Trimethylsilyl Trifluoromethanesulfonate-Promoted Cycloaddition of Nitrones with Silyl Enol Ethers: Synthesis and Reactivity of 5-Siloxyisoxazolidines

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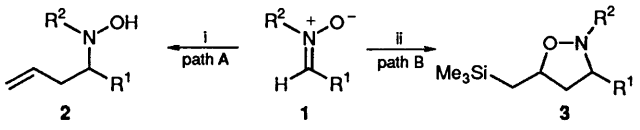
In the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf), the reaction of nitrones with silyl enol ethers affords 5-siloxyisoxazolidines under mild conditions, in good to excellent yields. 5-Siloxyisoxazolidines can undergo chemoselective reductions to Mannich bases or *N*-hydroxy-1,3-amino alcohols, and, in the presence of TMSOTf, react with silylated carbon nucleophiles at the acetalic C-5 carbon to give, for example, 5-allyl- and 5-cyano-isoxazolidines.

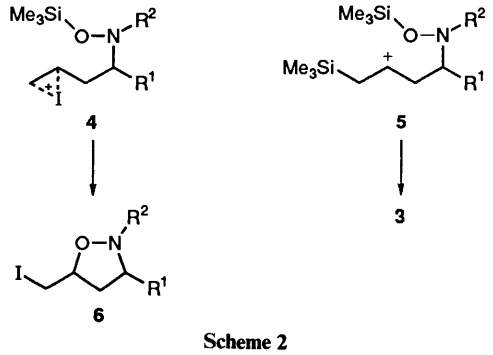
The reaction of nitrones **1** with η^1-allylic organometallic compounds can follow two alternative reaction pathways, depending on the nature of the metal involved (Scheme 1).



2 **1** **3**

Scheme 1 *Reagents:* i, CH_2=$CHCH_2MgCl$; ii, CH_2=$CHCH_2SiMe_3$

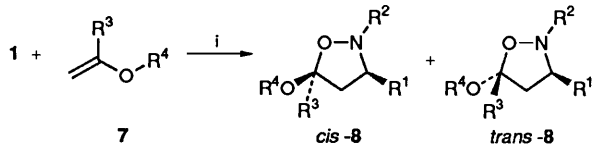
Allyl-magnesium and -zinc reagents, in analogy to the general behaviour displayed by organolithium and magnesium compounds,[1] give 1,3-addition to nitrones and lead to homoallylic hydroxylamines **2**[2] (path A). Allyltrimethylsilane, on the other hand, undergoes a thermal, concerted 1,3-dipolar cycloaddition to give 5-(trimethylsilylmethyl)isoxazolidines **3**[3] (path B). We recently re-examined these reactions and worked out novel approaches to the isoxazolidine ring system. They are based on the formation of *O*-silylated hydroxylamines **4** and **5** carrying an electrophilic centre at the γ position relative to the nitrogen atom, which spontaneously undergoes ring closure to products **6** and **3**, respectively (Scheme 2).



Scheme 2

The iodo adduct **4** was generated by the addition of an iodinating agent (*N*-iodosuccinimide, ICl) to the homoallylic hydroxylamine **2**, previously protected as its *O*-silyl derivative.[2]

Furthermore we found that the 1,3-dipolar cycloaddition of nitrones and allyltrimethylsilane can be catalysed by trimethylsilyl trifluoromethanesulfonate (TMSOTf).[4] In the presence of this promoter the reaction takes place at 0–20 °C, while the thermal process requires a higher temperature ($T \geqslant 100$ °C).[3] Under these conditions the reaction was proposed to occur *via* the intermediate carbonium ion **5** which undergoes cyclisation to the isoxazolidine **3**. As an extension of the latter work,[5] we recently reported preliminary results obtained in the TMSOTf-promoted 1,3-dipolar cycloaddition of nitrones and silyl enol ethers **7**, which, in analogy to allyltrimethylsilane, react under mild conditions ($T \leqslant 0$ °C) and give 5-siloxyisoxazolidines **8** (Scheme 3).†



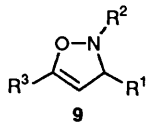
7 *cis*-**8** *trans*-**8**

Scheme 3 *Reagents and conditions:* i, TMSOTf, 0 °C

We now report further results of this TMSOTf-promoted reaction, and consider also possible elaborations of the isoxazolidines **8**.

Results and Discussion

We carried out a number of cycloadditions of simple (*Z*)-aldonitrones with four model silyl enol ethers **7** lacking α-substituents, in the presence of an equimolecular amount of TMSOTf in dichloromethane, at temperatures ranging from −20 to 20 °C. Besides isoxazolidines **8**, 2,3-dihydroisoxazoles **9** are sometimes present as secondary products. The results are collected in Table 1.



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When the steric demand of substituents is not severe, conversions into 5-siloxyisoxazolidines **8** are good to excellent and isolated yields range from 70 to 92%. Exceptions are found in run 5 (R^1 = Bu^t), run 7 (R^1 = Me_2C=CH), and run 8 (R^4 = $SiBu^tPh_2$).

