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Highly Efficient Asymmetric Aziridination of Unsaturated Aldehydes Promoted by Chiral Hetero-organic Catalysts

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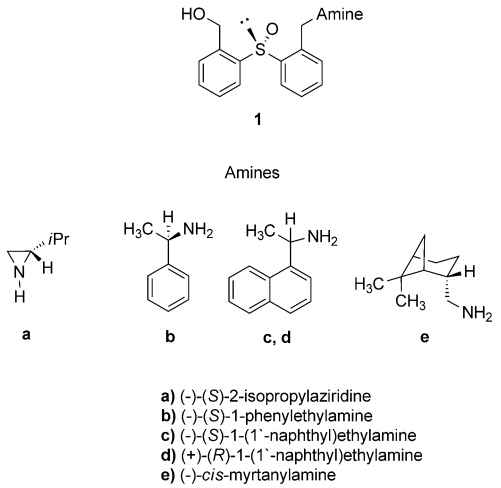
Optically pure hetero-organic catalysts that bear a hydroxyl moiety, a stereogenic sulfinyl group, and a chiral amine moiety, are highly efficient in the asymmetric aziridination of unsaturated aldehydes and lead to the desired chiral products in high yields (up to 93%) with enantiomeric excess values up to 92%. The influence of the stereogenic centers at the sulfinyl sulfur atom and in the amine moiety on the stereochemical outcome of the title reaction is discussed.

Introduction

The enantioselective construction of C–C and C–heteroatom bonds in the synthesis of various compounds in the enantiomerically pure state is still a challenge for modern organic chemists because of the high importance of such isolated stereoisomers in many industrial sectors such as the pharmaceutical, food, flavor, and fragrance industries.[1] The main factor that influences the chemical yield and optical purity of the desired chiral products is the use of an appropriate chiral catalyst. For this reason, studies on the synthesis and evaluation of new chiral systems for asymmetric catalysis are conducted extensively.[2–4]

Chiral aziridines constitute a very useful group of synthetic intermediates for the synthesis of amino acids, natural products, and pharmaceuticals.[5–8] The basic reaction for the construction of such chiral heterocycles with a three-membered ring is asymmetric aziridination,[9,10] which can generally be conducted using chiral auxiliaries[11–15] or chiral catalysts.[16–20] This kind of asymmetric transformation often constitutes one step in the synthetic pathway of many natural and biologically active compounds, for example, sphinganines.[21]

Previously, we have reported a synthesis of chiral tridentate ligands, which contain hydroxy, sulfinyl, and amine moieties, with two stereogenic centers at the sulfinyl sulfur atom and on the carbon atom in the amine function (Scheme 1).[22,23] Ligands that bear open-chain amine functionalities are very effective catalysts for the enantioselective Henry[24] and aza-Henry[25] reactions, direct aldol condensation,[26] and Mannich reaction,[27] whereas their analogs that contain an aziridine ring as the amine moiety exhibited high catalytic activity in diethyl- and phenylethynylzinc additions to aldehydes,[23,28] in the conjugate addition of diethylzinc to α,β-unsaturated carbonyl compounds (enones),[29] and in the asymmetric Simmons–Smith cyclopropanation.[30] An easy access to both enantiomeric products using diastereomeric forms of the ligand was demonstrated. Although the chirality of the amine substituent exerts a decisive effect on the stereochemical course of all the reactions, it was also found that the simultaneous contribution of each functional group was responsible for the high yields and enantiomeric excess (*ee*) of the products.[30,31] To continue our interest in the field of asymmetric transformations and in the synthesis of small heterocyclic systems[30] and, moreover, to take all the above results into account, we have decided to extend the scope of the applicability of our hetero-organic ligands[22,23] by investigating their catalytic activity in the asymmetric aziridination of unsaturated aldehydes.



Scheme 1. Catalysts for the asymmetric aziridination.

