Small Ring Systems

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An Amine-Promoted Aziridination of Chalcones**

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Aziridines are versatile building blocks that can undergo various synthetically useful transformations and are also an important part of many biologically active molecules.[1] Great efforts and progress have been made in the development of various aziridination methods.[1–15] As part of our general interest in the area of small-ring synthesis from olefins, we have been investigating new methods to prepare aziridines, particularly those without protecting groups on the nitrogen atom, such as the aziridination of electron-deficient olefins with aminimide **1** (Scheme 1).

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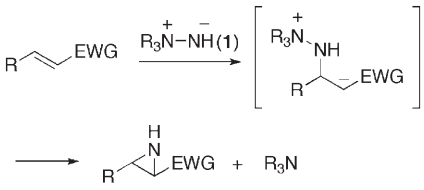
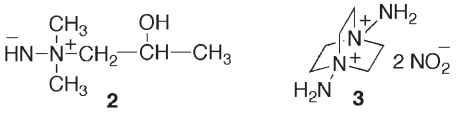
Supporting information for this article (aziridination procedures, characterization including an X-ray crystallographic analysis, and the determination of the *ee* values) is available on the WWW under http://www.angewandte.org or from the author.



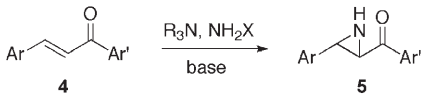
Scheme 1. Aziridination of electron-deficient olefins with aminimide **1**. EWG = electron-withdrawing group.

In 1980, Ikeda et al. reported that the aminimide **2** (prepared from 1,1-dimethylhydrazine and propylene oxide) can directly iminate chalcones to form aziridines.[16] Since



then, little has been reported on this reaction. Initial studies by our research group have shown that this aziridination could be extended to other aminimides. For example, the aminimide derived from hydrazinium nitrate **3** (prepared from 1,4-diazabicyclo[2.2.2]octane (DABCO) and hydroxylamine-*O*-sulfonic acid in the presence of barium oxide and barium nitrate)[17] can effectively aziridinate chalcones.[18] To further develop this aziridination reaction, we wanted to investigate whether this system could be developed into a catalytic and eventually an asymmetric process to form nonracemic α-keto aziridines, and herein report our preliminary results.

Our studies started with the investigation of a one-pot process which involved the in situ generation of a hydrazinium salt, deprotonation of the hydrazinium to form an aminimide, and subsequent aziridination (Scheme 2). It has

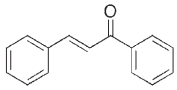
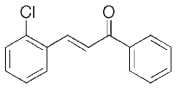
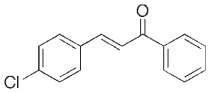
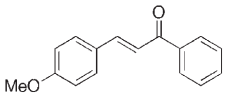
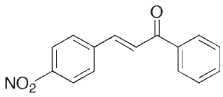
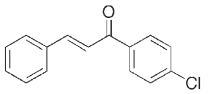
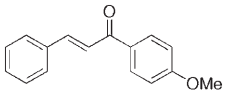
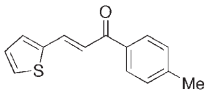


Scheme 2. Aziridination of chalcones **4** with aminimide formed in situ.

been shown that *O*-mesitylenesulfonylhydroxylamine (MSH) can readily aminate various tertiary amines to give the corresponding hydrazinium salts in high yield.[19,20] The aziridination was then examined by treating MSH and tertiary amines with base and chalcone **4**. Treating MSH (2.0 equiv) with DABCO (1.0 equiv), KOH (3.0 equiv), and **4** (Ar = Ar′ = Ph, 1.0 equiv) in CH_3CN at room temperature and stirring the reaction mixture for four hours gave the aziridine product **5** in 73% yield. A higher yield (85%) was obtained on using *N*-methylmorpholine (NMM; Table 1, entry 1a). As shown in Table 1 (entries 2a–8a), other chalcones can be efficiently aziridinated in a short time with good yield.