It is possible to carry out the reactions using catalytic amounts of TMSOTf (runs 2, 3), but higher reaction times or temperatures are required to achieve acceptable conversions. A detrimental effect of either prolonging the reaction time or increasing the reaction temperature is given by the formation of appreciable amounts of 2,3-dihydroisoxazoles **9**. It is worthy of note that there is an absence of 2,3-dihydroisoxazoles **9** when acetaldehyde silyl enol ethers are used under our standard conditions (1 mol equiv. of TMSOTf, 24 h, −10 to 0 °C), while they represent the major side-product when acetone and aceto-

† Ketene silyl acetals and Reformatsky reagents, more reactive than simple silyl enol ethers, do not require any activator for the addition to nitrones, which affords 5-isoxazolidinones at room temperature or below.[6]

Table 1 TMSOTf-promoted 1,3-dipolar cycloadditions[a]

Run	1		7			Product 8		Product 9
	R^1	R^2	R^3	R^4	T(°C)	(yield/%)	*cis*/*trans*	(yield/%)
1	Et	CH_2Ph	H	$SiBu^tMe_2$	−10	**8a** (92)	70/30	**9a** (0)
2	Et	CH_2Ph	H	$SiBu^tMe_2$	0	**8a** (42)[b,c]	58/42	**9a** (17)
3	Et	CH_2Ph	H	$SiBu^tMe_2$	20	**8a** (64)[b]	50/50	**9a** (32)
4	Pr^i	CH_2Ph	H	$SiBu^tMe_2$	−10	**8b** (95)	38/62	**9b** (0)
5	Bu^t	CH_2Ph	H	$SiBu^tMe_2$	−20	**8c** (52)	40/60	**9c** (0)
6	Ph	Me	H	$SiBu^tMe_2$	0	**8d** (87)	36/74	**9d** (0)
7	$Me_2C{=}CH$	CH_2Ph	H	$SiBu^tMe_2$	20	**8e** (59)	22/78	**9e** (0)
8	Et	CH_2Ph	H	$SiBu^tPh_2$	0	**8f** (28)	80/20	**9f** (0)
9	Et	CH_2Ph	Me	$SiMe_3$	0	**8g** (91)	35/65	**9g** (6)
10	Et	CH_2Ph	Me	$SiMe_3$	20	**8g** (70)[b]	40/60	**9g** (30)
11	Pr^i	CH_2Ph	Me	$SiMe_3$	0	**8h** (88)	40/60	**9h** (8)
12	Ph	Me	Me	$SiMe_3$	0	**8i** (77)	40/60	**9i** (15)
13	Et	CH_2Ph	Ph	$SiMe_3$	0	**8j** (76)[d]	50/50	**9j** (19)
14	Pr^i	CH_2Ph	Ph	$SiMe_3$	0	**8k** (74)[e]	55/45	**9k** (21)

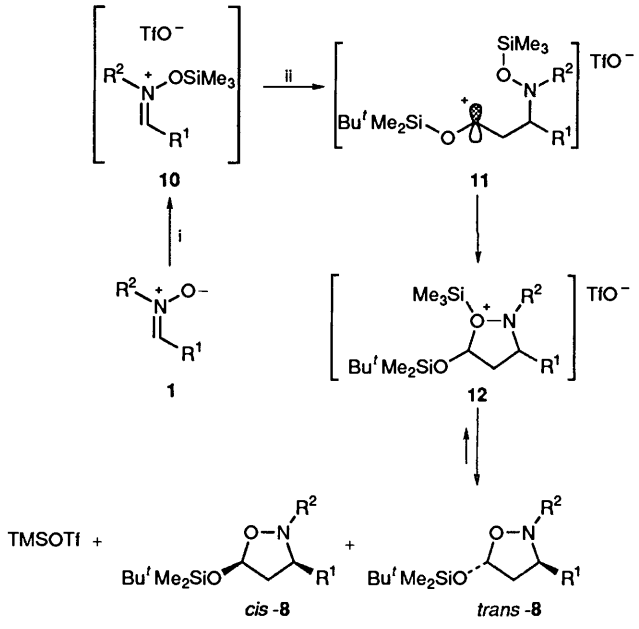
[a] All reactions were carried out in the presence of 1.0 mol equiv. of TMSOTf in 24 h, unless otherwise stated. [b] 0.1 Mol equiv. of TMSOTf was used. [c] Reaction was run for 67 h. [d] Yields were determined by ^1H NMR analysis of the reaction mixture; an attempted separation by flash chromatography of *cis* and *trans* isomers gave high conversion of compound **8j** into compound **9j**. [e] Yields were determined by GCMS analysis of the crude reaction mixture; flash chromatography gave almost complete conversion of compound **8k** into compound **9k**.

phenone silyl enol ethers are used (runs 9–14). Such observations can be accounted for by the greater stability of the C=C double bond in 5-substituted 2,3-dihydroisoxazoles, particularly when R^3 = Ph (runs 13, 14). In this regard, attempts to purify isoxazolidines **8j, k** by flash-chromatography failed since they were almost quantitatively converted by silica gel into compounds **9j, k**.

cis–trans Diastereoselectivity is in general poor, the best results being obtained in the case of *cis*-isoxazolidines **8a** (d.e. 40%)* and **8f** (d.e. 60%) (runs 1, 8) and in the case of *trans*-isoxazolidines **8d** (d.e. 38%) and **8e** (d.e. 56%) (runs 6,7). *cis*- and *trans*-Isoxazolidines **8** are not configurationally stable; in fact, they are in general easily separated by flash chromatography but undergo partial *cis–trans* equilibration in a few hours in the presence of catalytic amounts of TMSOTf in CH_2Cl_2, as well as upon storage in the pure state at room temperature within a month. For example, *cis*-**8d** is converted into a 56/44 mixture of *trans*-**8d** and *cis*-**8d** after being stirred with 1 mol equiv. of TMSOTf in $CHCl_3$ at 0 °C for 3.5 h.