Results and Discussion

Catalyst screening

Five chiral tridentate ligands prepared as described previously[21,22] were applied as catalysts to the title reaction

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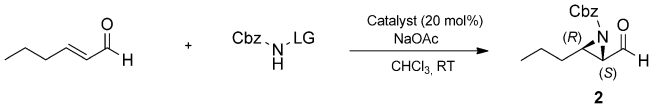
(Scheme 1). Ligands **1 c** and **1 d**, which originated from both enantiomers **c** and **d** of 1-(1′-naphthyl)ethylamine, were used to study the possible match–mismatch effect of the two stereogenic centers, which are located at the sulfinyl sulfur atom and on the carbon atom in the amine function. Ligand **1 a**, which bears an aziridine moiety, was selected according to the best results in terms of chemical yield and *ee* obtained for the previous asymmetric reactions catalyzed by aziridine-containing ligands.[22,27–29] Following the procedure described previously,[19] we chose the asymmetric aziridination of (*E*)-2-hexenal to screen our catalysts. The reactions were performed for 4 h (after optimization) in chloroform, using benzyl *N*-tosyloxycarbamate or *N*-acetoxycarbamate as "nitrene equivalents" in the presence of 20 mol% of ligand **1** and three equivalents of sodium acetate as a base (Scheme 2). All the reactions were performed at room temperature. Interestingly, in all cases *trans* products were obtained as the major diastereomers, which indicates that the configuration of the starting alkene is retained in the product. The results are collected in Table 1.



Scheme 2. Asymmetric aziridination of (*E*)-2-hexenal. Cbz = Carboxybenzyl.

Table 1. Screening of catalyst **1 a–e**.

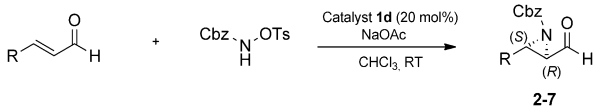
Entry	Catalyst	LG	Product **2**				
			Yield [%]	$[\alpha]_D$[a]	*ee* [%][b]	*dr*	Absolute configuration[c]
1	**1 a**	OTs	20	−1.7	15	2:1	2*S*,3*R*
2	**1 b**	OTs	62	−7.7	65	5:1	2*S*,3*R*
3	**1 c**	OTs	89	−10.3	87	15:1	2*S*,3*R*
4	**1 d**	OTs	93	+10.8	91	15:1	2*R*,3*S*
5	**1 e**	OTs	67	−8.5	72	5:1	2*S*,3*R*
6	**1 d**	OAc	90	+10.2	86	15:1	2*R*,3*S*

[a] In chloroform ($c = 1$) at RT. [b] Determined using chiral HPLC for the major diastereoisomer. [c] According to Ref. [19].

An inspection of the results given in Table 1 reveals some interesting findings. First, the title reaction, tested in the presence of catalyst **1 a**, which bears an aziridine moiety, proceeded insignificantly in terms of yield and *ee* (20 and 15%, respectively). Second, the application of both diastereomeric catalysts **1 c** and **1 d**, which contain opposite enantiomers of 1-(1′-naphthyl)ethylamine, led to the formation of chiral products **2** with opposite absolute configurations. This means that the stereogenic centers located in the amino moieties exerted a decisive influence on the absolute configuration of the products. The small differences in their optical rotation and *ee* values may be explained in terms of "match" and "mismatch" interactions with the sulfinyl stereogenic center. Thus, the characteristic feature of our catalysts was confirmed also in this case and allowed both stereoisomers of product **2** to be prepared using easily available diastereomeric catalysts with opposite enantiomeric amine moieties.

Asymmetric aziridination of various unsaturated aldehydes in the presence of catalyst 1 d

As the best results were achieved with catalyst **1 d**, we decided to study the scope of the title reaction for a series of unsaturated (*E*)-aldehydes[19] in the presence of catalyst **1 d** under the same conditions as used previously (Scheme 3). The results are collected in Table 2.



Scheme 3. Asymmetric aziridination of unsaturated aldehydes in the presence of catalyst **1 d**. OTs = OTosyl.