Encouraged by the feasibility of this one-pot reaction, we next pursued the possibility of making the process catalytic. When NMM was reduced to 0.1 equivalents, the aziridine **5** was obtained in 52% yield (Table 1, entry 1b). A slightly

Table 1: Stoichiometric[a] and catalytic[b] aziridination of chalcones.

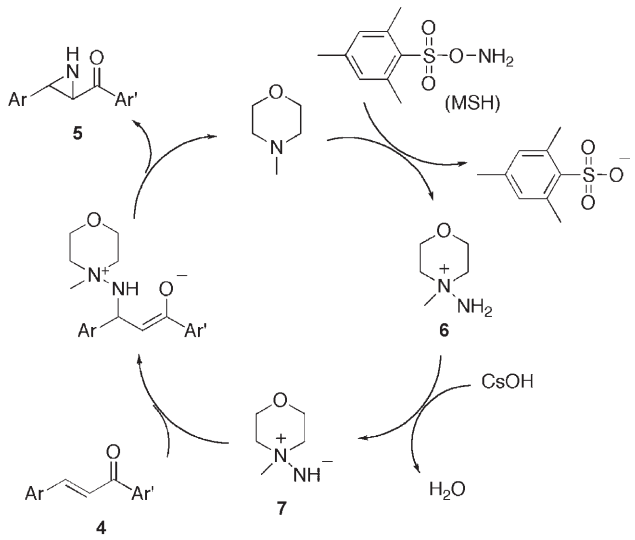
Entry	Substrate	Equiv. of amine	Yield [%][c]
1a		1.0	85
1b		0.1	52[d]
1c		0.1	65
1d		0.2	80
2a		1.0	80
2b		0.2	60
3a		1.0	82
3b		0.2	59
4a		1.0	49
4b		0.2	65
5a		1.0	56
5b		0.2	21
6a		1.0	64
6b		0.2	39
7a		1.0	78
7b		0.2	67
8a		1.0	54
8b		0.2	42

[a] All reactions were carried out with substrate (0.5 mmol), NMM (0.5 mmol), MSH (1.0 mmol), and KOH (1.5 mmol) in CH_3CN (1.5 mL) at room temperature for 4 h (for entry 5a, 3 h; for entry 8a, 5 h). [b] All reactions were carried out with substrate (0.5 mmol), NMM (0.05–0.10 mmol), MSH (1.0 mmol), and $CsOH·H_2O$ (3.0 mmol) in CH_3CN/CH_2Cl_2 (2:1, 2.5 mL) at 0°C to room temperature for 7 h unless otherwise noted. [c] Yield of isolated product. [d] KOH was used as the base and CH_3CN was used as the solvent.

higher yield was obtained by replacing KOH with $CsOH·H_2O$ (Table 1, entry 1c). This catalytic process was further illustrated by the aziridination of a number of substrates (Table 1, entries 2b–8b). In some cases, the yields achieved were similar to those obtained with a stoichiometric amount of tertiary amine. However, in other cases (Table 1, entries 5b and 6b), the yields dropped significantly.

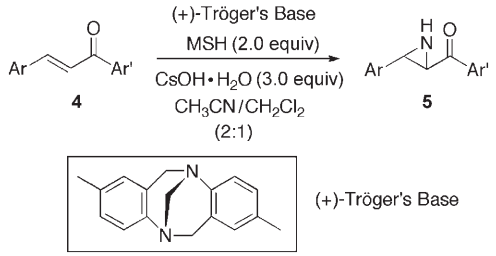
While a detailed understanding of the reaction mechanism awaits further study, a plausible catalytic cycle is shown in Scheme 3.[21] The tertiary amine NMM reacts with MSH to form the hydrazinium salt **6**, which then reacts with $CsOH·H_2O$ to give the aminimide **7**. The aminimide **7** then undergoes conjugate addition to the chalcone **4** followed by cyclization to form the aziridine **5** and regenerate the tertiary amine. No aziridination was observed in the absence of NMM or $CsOH·H_2O$, thereby indicating that a tertiary amine and base are required for the reaction, which is consistent with the proposed mechanism.