The assignment of the *cis* and *trans* stereochemistry to isoxazolidines **8** was made possible by the general observation that R_f-values of *cis* isomers are always higher than those of *trans* forms, and that multiplets relative to 4-H protons of *cis* isomers are broader in ^1H NMR spectra, better resolved, and well separated [2–4] (see Tables 2 and 3) compared with those for the *trans* isomers. In the case of 5-disubstituted isoxazolidines **8g–j**, NOE experiments confirmed the proposed stereochemical assignments.

We propose, for the TMSOTf-promoted cycloaddition process, the reaction mechanism depicted in Scheme 4. The first step involves the silylation of nitrone **1** by TMSOTf to give *O*-siloxyiminium ion **10**. The evidence of the formation of intermediate **10** was obtained by recording the NMR spectra of *N*-propylidenebenzenemethanamine *N*-oxide in the presence of 1 mol equiv. of TMSOTf in $CDCl_3$. The comparison between δ-values in the presence and in the absence of TMSOTf (Table 4) unambiguously confirmed that a strong complexation occurs. The subsequent 1,3-addition of silyl enol ether to intermediate **10** affords, in our opinion, the positively charged intermediate **11**, which then cyclises to give oxonium species **12**. Elimination of TMSOTf from intermediate **12** generates *cis*- and *trans*-**8** as products. The last process is reversible; in fact, the ^1H NMR spectrum of pure isoxazolidine *trans*-**8a** treated with 1 mol equiv. of TMSOTf shows, after 5 min, a general line-broadening and deshielding of all signals. In particular, 5-H is shifted downfield by 0.28 ppm, 3-H by 0.44 ppm, the two benzylic CH_2s by 0.37 and 0.32 ppm, respectively, and, finally, the multiplets of the two 4-H protons collapse to δ 2.41. These observations make us believe that oxonium ion **12** is actually in fast equilibrium with other species, namely **13** and **14** (Scheme 5).



Scheme 4 *Reagents:* i, TMSOTf; ii, $CH_2{=}CHOSiMe_2Bu^t$

Formation of hydroxylaminium ion **13** is supported by the observation that the strongest deshielding among the various protons is shown by 3-H and benzylic protons. This is consistent with the fact that the energy of a nitrogen lone pair is generally higher than that of an oxygen lone pair, the energy gap being amplified by the so-called α-effect when N–O bonds are involved. As concerns oxonium species **14**, it is responsible for the partial silyl scrambling observed in runs 1–7. In fact, when acetaldehyde *tert*-butyldimethylsilyl enol ether was used, we always observed, besides 5-(*tert*-butyldimethylsiloxy)isoxazolines **8a–e**, small amounts (generally limited to less than 5%) of 5-(trimethylsiloxy)isoxazolidines. These products have slightly lower R_f-values than do the corresponding *tert*-butyldimethylsiloxyisoxazolidines and arise by detachment of *tert*-butyl-

* Diastereoisomeric excess.