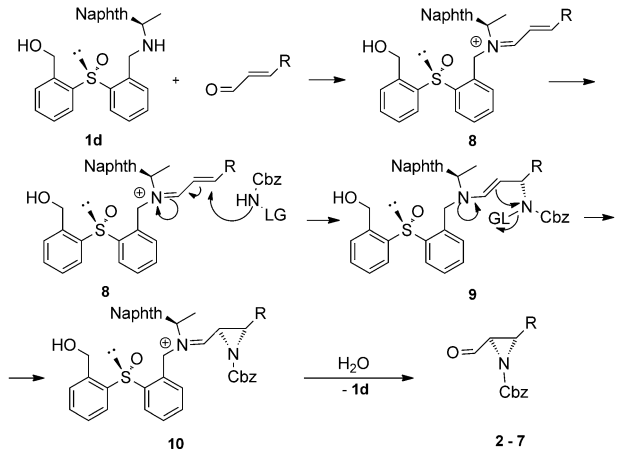
Table 2. Asymmetric aziridination of unsaturated aldehydes in the presence of catalyst **1 d**.

Entry	R (number)	Yield [%]	$[\alpha]_D$[a]	*ee* [%][b]	*dr*	Absolute configuration[c]
1	*n*-Pr (2)	93	+10.8	91	15:1	2*R*,3*S*
2	H (3)	70	+5.3	87	–	*R*
3	Me (4)	61	+20.0	88	10:1	2*R*,3*S*
4	Ph (5)	50	+0.5	92[d]	15:1	2*R*,3*S*
5	4-NO_2-C_6H_4 (6)	60	+5.6	90[d]	15:1	2*R*,3*S*
6	4-Cl-C_6H_4 (7)	37	+47.1	92[d]	15:1	2*S*,3*R*

[a] In chloroform ($c = 1$) at RT. [b] Determined using chiral HPLC for the major diastereoisomer. [c] According to Ref. [19]. [d] Determined using chiral HPLC after reduction to the corresponding alcohol.

The results summarized in Table 2 show clearly that **1 d** is an effective catalyst for the asymmetric aziridination of selected unsaturated aldehydes to lead to the desired chiral aziridine derivatives in good chemical yields and with high *ee* values. The yields for the reactions of cinnamaldehyde and *p*-chlorocinnamaldehyde (Table 1, entries 4 and 6) were moderate, which is in agreement with reported data.[19] However, in contrast to the literature data, no side products were observed. The crude reaction mixture contained only the main product and the unreacted substrates.

Although the detailed mechanism of the title reaction cannot be presented at this stage, it seems reasonable to assume, according to suggestions in the literature,[19] that an initial reversible formation of the iminium intermediate **8** between enals and the amino group of the catalyst takes place. A chiral environment in this intermediate makes the subsequent aza-conjugated attack of a "nitrene equivalent" proceed stereoselectively to form a chiral enamine intermediate **9**. Next, this intermediate undergoes an intramolecular ring closure with the release of a leaving group (LG), which is assumed to be responsible for the general stereochemistry of the aziridination. The final iminium intermediate **10** undergoes hydrolysis



Scheme 4. Possible mechanism of catalytic asymmetric aziridination of unsaturated aldehydes.

to afford the desired aziridines (Scheme 4, which shows the reaction in the presence of catalyst **1 d**). The unsuccessful application of the aziridine-containing catalyst **1 a** (Table 1, entry 1) speaks in favor of this mechanism as the formation of the initial iminium intermediate is impossible for a tertiary amine, the functional group present in this catalyst.

Conclusions

Chiral hetero-organic tridentate ligands that bear two stereogenic centers were found to be efficient catalysts for the asymmetric aziridination of unsaturated aldehydes. The stereogenic centers located in the amino moieties exerted a decisive influence on the stereochemical outcome of the reactions. Moreover, it should be stressed that each enantiomer of the desired product may be achieved by the application of the respective diastereomeric ligands.

