, and the mixture was stirred at −35 °C for 8 h and then at room temperature overnight. All the volatile components were evaporated and the crude mixture was purified via column chromatography (hexane:ethyl acetate in gradient) to obtain optically active products **3a**–**e**. The yields, specific rotations and enantiomeric excesses are collected in Tables 1 and 2.

4.2.1. *tert*-Butyl (*R*)-2-nitro-1-phenylethylcarbamate 3a

White solid, mp 107 °C. ^{1}H NMR ($CDCl_3$): δ = 1.44 (s, 9H), 4.70 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.85 (br s, 1H), 5.28 (br s, 1H), 5.38 (br s, 1H), 7.30–7.41 (m, 5H). Other spectroscopic data of compound **3a** are in agreement with those reported in the literature.[2]

4.2.2. *tert*-Butyl (*R*)-2-nitro-1-(4-methylphenyl)ethylcarbamate 3b

White solid, mp 127 °C. ^{1}H NMR ($CDCl_3$): δ = 1.44 (s, 9H), 2.34 (s, 3H), 4.68 (dd, *J* = 12.6, 6.0 Hz, 1H), 4.83 (br s, 1H), 5.20 (br s, 1H), 5.32 (m, 1H), 7.18 (s, 4H). Other spectroscopic data of compound **3b** are in agreement with those reported in the literature.[2]

4.2.3. *tert*-Butyl (*R*)-2-nitro-1-(4-methoxyphenyl)ethylcarbamate 3c

White solid, mp 133 °C. ^{1}H NMR ($CDCl_3$): δ = 1.44 (s, 9H), 3.80 (s, 3H), 4.66 (dd, *J* = 12.0, 5.4 Hz, 1H), 4.84 (br s, 1H), 5.17 (br s, 1H), 5.30 (br s, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H). Other spectroscopic data of compound **3b** are in agreement with those reported in the literature.[2]

4.2.4. *tert*-Butyl (*R*)-2-nitro-1-(4-nitrophenyl)ethylcarbamate 3d

Yellow solid, mp 133 °C. ^{1}H NMR ($CDCl_3$): δ = 1.44 (s, 9H), 4.75 (dd, *J* = 12.6, 4.6 Hz, 1H), 4.85 (m, 1H), 5.45 (m, 1H), 5.52 (br s, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 8.15 (d, *J* = 8.4 Hz, 2H). Other spectroscopic data of compound **3b** are in agreement with those reported in the literature.[4]

4.2.5. *tert*-Butyl (*R*)-2-nitro-1-(4-bromophenyl)ethylcarbamate 3e

White solid, mp 140 °C. ^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 9H), 4.51 (m, 1H), 4.58 (m, 1H), 5.44 (m, 1H), 7.30 (d, *J* = 6.6 Hz, 2H), 7.54 (d, *J* = 6.6 Hz, 2H). Other spectroscopic data of compound **3e** are in agreement with those reported in the literature.[2]

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