Table 2 ^{1}H NMR data for compounds **8** and **9** at 300 MHz

Compd.	3-H	4-H	5-H	Others
cis-**8a**	2.66–2.75 (m)	1.95 (ddd, *J* 2.4, 7.2, 12.6), 2.60 (ddd, *J* 6.0, 7.7, 12.6)	5.52 (dd, *J* 2.4, 6.0)	0.01 (3 H, s, SiMe), 0.03 (3 H, s, SiMe), 0.86 (9 H, s, SiBu^t), 0.91 (3 H, t, *J* 7.4, CH_2*Me*), 1.45–1.75 (2 H, m, CH_2Me), 3.81 (1 H, d, *J* 13.8, CH_2Ph), 4.03 (1 H, d, *J* 13.8, CH_2Ph), 7.23–7.42 (5 H, m, Ph)
trans-**8a**	3.11–3.25 (m)	2.08 (ddd, *J* 4.8, 8.4, 12.3), 2.38 (ddd, *J* 1.0, 6.4, 12.3)	5.51 (dd, *J* 1.0, 4.8)	0.12 (3 H, s, SiMe), 0.14 (3 H, s, SiMe), 0.89 (3 H, t, *J* 7.5, CH_2*Me*), 0.94 (9 H, s, SiBu^t), 1.34–1.45 (1 H, m, CH_2Me), 1.46–1.59 (1 H, m, CH_2Me), 4.08 (1 H, d, *J* 13.2, CH_2Ph), 4.25 (1 H, d, *J* 13.2, CH_2Ph), 7.22–7.46 (5 H, m, Ph)
cis-**8b**	2.61–2.72 (m)	2.06 (ddd, *J* 1.8, 6.3, 12.9), 2.37 (ddd, *J* 5.9, 8.7, 12.9)	5.52 (dd, *J* 1.8, 5.9)	0.01 (3 H, s, SiMe), 0.02 (3 H, s, SiMe), 0.85 (9 H, s, SiBu^t), 0.91 (3 H, d, *J* 6.8, CHMe_2), 0.94 (3 H, d, *J* 6.8, CHMe_2), 1.90 (1 H, octet, *J* 6.7, C*H*Me$_2$), 3.83 (1 H, d, *J* 13.7, CH_2Ph), 3.98 (1 H, d, *J* 13.7, CH_2Ph), 7.23–7.42 (5 H, m, Ph)
trans-**8b**[a]	3.02–3.12 (m)	2.11–2.17 (m, B), 2.17–2.25 (m, A), 2.29 (ddd, *J* 1.4, 3.9, 7.2, A), 2.30–2.36 (m, B)	5.49 (dd, *J* 1.4, 4.7)	0.10 (1.2 H, s, SiMe, B), 0.13 (1.2 H, s, SiMe, B), 0.17 (3.6 H, s, SiMe, A), 0.87 (1.8 H, d, *J* 6.7, CHMe_2, A), 0.88 (1.8 H, d, *J* 6.7, CHMe_2, A), 0.91 (1.2 H, d, *J* 6.7, CHMe_2, B), 0.92 (1.2 H, d, *J* 6.7, CHMe_2, B), 0.93 (9 H, s, SiBu^t), 1.68 (1 H, m, C*H*Me$_2$), 4.06 (1H, broad d, *J* 13.4, CH_2Ph), 4.28 (0.4 H, d, *J* 13.4, CH_2Ph, B), 4.30 (0.6 H, d, *J* 13.4, CH_2Ph, A), 7.21–7.43 (5 H, m, Ph)
cis-**8c**	2.75 (dd, *J* 5.1, 10.2)	2.05 (ddd, *J* 2.7, 5.1, 13.1), 2.46 (ddd, *J* 5.9, 10.2, 13.1)	5.57 (dd, *J* 2.7, 5.9)	0.01 (3 H, s, SiMe), 0.02 (3 H, s, SiMe), 0.85 (9 H, s, Bu^t), 0.93 (9 H, s, SiBu^t), 3.92 (1 H, d, *J* 13.7, CH_2Ph), 4.03 (1 H, d, *J* 13.7, CH_2Ph), 7.21–7.45 (5 H, m, Ph)
trans-**8c**	3.10 (t, *J* 7.7)	2.20–2.35 (2 H, m)	5.47–5.53 (m)	0.09 (3 H, s, SiMe), 0.10 (3 H, s, SiMe), 0.84 (9 H, s, Bu^t), 0.93 (9 H, s, SiBu^t), 4.05 (1 H, d, *J* 13.6, CH_2Ph), 4.44 (1 H, d, *J* 13.6, CH_2Ph), 7.21–7.45 (5 H, m, Ph)
cis-**8d**	3.46 (m)	2.34 (ddd, *J* 2.6, 9.4, 13.1), 2.92 (ddd, *J* 6.1, 8.1, 13.1)	5.57 (dd, *J* 2.6, 6.1)	0.16 (3 H, s, SiMe), 0.20 (3 H, s, SiMe), 0.96 (9 H, s, SiBu^t), 2.58 (3 H, s, NMe), 7.28–7.48 (5 H, m, Ph)
trans-**8d**	4.04 (br t, *J* ~ 8.6)	2.44–2.50 (2 H, m)	5.56 (m)	0.16 (3 H, s, SiMe), 0.19 (3 H, s, SiMe), 0.96 (9 H, s, SiBu^t), 2.82 (3 H, s, NMe), 7.28–7.45 (5 H, m, Ph)
cis-**8e**	3.37–3.48 (m)	2.02 (ddd, *J* 3.2, 9.7, 12.9), 2.60 (dt, *J* 6.4, 12.9)	5.45 (dd, *J* 3.2, 6.4)	−0.06 (3 H, s, SiMe), −0.02 (3 H, s, SiMe), 0.81 (9 H, s, SiBu^t), 1.67 (3 H, s, Me), 1.72 (3 H, s, Me), 3.61 (1 H, d, *J* 14.1, CH_2Ph), 4.02 (1 H, d, *J* 14.1, CH_2Ph), 5.25 (1 H, d, *J* 9.1, CH=), 7.18–7.40 (5 H, m, Ph)
trans-**8e**	3.95–4.07 (m)	2.10–2.24 (2 H, m)	5.42–5.47 (m)	0.10 (3 H, s, SiMe), 0.14 (3 H, s, SiMe), 0.93 (9 H, s, SiBu^t), 1.67 (3 H, s, Me), 1.72 (3 H, s, Me), 3.95–4.07 (2 H, m, CH_2Ph), 5.16 (1 H, d, *J* 9.1, CH=), 7.22–7.39 (5 H, m, Ph)