Experimental Section

General

Unless otherwise specified, all reagents were purchased from commercial suppliers and used without further purification. Chloroform was distilled from phosphorus pentoxide. ^{1}H NMR spectra were recorded by using a Bruker instrument at 600 MHz with $CDCl_3$ as solvent and relative to tetramethylsilane (TMS) as the internal standard. Data are reported as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. Optical rotations were measured by using a PerkinElmer 241 MC polarimeter with a sodium lamp at RT ($c = 1$). Column chromatography was performed on Merck 60 silica gel. TLC was performed on Merck 60 F_{254} silica gel plates, and visualization was accomplished with UV light (254 nm). The diastereomer ratios (*dr*) were determined based on the ^{1}H NMR spectra of the crude reaction mixtures. The *ee* values were determined by chiral HPLC (Knauer, Chiralcel ODH). Chiral tridentate ligands **1 a–e** were synthesized using procedures described previously.[21,22]

Benzyl *N*-tosyloxycarbamate and benzyl *N*-acetoxycarbamate were synthesized according to the literature methods.[32]

General protocol for the asymmetric aziridination of unsaturated aldehydes using chiral ligands[19]

In a round-bottomed flask, chiral catalyst **1** and benzyl *N*-tosyloxycarbamate (or *N*-acetoxycarbamate) (1.2 mmol) were dissolved in chloroform (4.0 mL). To the aforementioned stirred solution, an unsaturated aldehyde (1.0 mmol) and sodium acetate were subsequently added, and the reaction mixture was stirred for 5 h at RT. After completion (TLC test), the solvent was evaporated, and the residue was subjected to column chromatography using silica gel and hexane with ethyl acetate in gradient as an eluent. Chemical yields, *ee* (determined by chiral HPLC), optical rotation values, and *dr* are collected in Tables 1 and 2.

(2*R*,3*S*)-Benzyl 2-formyl-3-propylaziridine-1-carboxylate (2; Table 2, entry 1): Colorless oil; ^{1}H NMR ($CDCl_3$): $\delta = 0.93$ (t, $J = 7.2$ Hz, 3H), 1.43–1.65 (m, 4H), 2.77–2.85 (m, 1H), 2.97–3.03 (m, 1H), 5.14 (t, $J = 12.8$ Hz, 1H), 5.20 (d, $J = 12.8$ Hz, 1H), 7.32–7.37 (m, 5H), 9.15 ppm (d, $J = 5.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 13.5$, 20.2, 33.3, 44.5, 47.1, 68.5, 128.6, 128.7, 128.8, 128.9, 136.0, 160.3, 195.7 ppm. The *ee* was determined as described previously[19] (ODH-column, *n*-hexane/*i*PrOH 95:5, $\lambda = 210$ nm, 1.0 mL min^{-1}), t_r (major enantiomer) = 12.1 min, t_r (minor enantiomer) = 13.5 min. Other spectroscopic data for **2** are in agreement with that in Ref. [19].

(*R*)-Benzyl 2-formylaziridine-1-carboxylate (3; Table 2, entry 2): Colorless oil; ^{1}H NMR ($CDCl_3$): $\delta = 2.54$ (d, $J = 3.0$ Hz, 1H), 2.65 (d, $J = 5.2$ Hz, 1H), 3.10–3.17 (m, 1H), 5.10–5.20 (m, 2H), 7.31–7.35 (m, 5H), 9.06 ppm (d, $J = 5.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 30.0$, 41.2, 69.3, 128.6, 128.7, 128.8, 135.5, 160.8, 196.2 ppm. The *ee* was determined as described previously[19] (OJ-column, *n*-hexane/*i*PrOH 90:10, $\lambda = 210$ nm, 1.0 mL min^{-1}), t_r (major enantiomer) = 32.1 min, t_r (minor enantiomer) = 42.0 min. Other spectroscopic data for **3** are in agreement that in with Ref. [19].

