Chiral Aziridines

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Enantioselective Synthesis of 1,2-Diarylaziridines by the Organocatalytic Reductive Amination of α-Chloroketones

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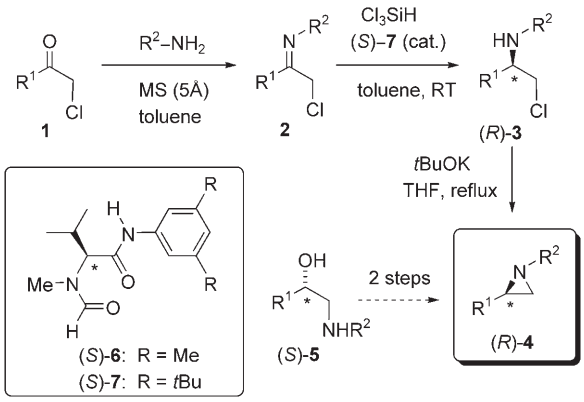
Aziridines constitute the key structural feature of several classes of natural products and have served in synthesis as chiral building blocks, intermediates, auxiliaries, and ligands.[1] To some extent, the synthetic approaches to enantiopure aziridines mirror those designed for epoxides, but are often less developed or less general.[1] Aziridine chemistry is further complicated as a result of the diversity that is introduced by the N-substituent, a problem that does not exist with epoxides. Chiral 1,2-disubstituted (terminal) aziridines **4** (R^2 = aryl, Scheme 1) represent a particularly challenging synthetic target for catalytic protocols.



Scheme 1. Enantioselective synthesis of aziridines; for R^1 and R^2, see Table 1. MS = molecular sieves.

To date, a number of approaches to aziridines with varying degrees of success and limitations have been developed.[1h,2–5] The most versatile and efficient route to aziridines **4** is the S_N2-type cyclization of enantiopure vicinal amino alcohols **5**, which can be conveniently synthesized by opening of the corresponding epoxides.[6] An alternative route to **5** employs an asymmetric reduction (for example, transfer hydrogenation) of N-protected α-amino ketones, which were obtained from the corresponding α-haloketones **1**.[7] However, α-amino ketones are a rather capricious class of compounds and the whole sequence requires five steps from a ketone. Enantiomerically enriched aziridines can also be synthesized from chloroaldimines with a chiral auxiliary on the nitrogen atom, by using a diastereoselective alkylation, followed by a base-induced cyclization.[8,9]

Among the terminal aziridines, 1,2-diaryl-substituted derivatives **4** have received little attention despite the fact that some of them constitute an interesting class of pesticides with a very low oral mammalian toxicity. Their enantiopure forms have never been synthesized[10] and early attempts at asymmetric synthesis have resulted in poor enantioselectivity.[4a] Herein, we report on a new and practical synthesis of 1,2-diaryl aziridines **4** by the enantioselective reductive amination of α-chloroketones **1**.

We recently developed an efficient procedure for the asymmetric reduction of prochiral *N*-aryl ketimines with trichlorosilane (up to 94% *ee*), catalyzed by Lewis basic formamides derived from *N*-methylvaline (for example, **6** and **7**; Scheme 1).[11–13] We reasoned that an analogous reduction of α-chloroimines **2** would represent an attractive approach to *N*-aryl aziridines **4**. Despite its apparent simplicity, this methodology has never been explored in detail. One of the reasons could be that reduction of α-chloroimines with complex metal hydrides usually produces mixtures of the corresponding α-chloroamines, aziridines, and dehalogenated amines, which has hampered the development of practical methods.[9] Furthermore, α-chloroketones **1**, on reaction with aliphatic amines, are known to undergo a substitution of the chlorine atom rather than to form the desired imine.[7] By contrast, and to our advantage, the less nucleophilic anilines preferentially form imines **2**.

The α-chloroimines **2a–g** were prepared from the corresponding α-chloroketones **1** and aniline derivatives (reflux in toluene with molecular sieves, Scheme 1). Reduction of **2a–g** with Cl_3SiH at room temperature, catalyzed by **7** (5 mol%), proceeded successfully to afford the α-chloroamines (*R*)-**3a–g** in good yields and with up to 96% *ee* (Table 1, entries 1–8, method A).