cis-**8f**	2.67–2.83 (m)	2.15 (ddd, *J* 2.4, 7.2, 12.7), 2.60 (ddd, *J* 6.1, 7.7, 12.7)	5.46 (dd, *J* 2.4, 6.1)	0.99 (3 H, t, *J* 7.2, CH_2*Me*), 1.02 (9 H, s, SiBu^t), 1.55–1.85 (2 H, m, CH_2Me), 3.80 (1 H, d, *J* 13.7, CH_2Ph), 4.03 (1 H, d, *J* 13.7, CH_2Ph), 7.25–7.46 (10 H, m, Ph), 7.62–7.75 (5 H, m, Ph)
trans-**8f**	3.26–3.38 (m)	2.08 (ddd, *J* 4.7, 8.0, 13.1), 2.46–2.57 (m)	5.52 (d, *J* 4.7)	0.91 (3 H, t, *J* 7.2, CH_2*Me*), 1.10 (9 H, s, SiBu^t), 1.48–1.75 (2 H, m, CH_2Me), 4.21 (1 H, d, *J* 13.4, CH_2Ph), 4.42 (1 H, d, *J* 13.4, CH_2Ph), 7.28–7.48 (10 H, m, Ph), 7.65–7.78 (5 H, m, Ph)
cis-**8g**	2.66–2.80 (m)	2.16 (dd, *J* 9.4, 12.5), 2.40 (dd, *J* 7.4, 12.5)		0.01 (9 H, s, $SiMe_3$), 0.92 (3 H, t, *J* 7.4, CH_2*Me*), 1.47 (3 H, s, 5-Me), 1.52–1.77 (2 H, m, CH_2Me), 3.75 (1 H, d, *J* 13.5, CH_2Ph), 4.03 (1 H, d, *J* 13.5, CH_2Ph), 7.22–7.42 (5 H, m, Ph)
trans-**8g**	3.15–3.27 (m)	1.94 (dd, *J* 9.4, 12.1), 2.49 (dd, *J* 6.4, 12.1)		0.21 (9 H, s, $SiMe_3$), 0.86 (3 H, t, *J* 7.4, CH_2*Me*), 1.54 (3 H, s, 5-Me), 1.61–1.75 (2 H, m, CH_2Me), 4.07 (1 H, d, *J* 13.2, CH_2Ph), 4.27 (1 H, d, *J* 13.2, CH_2Ph), 7.21–7.42 (5 H, m, Ph)
cis-**8h**	2.67–2.79 (m)	2.10–2.30 (2 H, m)		0.01 (9 H, s, $SiMe_3$), 0.91 (3 H, d, *J* 6.7, CHMe_2), 0.96 (3 H, d, *J* 6.7, CHMe_2), 1.47 (3 H, s, 5-Me), 1.81–1.96 (1 H, m, C*H*Me$_2$), 3.72 (1 H, d, *J* 13.5, CH_2Ph), 4.02 (1 H, d, *J* 13.5, CH_2Ph), 7.25–7.46 (5 H, m, Ph)
trans-**8h**	3.11 (dt, *J* 7.0, 9.4)	2.02 (dd, *J* 9.4, 12.2), 2.41 (dd, *J* 7.0, 12.2)		0.21 (9 H, s, $SiMe_3$), 0.89 (3 H, d, *J* 6.7, CHMe_2), 0.92 (3 H, d, *J* 6.7, CHMe$_2$), 1.54 (3 H, s, 5-Me), 1.62–1.75 (1 H, m, C*H*Me$_2$), 4.06 (1 H, d, *J* 13.7, CH_2Ph), 4.36 (1 H, d, *J* 13.7, CH_2Ph), 7.21–7.46 (5 H, m, Ph)
cis-**8i**	3.52 (dd, *J* 7.7, 10.0)	2.52 (dd, *J* 10.0, 12.8), 2.67 (dd, *J* 7.7, 12.8)		0.26 (9 H, s, $SiMe_3$), 1.56 (3 H, s, 5-Me), 2.54 (3 H, s, NMe), 7.25–7.47 (5 H, m, Ph)
trans-**8i**	4.04 (dd, *J* 5.8, 11.0)	2.32 (br t, *J* ~ 11.5), 2.58 (dd, *J* 5.8, 12.0)		0.25 (9 H, s, $SiMe_3$), 1.61 (3 H, s, 5-Me), 2.76 (3 H, s, NMe), 7.23–7.46 (5 H, m, Ph)
cis-**8j**	2.83–2.95 (m)	2.46 (dd, *J* 8.9, 12.7), 2.56 (dd, *J* 7.5, 12.7)		−0.12 (6 H, s, $SiMe_3$), 0.00 (3 H, s, $SiMe_3$), 0.87 (3 H, t, *J* 7.4, CH_2*Me*), 1.60–1.78 (2 H, m, CH_2Me), 3.98 (1 H, d, *J* 13.2, CH_2Ph), 4.13 (1 H, d, *J* 13.2, CH_2Ph), 7.25–7.56 (10 H, m, Ph)
trans-**8j**	3.29–3.40 (m)	2.14 (dd, *J* 10.2, 12.2), 2.81 (dd, *J* 5.6, 12.2)		0.19 (9 H, s, $SiMe_3$), 0.90 (3 H, t, *J* 7.4, CH_2*Me*), 1.51–1.68 (2 H, m, CH_2Me), 4.23 (1 H, d, *J* 13.6, CH_2Ph), 4.34 (1 H, d, *J* 13.6, CH_2Ph), 7.25–7.57 (10 H, m, Ph)
trans-**8k**	3.27 (dt, *J* 6.3, 10.0)	2.24 (dd, *J* 10.0, 12.2), 2.72 (dd, *J* 6.3, 12.2)		−0.02 (9 H, s, $SiMe_3$), 0.86 (3 H, d, *J* 6.9, CHMe_2), 0.92 (3, H, d, *J* 6.9, CHMe_2), 1.65–1.75 (1 H, m, C*H*Me$_2$), 4.23 (1 H, d, *J* 14.0, CH_2Ph), 4.39 (1 H, d, *J* 14.0, CH_2Ph), 7.25–7.57 (10 H, m, Ph)
9g	3.62–3.73 (m)	4.53 (d, *J* 2.3)		1.81 (3 H, t, *J* 7.4, CH_2*Me*), 1.37–1.48 (2 H, m, CH_2Me), 1.85 (3 H, s, 5-Me), 3.84 (1 H, d, *J* 12.7, CH_2Ph), 4.19 (1 H, d, *J* 12.7, CH_2Ph), 7.25–7.46 (5 H, m, Ph)
9h	3.49 (dq, *J* 1.1, 6.6)	4.52 (q, *J* 1.1)		0.82 (6 H, d, *J* 6.6, CHMe_2), 1.50–1.62 (1 H, octet, *J* 6.6, C*H*Me$_2$), 1.85 (3 H, t, *J* 1.1, Me), 3.81 (1 H, d, *J* 12.9, CH_2Ph), 4.16 (1 H, d, *J* 12.9, CH_2Ph), 7.25–7.46 (5 H, m, Ph)