The feasibility of the aziridination using a catalytic amount of the tertiary amine and MSH in the presence of



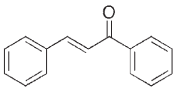
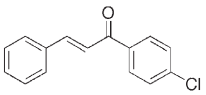
Scheme 3. A proposed catalytic cycle for the aziridination.

$CsOH{\cdot}H_2O$ prompted us to investigate whether a chiral tertiary amine could induce any enantioselectivity for the aziridination. Treating chalcone **4** with 30 mol% (+)-Tröger's base, MSH, and $CsOH{\cdot}H_2O$ afforded the aziridine in 81% yield and 55% *ee* (Scheme 4; Table 2, entry 3).[22] A slightly higher enantioselectivity was obtained with 4′-chlorochalcone (Table 2, entries 5 and 6), and the *ee* value could be improved to 98% upon recrystallization (Table 2, entry 7). These results illustrate that a catalytic asymmetric aziridination process occurs.



Scheme 4. Asymmetric aziridination of **4** using Tröger's base.

Table 2: Asymmetric aziridination of chalcones.[a]

Entry	Substrate	Equiv. of (+)-Tröger's base	Yield [%][b]	*ee* [%][c]
1		1.0	90	55[d]
2		0.6	85	55
3		0.3	81	55
4		1.0	93	62
5		0.6	62	62
6		0.3	50	62
7		0.6[e]	66	67 (98[f])

[a] All reactions were carried out at 0°C with substrate (0.1 mmol), (+)-Tröger's base (0.03–0.1 mmol), MSH (0.2 mmol), and $CsOH{\cdot}H_2O$ (0.3 mmol) in CH_3CN/CH_2Cl_2 (2:1, 1.5 mL) for 7 h (entries 1–3) or 5 h (entries 4–6). [b] Yield of isolated product. [c] The enantioselectivity was determined by HPLC on a chiral stationary phase (chiracel OD). [d] The absolute configuration was determined by comparing the rotation of a known compound and is 2*R*,3*S* (see Ref. [9c]). [e] At −20°C for 24 h. [f] After recrystallization.

In summary, we have found that the aminimide generated in situ from tertiary amine and MSH in the presence of a base is an effective NH-transfer reagent for the aziridination of chalcones. The amine promoter in this aziridination process can be used in a catalytic amount, and a reasonable level of enantioselectivity can be obtained when the chiral tertiary amine, Tröger's base, is used. More effective tertiary amine catalysts and also an expansion of the substrate scope are currently being pursued.

Experimental Section

Representative procedure asymmetric aziridination (Table 2, entry 7): MSH (22.0 mg, 0.10 mmol) and $CsOH{\cdot}H_2O$ (25.0 mg, 0.15 mmol) were added to a solution of (+)-Tröger's base (15.0 mg, 0.06 mmol) and 4′-chlorochalcone (24.0 mg, 0.10 mmol) in CH_3CN/CH_2Cl_2 (1.5 mL, 2:1, v/v) at −20°C. After stirring the reaction mixture for 1 h, further MSH (11.0 mg, 0.05 mmol) and $CsOH{\cdot}H_2O$ (12.5 mg, 0.075 mmol) were added. After another 1 h, additional MSH (11.0 mg, 0.05 mmol) and $CsOH{\cdot}H_2O$ (12.5 mg, 0.075 mmol) were added. The reaction was stirred for a further 22 h at −20°C (total reaction time of 24 h), then diluted with EtOAc (10 mL), filtered, and the filter cake washed with EtOAc (2 × 5 mL). The filtrate was subsequently concentrated and purified by flash chromatography (the silica gel was buffered with 1% Et_3N in hexanes, hexanes/EtOAc = 10:1) to give the aziridine as a pale yellow solid (17.0 mg, 66% yield, 67% *ee*).

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