(2*R*,3*S*)-Benzyl 2-formyl-3-methylaziridine-1-carboxylate (4; Table 2, entry 3): Colorless oil; ^{1}H NMR ($CDCl_3$): $\delta = 1.35$ (d, $J = 5.6$ Hz, 3H), 2.85–2.94 (m, 1H), 2.95 (dd, $J = 4.8$, 1.8 Hz, 1H), 5.15 (q, $J = 12.0$ Hz, 2H), 7.32–7.37 (m, 5H), 9.10 ppm (d, $J = 4.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 16.5$, 40.0, 48.2, 69.1, 128.8, 128.9, 130.0, 135.9, 160.3, 196.2 ppm. The *ee* was determined as described previously[19] (ODH-column, *n*-hexane/*i*PrOH 92:8, $\lambda = 254$ nm, 0.5 mL min^{-1}), t_r (major enantiomer) = 23.1 min, t_r (minor enantiomer) = 25.7 min. Other spectroscopic data for **4** are in agreement with that in Ref. [19].

(2*R*,3*S*)-Benzyl 2-(hydroxymethyl)-3-phenylaziridine-1-carboxylate (5; after reduction; Table 2, entry 4): Colorless oil; ^{1}H NMR ($CDCl_3$): $\delta = 3.65$ (dd, $J = 2.8$, 2.4 Hz, 2H), 4.12 (d, $J = 5.2$ Hz, 1H), 4.40 (d, $J = 7.2$ Hz, 1H), 5.15 (s, 2H), 7.25–7.38 ppm (m, 10H); ^{13}C NMR ($CDCl_3$): $\delta = 42.0$, 47.9, 61.5, 68.9, 126.9, 128.4, 128.6, 128.7, 128.8, 128.9, 136.2, 163.0 ppm. The *ee* was determined as described previously[19] (ODH-column, *n*-hexane/*i*PrOH 90:10, $\lambda = 220$ nm, 1.0 mL min^{-1}), t_r (major enantiomer) = 21.6 min, t_r (minor enantiomer) = 15.8 min. Other spectroscopic data for **5** are in agreement with that in Ref. [19].

(2*R*,3*S*)-Benzyl 2-formyl-3-(4-nitrophenyl)aziridine-1-carboxylate (6; Table 2, entry 5): Yellowish oil; ^{1}H NMR ($CDCl_3$): $\delta = 3.35$ (t, $J = 2.6$ Hz, 1H), 3.95 (d, $J = 2.6$ Hz, 1H), 5.18 (q, $J = 12.0$ Hz, 2H), 7.30–7.37 (m, 5H), 7.42–7.49 (m, 2H), 8.16–8.20 (m, 2H), 9.48 ppm (d, $J = 2.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 45.5$, 50.2, 69.8, 124.8, 128.1, 128.9, 129.1, 129.3, 135.7, 142.0, 148.5, 160.1, 193.7 ppm. The *ee* was determined as described previously[19] (ODH-column, *n*-hexane/*i*PrOH 94:6, $\lambda = 210$ nm, 0.5 mL min^{-1}), t_r (major enantio-

mer) = 56.7 min, t_r (minor enantiomer) = 61.5 min. Other spectroscopic data for **6** are in agreement with that in Ref. [19].

(2*S*,3*R*)-Benzyl 2-(4-chlorophenyl)-3-(hydroxymethyl)aziridine-1-carboxylate (7; Table 2, entry 6): Yellow oil; ^{1}H NMR ($CDCl_3$): δ = 2.30 (s, 3H), 2.71–2.76 (m, 1H), 3.48 (d, J = 3.2 Hz, 1H), 3.61–3.70 (m, 1H), 4.14–4.20 (m, 1H), 5.11–5.17 (m, 2H), 7.08–7.36 ppm (m, 9H); ^{13}C NMR ($CDCl_3$): δ = 41.2, 47.9, 61.0, 68.8, 128.1, 128.7, 128.8, 128.9, 130.2, 134.2, 134.9, 136.1, 162.4 ppm. The *ee* was determined as described previously[19] (OJ-column, *n*-hexane/*i*PrOH 90:10, λ = 238 nm, 1.0 mL min^{-1}), t_r (major enantiomer) = 35.5 min, t_r (minor enantiomer) = 25.5 min. Other spectroscopic data for **7** are in agreement with that in Ref. [19].

Keywords: asymmetric catalysis · aldehydes · C–C coupling · enantioselectivity · organocatalysis

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