Table 2 (*continued*)

Compd.	3-H	4-H	5-H	Others
9i	4.62–4.71 (m)	4.62–4.71 (m)		1.92 (3 H, s, 5-Me), 2.90 (3 H, s, NMe), 7.23–7.46 (5 H, m, Ph)
9j	3.88 (dt, *J* 2.7, 6.9)	5.33 (d, *J* 2.7)		0.89 (3 H, t, *J* 7.4, CH_2Me), 1.49–1.63 (2 H, m, CH_2Me), 3.90 (1 H, d, *J* 12.6, CH_2Ph), 4.32 (1 H, d, *J* 12.6, CH_2Ph), 7.25–7.58 (10 H, m, Ph)
9k	3.69 (dd, *J* 2.8, 6.8)	5.32 (d, *J* 2.8)		0.87 (3 H, d, *J* 6.8, $CHMe_2$), 0.90 (3 H, d, *J* 6.8, $CHMe_2$), 1.65–1.75 (1 H, octet, *J* 6.8, $CHMe_2$), 3.87 (1 H, d, *J* 12.6, CH_2Ph), 4.29 (1 H, d, *J* 12.6, CH_2Ph), 7.25–7.57 (10 H, m, Ph)

[a] Two invertomers A and B were observed in the ratio 60:40.