The absolute configuration of the α-chloroamines **3** was established by a chemical correlation (Scheme 2): (−)-**3a** was deprotected by treatment with trichloroisocyanuric acid (TCCA)[14] to afford the primary amine **8**, which was then acylated with benzoyl chloride to give the benzamide **9**. Benzamide **9** thus prepared was identical to the material which was prepared from commercially available (*R*)-phenylglycinol ((*R*)-**10**) by using the benzoylation/chlorination sequence, and therefore (−)-**3a** must have an *R* configuration. Since this stereogenic center is not affected by the ring closure of (*R*)-**3a**, the absolute configuration of aziridine **4a** remains *R*. This assignment can be extrapolated to the whole

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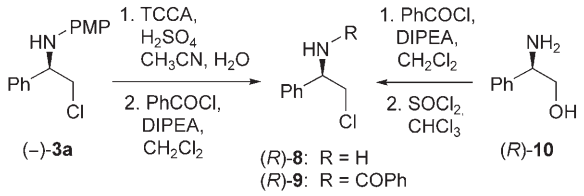
Table 1: Synthesis of (*R*)-**3** by reduction of **2** (method A)[a] and reductive amination of **1** (method B),[b] and their cyclization to (*R*)-**4**.

Entry	Amine **3**	R^1	R^2	α-Chloroamines		Aziridine **4**[d]
				method A[a] yield [%] (*ee* [%])[c]	method B[b] yield [%] (*ee* [%])[c]	yield [%] (*ee* [%])[c]
1	**3a**	Ph	4-$MeOC_6H_4$	98 (96)	94 (89)	98 (95)[g]
2	**3b**	4-FC_6H_4	4-$MeOC_6H_4$	92 (94)	71 (82)	98 (94)[g]
3	**3c**	4-ClC_6H_4	4-$MeOC_6H_4$	87 (91)	68 (91)	94[g,h]
4	**3d**	Ph	Ph	47 (91)	–	92 (90)
5	**3d**	Ph	Ph	84 (91)[e]	–	–
6	**3e**	4-FC_6H_4	Ph	78 (87)	–	94 (86)
7	**3f**	4-ClC_6H_4	Ph	69 (81)[e]	–	98 [h]
8	**3g**	2-naphthyl	Ph	83 (90)[e]	–	92 (90)
9	**3h**	4-MeC_6H_4	4-$MeOC_6H_4$	–	65 (93)	96 (92)
10	**3i**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	–	86 (91)	76 [h]
11	**3j**	4-$CF_3C_6H_4$	4-$MeOC_6H_4$	–	88 (84)	73 [h]
12	**3k**	2-naphthyl	4-$MeOC_6H_4$	–	92 (91)	91 [h]
13	**3l**	3-MeC_6H_4	4-$MeOC_6H_4$	–	80 (92)	97 (92)
14	**3m**	3-$MeOC_6H_4$	4-$MeOC_6H_4$	–	84 (92)[f]	94 (92)
15	**3n**	2-ClC_6H_4	4-$MeOC_6H_4$	–	54 (96)[f]	96 (96)
16	**3o**	2-ClC_6H_4	4-ClC_6H_4	–	87 (95)	97[h]
17	**3p**	2-ClC_6H_4	4-FC_6H_4	–	86 (95)	91[h]

[a] Reduction of the imine was carried out on a 0.4-mmol scale with Cl_3SiH (2.0 equiv) at RT (18 °C) for 24 h with catalyst **7** (5 mol%), unless stated otherwise. [b] The reactions were performed with aniline (0.2 mmol) and α-chloroacetophenone (3 equiv) for 24 h, followed by reduction with Cl_3SiH (2.0 equiv) for 24 h, both at RT. [c] Determined by HPLC on a chiral stationary phase with a Chiralpak IB column. [d] Cyclization was carried out in THF on a 0.15-mmol scale with *t*BuOK (2.0 equiv) at reflux for 0.5 h. [e] Catalyst loading of 10 mol% was used. [f] The *ee* value was determined for the corresponding aziridine. [g] The starting amine **3** was obtained by using method A. [h] The enantiopurity could not be established, but is assumed to reflect that of the chloroamine employed.



Scheme 2. Chemical correlation of the absolute configuration of (−)-**3a** with (*R*)-**10**. PMP = *para*-methoxyphenyl, DIPEA = *N*,*N*-diisopropylethylamine.

series of **3b–p** and **4b–p**. It is pertinent to note that for the deprotection of the nitrogen atom (**3**→**8**), which features the oxidative removal of the PMP group, use of TCCA[14] proved to be superior to the known methods that employ Ce^{IV} or $PhI(OAc)_2$, which gave intractable mixtures.

