Catalytic Formation of Aziridines from Imines and Diazoacetate

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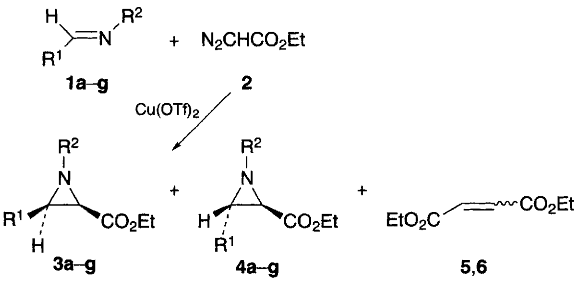
A catalytic method for the preparation of aziridines from imines and diazoacetate is developed using copper complexes as catalyst; the synthetic, diastereo- and enantio-selective scope of the reaction are presented.

During the last decades much effort has been devoted to the development of efficient catalysts for the synthesis, and enantioselective synthesis, of organic building blocks such as epoxides[1] and aziridines.[2] For the preparation of aziridines a variety of methods has been developed using *e.g.* a ring-closure reaction of 1,2-amino alcohols or their derivatives.[3] This method has often been performed with optically pure starting materials derived from amino acids.[3] Another common way for the preparation of chiral aziridines is by ring opening of chiral epoxides with sodium azide and subsequent treatment with triphenylphosphine.[4] Chiral aziridines can also be synthesised from *N*-benzylideneaniline and an anion derived from chiral 1-chloroalkyl tolyl-*p*-sulfoxides,[5] or by the addition of dimethyloxosulfonium methylide or dimethylsulfonium methylide to (*S*)-(+)-*N*-tolyl-*p*-sulfinyl phenylamine,[6] whereas the addition of α-halo ester enolates to *N*-trimethylsilyl imines yields racemic aziridines.[7] With regard to the catalytic preparation of aziridines, only very few methods are available.[8–10] Recently, the catalytic activation of [*N*-(tolyl-*p*-sulfonyl)imino]phenyliodinane, PhI=NTs, has been used for the direct synthesis of aziridines from alkenes using copper salts,[8] 4,4′-disubstituted-bis(oxazoline)–copper complexes[9] or chiral copper–Schiff bases[10] as the catalysts.

We here present our preliminary results for the preparation of aziridines using group-transfer from mainly ethyl diazoacetate to imines catalysed by simple copper complexes (Scheme 1).[11]

Treatment of the imines **1a–g** with ethyl diazoacetate **2** in the presence of a catalytic amount of $Cu(OTf)_2$ yields a mixture of the corresponding *cis*-aziridines **3a–g** and *trans*-aziridines **4a–g**.† Diethyl maleate **5** and diethyl fumarate **6** are common by-products. The yields and diastereoselectivities for the reactions of **1a–g** are presented in Table 1.

The results in Table 1 show that the aziridines can be formed in relatively good yields and the reaction is especially dependent on the R^2-substituent. Imines substituted with R^2 = Ph give high yields of the corresponding aziridines with variable diastereoselectivity. The best yield (95%) and diastereoselectivity (6 : 1) is obtained for **1a** (entry 2). The imine with R^2 = $SiMe_3$ gives an acceptable yield of the aziridine with a very high diastereoselectivity (entry 5), whereas imines having a bulky substituent or an electron-withdrawing substituent at the nitrogen atom afford lower yields of the aziridines (entries 3, 4, 8). These results indicate that the reaction course is very dependent on the substituent at the nitrogen atom (*vide infra*). Changing the solvent from CH_2Cl_2 to THF results in a faster reaction, and we assume that the change is associated with the donor abilities of the imine, as the addition of the imine to $Cu(OTf)_2$ suspended in CH_2Cl_2 immediately results in the formation of a green solution. It is also observed that imine **1a** suppresses the formation of **5** and **6**, compared with the more weakly coordinating imine **1f** (entries 1, 8).



Scheme 1

The aziridine **3d** undergoes a smooth deprotection reaction at the nitrogen atom (Scheme 2) to the corresponding *N*-deprotected aziridine **7** during purification on a silica gel column. This matter is important with respect to the synthetic applicability of the present reaction. It is also notable that the configuration of the aziridine changes from *cis* (J = 6.6 Hz) for **3c** to *trans* (J = 2.2 Hz) for **7** (Scheme 2).

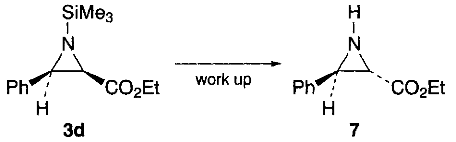
The results obtained from imines having R^1 = Ph, Bu^t (**1a, e**; entries 1, 2, 6, 7) prompted us to extend the reaction to *N*-methylidene aniline which exists as a trimeric compound **1g**. The addition of **2** to a solution of **1g** and a catalytic amount of $Cu(OTf)_2$ in CH_2Cl_2 at 0 °C resulted in the smooth formation of ethyl *N*-phenylaziridine-2-carboxylate **3g** in good yield within 4 h (entry 9; Scheme 3), with only very minor amounts of **5** and **6**.