Table 3 ^{13}C NMR data for compounds **8** and **9** at 75 MHz

Compd.	C-3	C-4	C-5	CH_2Ph	Ph	NMe	Others
cis-**8a**	67.0	44.3	96.0	61.1	126.8, 127.9, 129.1, 137.7		−5.2 (MeSi), −4.4 (MeSi), 10.9 ($MeCH_2$), 17.8 (Me_3C), 25.4 ($MeCH_2$), 25.7 (Me_3C)
trans-**8a**	65.4	44.4	98.1	64.9	127.0, 128.2, 129.1, 138.3		−5.2 (MeSi), −4.1 (MeSi), 11.1 ($MeCH_2$), 17.9 (Me_3C), 25.7 (Me_3C), 27.0 ($MeCH_2$)
cis-**8b**	70.3	39.9	96.4	61.8	126.9, 127.9, 129.2, 138.0		−5.2 (MeSi), −4.3 (MeSi), 17.5 (Me_2CH), 17.8 (Me_3C), 20.7 (Me_2CH), 25.7 (Me_3C), 29.3 (Me_2CH)
trans-**8b**[a]	69.5	41.5, 41.8	98.5, 98.7	65.5, 65.7	126.9, 128.1, 128.9, 138.7		−5.2 (MeSi), −4.1 (MeSi), 0.2 (2 × MeSi), 17.9 (Me_3C), 18.5 (Me_2CH), 18.6 (Me_2CH), 20.3 (2 × Me_2CH), 25.7 (Me_3C), 31.5 (Me_2CH), 31.6 (Me_2CH)
cis-**8c**	73.1	40.1	97.0	64.4	126.8, 127.9, 129.1, 138.2		−5.4 (MeSi), −4.4 (MeSi), 17.8 (Me_3CSi), 25.7 (Me_3CSi), 27.2 (Me_3C), 33.8 (Me_3C)
trans-**8c**	72.5	40.5	99.9	66.7	126.8, 128.0, 128.9, 139.0		−5.4 (MeSi), −4.2 (MeSi), 17.8 (Me_3CSi), 25.7 (Me_3CSi), 26.5 (Me_3C), 33.5 (Me_3C)
cis-**8d**	73.6	50.1	95.8		127.8, 128.0, 128.5, 138.7	43.2	−4.9 (MeSi), −4.1 (MeSi), 18.0 (Me_3C), 25.8 (Me_3C)
trans-**8d**	70.2	48.9	97.0		127.4, 127.5, 128.4, 139.3	46.5	−5.1 (MeSi), −4.0 (MeSi), 17.8 (Me_3C), 25.7 (Me_3C)
cis-**8e**	59.9	46.3	95.9	65.2	126.7, 127.8, 128.8, 138.0		−5.1 (MeSi), −4.4 (MeSi), 17.9 (=CMe_2), 18.4 (=CMe_2), 18.4 (Me_3C), 25.9 (Me_3C), 122.4 (CH=), 136.7 (=CMe_2)
trans-**8e**	62.3	45.5	96.9	63.3	126.9, 128.1, 128.9, 138.3		−5.1 (MeSi), −4.0 (MeSi), 17.9 (=CMe_2), 18.2 (=CMe_2), 18.2 (Me_3C), 25.7 (Me_3C), 123.1 (CH=), 135.9 (=CMe_2)
cis-**8f**	67.0	44.3	96.3	61.2	126.9, 127.3, 127.5, 127.7, 128.0, 129.1, 129.4, 129.5, 133.4, 133.9, 135.6, 135.9 137.8		10.9 ($MeCH_2$), 19.1 (Me_3C), 25.5 ($MeCH_2$), 26.6 (Me_3C)
trans-**8f**	65.4	44.4	98.6	65.5	127.6, 127.7, 128.2, 129.2, 129.6, 129.7, 134.8, 135.2, 135.5, 135.8		11.1 ($MeCH_2$), 19.0 (Me_3C), 26.6 (Me_3C), 26.9 ($MeCH_2$)
cis-**8g**	68.3	50.4	103.3	61.4	126.9, 127.8, 129.6, 137.7		1.5 (Me_3Si), 10.6 ($MeCH_2$), 24.9 (5-Me), 29.0 ($MeCH_2$)
trans-**8g**	67.0	49.5	105.4	64.2	126.9, 128.1, 128.9, 138.2		2.0 (Me_3Si), 11.0 ($MeCH_2$), 26.7 (5-Me), 30.1 ($MeCH_2$)
cis-**8h**	72.0	45.0	103.7	62.1	127.0, 127.9, 129.7, 138.2		1.4 (Me_3Si), 17.3 (Me_2CH), 20.9 (Me_2CH), 24.5 (5-Me), 29.2 (Me_2CH)
trans-**8h**	71.2	46.8	105.9	65.2	126.8, 128.1, 128.8, 138.7		1.9 (Me_3Si), 18.3 (Me_2CH), 20.5 (Me_2CH), 26.2 (5-Me), 31.4 (Me_2CH)
cis-**8i**	74.4	55.6	103.4		127.8, 127.9, 128.5, 138.8	43.0	1.8 (Me_3Si), 28.5 (5-Me)
trans-**8i**	71.7	53.8	104.6		127.5, 127.7, 128.1, 128.2, 139.9.	45.5	2.1 (Me_3Si), 29.7 (5-Me)
cis-**8j**	68.1	53.1	104.2	61.5	125.6, 125.7, 127.1, 127.5, 127.9, 128.4, 128.8, 129.2 136.6, 145.4		1.1 (Me_3Si), 10.6 ($MeCH_2$), 25.0 ($MeCH_2$)
trans.**8j**	67.2	51.9	105.7	63.5	125.8, 127.0, 127.4, 127.8, 128.4, 129.6, 138.2, 144.0		1.7 (Me_3Si), 11.0 ($MeCH_2$), 25.7 ($MeCH_2$)
trans-**8k**	70.8	48.1	106.0	64.1	125.8, 126.8, 127.6, 127.7, 128.4, 129.0, 139.2		1.7 (Me_3Si), 17.7 (Me), 20.6 (Me), 30.1 (Me_2CH)
9j	71.8	95.3	152.2	63.2	125.5, 127.0, 127.1, 127.3, 127.4, 127.6, 128.0, 128.3, 128.4, 128.5, 128.7, 129.8, 136.6		9.9 (CH_2Me), 29.2 (CH_2Me)
9k	76.4	93.5	152.4	63.8	125.5, 127.3, 128.1, 128.2, 128.3, 129.6, 136.7		18.2 (Me), 18.5 (Me), 33.7 (Me_2CH)

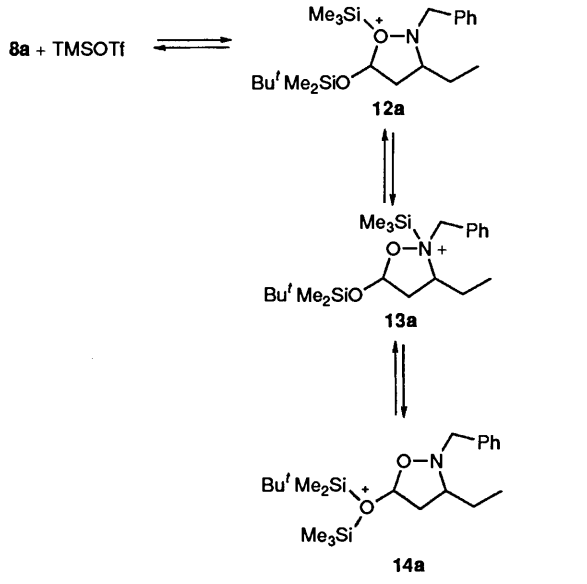
[a] Two invertomers were observed in the ratio 60:40.

dimethylsilyl trifluoromethanesulfonate from oxonium intermediate **14**. Moreover, intermediate **14** is probably responsible for the already mentioned TMSOTf-induced *cis–trans* equilibration of compounds **8**.