In the case of the electron-rich α-chloroketones **1**, the isolation of the corresponding α-chloroimines proved difficult to the extent that the subsequent reduction could not be carried out. Therefore, we examined a direct reductive amination protocol (Table 1, method B), which has never been attempted before in the reductions with trichlorosilane.[15] The α-chloroimines **2a–c** were generated in situ (toluene, 5-Å MS, RT) and, without isolation, treated with trichlorosilane in the presence of the catalyst (Table 1, entries 1–3, method B). Here, we observed a detrimental effect caused by the unreacted amine that lowered both the enantioselectivity and conversion. Model studies carried out with preformed imines showed that addition of one equivalent of a tertiary amine or proton sponge almost completely stopped the reaction, thus resulting in a very low conversion and selectivity. Conversely, addition of a Brønsted acid (for example, 10 mol% of triflic acid) to the original reaction mixture did not affect the conversion or enantioselectivity, which suggests that a trace amount of Brønsted acid plays a crucial role in the catalytic cycle by activating the imine by protonation of the nitrogen atom. In an optimized protocol for the reductive amination, a threefold excess of the ketone was used to consume all of the aniline derivative. Since the ketones are almost inert to the reducing agent,[13a] they could be easily separated from the product. The direct reductive amination protocol was employed for a wide range of α-chloroketones **1**, in which the steric and electronic properties of the aromatic group were systematically varied (Table 1). The reaction proved very efficient and produced the α-chloroamines (*R*)-**3h–p** in high yield and with up to 96% *ee* (Table 1, entries 9–17, method B). Significantly, the α-chloroketones underwent facile reductive amination in high yield even with the less nucleophilic anilines (Table 1, entries 16 and 17).

The cyclization of all the α-chloroamines (*R*)-**3a–p** with *t*BuOK in THF proceeded readily to furnish the corresponding aziridines (*R*)-**4a–p** with no loss in stereochemical integrity (Table 1).[16,17] Aziridines **4o** and **4p** represent single enantiomers of the known racemic pesticides.[10]

In summary, we have developed a new, expedient protocol for the synthesis of 1,2-diaryl aziridines **4** that have not been prepared previously as pure enantiomers. The method relies on an in situ conversion of the readily available α-chloroacetophenones **1** into the corresponding α-chloroimines **2** at RT, followed by reduction of **2** with Cl_3SiH, catalyzed by the L-valine-derived formamide **7** (5 mol%), to afford the corresponding vicinal α-chloroamines (*R*)-**3** in good yields and high enantioselectivity (≤96% *ee*). Base-mediated ring closure of these α-chloroamines (*R*)-**3** afforded the aziridines (*R*)-**4** with preservation of enantiopurity. This new methodology is characterized by the use of a metal-free catalyst (**7**) and toluene as an environmentally friendly solvent in the key steps.

Experimental Section

General procedure for the asymmetric reduction of imines **2** with trichlorosilane (method A): Trichlorosilane (80 μL, 0.8 mmol, 2.0 equiv) was added dropwise to a solution of **7** (6.9 mg, 0.02 mmol, 5 mol%) and the corresponding imine **2** (0.4 mmol, 1.0 equiv) in dry toluene (4 mL), precooled to 0 °C. The reaction mixture was stirred at room temperature for 24 h, after which time a

saturated aqueous solution of $NaHCO_3$ (5 mL) was added to quench the reaction. The mixture was extracted with EtOAc (2 × 20 mL) and the combined organic extracts were dried over $MgSO_4$. Concentration in vacuo, followed by flash chromatography on silica gel with a mixture of petroleum ether and ethyl acetate (95:5) afforded amines **3**.

General procedure for the asymmetric reductive amination of ketones **1** (method B): Molecular sieves (5 Å, 200 mg) were added to a solution of α-chloroketone **1** (0.6 mmol, 3.0 equiv) and the corresponding aniline derivative (0.2 mmol) in dry toluene (2 mL) and the reaction mixture was stirred at room temperature under argon for 24 h. The reaction mixture was cooled to 0 °C and catalyst **7** (250 μL, 0.04 M solution in dry toluene, 5 mol %) was added, followed by trichlorosilane (40 μL, 0.4 mmol, 2.0 equiv). The reaction mixture was stirred at room temperature for 24 h, after which time a saturated aqueous solution of $NaHCO_3$ (5 mL) was added to quench the reaction. The mixture was extracted with EtOAc (2 × 20 mL) and the combined organic extracts were dried over $MgSO_4$. Concentration in vacuo, followed by flash chromatography on silica gel with a mixture of petroleum ether and diethyl ether (97:3 to 90:10) furnished the amines **3**.

General procedure for the synthesis of aziridines **4**: *t*BuOK (33.5 mg, 0.30 mmol, 2.0 equiv) was added to a stirred solution of α-chloroamine **3** (0.15 mmol, 1.0 equiv) in dry THF (1.5 mL) and the resulting suspension was heated at 70 °C under argon for 0.5 h. The reaction mixture was cooled to room temperature and filtered through a pad of celite, the pad was washed with diethyl ether, and the filtrate was evaporated to dryness. The residue was purified by column chromatography on silica gel (7 g), pretreated overnight with triethylamine (1.5 mL) in petroleum ether (50 mL), using a mixture of petroleum ether and diethyl ether (90:10) as eluent to afford the corresponding aziridines **4**.

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