We have also attempted to perform the reaction in an diastereoselective manner. The reaction of the *N*-methylidene aniline trimer **1g** with (−)-menthyl diazoacetate **8** in the presence of $Cu(OTf)_2$ resulted in the formation of the aziridine **9** in 85% yield; according to GC‡ and ^1H NMR spectroscopy only one diastereoisomer is observed whereas ^{13}C NMR

Table 1 Catalytic formation of aziridines **3a–g** and **4a–g** from imines **1a–g** and ethyl diazoacetate **2** using $Cu^{II}(OTf)_2$ as the catalyst

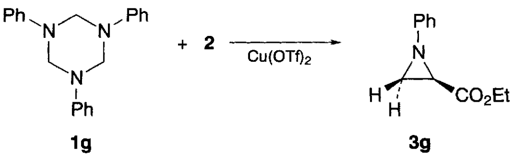
Entry	Imine	R^1	R^2	Solvent	T/°C	**3** : **4**	Total yield (%)
1	**1a**	Ph	Ph	CH_2Cl_2	−25	1.7 : 1	80
2	**1a**	Ph	Ph	THF	−25	6 : 1	95
3	**1b**	Ph	Pr^i	CH_2Cl_2	−25	n.d.[a]	< 5
4	**1c**	Ph	Bu^t	CH_2Cl_2	−25	4 : 1	10
5	**1d**	Ph	$SiMe_3$	CH_2Cl_2	−25	> 20 : 1	35
6	**1e**	Bu^t	Ph	CH_2Cl_2	−25	0.6 : 1	90
7	**1e**	Bu^t	Ph	THF	−25	0.4 : 1	90
8	**1f**	Ph	SO_2Ph	CH_2Cl_2	0	n.d.[a]	< 5
9	**1g**	H	Ph	CH_2Cl_2	0	—	85

[a] n.d. = not determined.

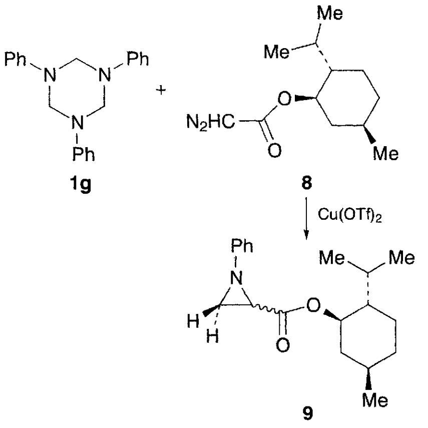


3d **7**

Scheme 2



Scheme 3



Scheme 4

spectroscopy and HPLC§ showed two diastereoisomers with a d.e. of 25% (Scheme 4).

We have also tried to perform the reaction of **1a** with **2** using Cu(OTf)$_2$ as the catalyst in the presence of chiral ligands such as the 4,4′-disubstituted-bis(oxazolines).[12,13] Using (*R*)-(+)-2,2′-isopropylidenebis(4-phenyl-2-oxazoline) as chiral ligand leads to the formation of the corresponding aziridines **3a** and **4a** in about 50–60% yield depending on the reaction conditions. According to ^{1}H NMR spectroscopy the diastereoselectivity obtained under these reactions conditions is similar to those given in Table 1. Unfortunately, the aziridines from this reaction show a low e.e.

The catalytic transformation of imines to aziridines is dependent on the substituent at the nitrogen atom. The low reactivity of *e.g.* imine **1f** might be that the reaction of the copper catalyst with the diazoacetate generates an electrophilic species which has a low reactivity with the electrophilic imine **1f**.

Note added in proof: After the submission of this manuscript, Jacobsen and coworkers,[14] have presented the aziridination of *N*-benzylidene anilines by diazocarbonyl derived carbenes catalysed by copper(I) hexafluorophosphate in the presence of bis(oxazolines).

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Footnotes

† The following procedure for the catalytic preparation of aziridines from imines and diazoacetate was used: 0.08 mmol (30 mg) of Cu^{II}(OTf)$_2$ was added to 2–4 ml solvent (CH$_2$Cl$_2$ or THF). Imine (0.8 mmol) and diazoacetate (0.4 mmol) were added and the reaction mixture stirred at the temperature given in Table 1 until the evolution of N$_2$ gradually ceased (4–6 h). The reaction mixture was filtered through silica. The silica was then washed with 2–4 ml of CH$_2$Cl$_2$. The aziridines were purified on a column using silica gel and 3–10% ethyl acetate : hexane. The products were analysed by NMR spectroscopy and MS.

‡ The GC was performed on a HP-5890 using a HP-1 column.

§ The HPLC was performed on a Waters 600E using a Daicel OD column.

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