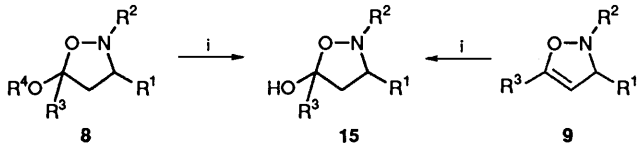
5-Siloxyisoxazolidines **8** are versatile synthetic intermediates. First of all, acidic protodesilylation of compounds **8** occurs in good yield by the action of aqueous trifluoroacetic acid (TFA) at 20 °C. For example, diastereoisomeric mixtures of *cis*- and *trans*-**8a**,-**8d** and -**8i** were converted into the corresponding 5-hydroxyisoxazolidines **15a**, **15d** and **15i**, which were isolated by flash chromatography. The same 5-hydroxyisoxazolidines **15** could be obtained by TFA-promoted hydration of 2,3-dihydroisoxazoles **9** (Scheme 6).

cis- and *trans*-5-Hydroxyisoxazolidines **15** undergo fast equilibration (ring–chain tautomerism) and appear as single spots on TLC using different solvents (traces of open product

are detected in the $\nu_{C=O}$ region of the IR spectrum of compound **15i**). It is interesting to note that while isoxazolidines **15g–k**, deriving from ketone silyl enol ethers, could be obtained, in principle, following a different route, namely the conjugate addition of *N*-alkylhydroxylamines to α,β-unsaturated ketones [7] (the analogous reaction involving α,β-unsaturated esters is known to lead to isoxazolidin-5-ones [8]), no reports are found in the literature about the analogous addition to α,β-unsaturated aldehydes, which should give access to isoxazolidines **15a–f**.* We demonstrated that the reaction of *N*-benzylhydroxylamine hydrochloride in aq. ethanol with 3-methylbut-2-enal in the presence of sodium acetate regioselectively affords, *via* 1,3-addition, 3-methyl-but-2-enylidenebenzylamine *N*-oxide (used in run 7 of Table 1).

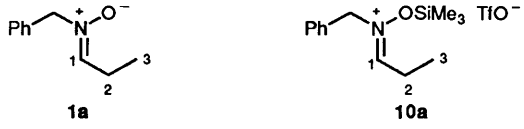


Scheme 5



Scheme 6 *Reagents:* i, aq. TFA

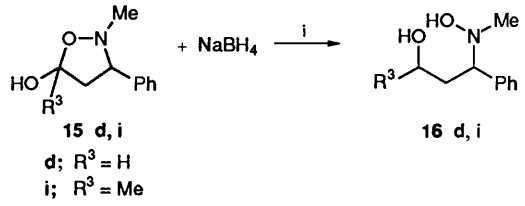
Table 4 NMR spectra of *N*-propylidene-*N*-trimethylsiloxybenzylammonium triflate **10a** and the corresponding nitrone **1a**



	δ	δ
1-H	6.60 (t, *J* 5.8)	8.60 (br s)[a]
2-H_2	2.47 (dq, *J* 5.8, 7.7)	2.75 (dq, *J* 5.8, 7.7)
3-H_3	1.05 (t, *J* 7.7)	1.28 (t, *J* 7.7)
PhCH_2	4.85 (s)	5.33 (s)
Ph	7.37 (pseudo-s)	7.45 (pseudo-s)
$SiMe_3$		0.48 (s)
C-1	140.5	167.4
C-2	20.1	22.6
C-3	9.8	8.8
PhCH_2	68.9	66.0
Ph	132.8, 129.1, 128.8	130.6, 130.2, 129.6
$SiMe_3$		1.9

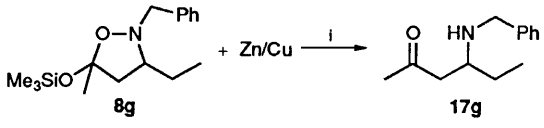
[a] Upon irradiation at δ_H 8.60, the signal at δ_H 2.75 appears as a quartet (*J* 7.7 Hz).

The second aspect of the chemistry of isoxazolidines we wish to discuss is the possibility of carrying out different chemoselective reductions to open-chain derivatives. An example is offered by the reaction of compound **15d** with $NaBH_4$ which affords hydroxylamino alcohol **16d** in high yield (Scheme 7).



Scheme 7 *Solvent:* i, MeOH

On the other hand, reduction of 5-siloxyisoxazolidines derived from ketone silyl enol ethers, such as compound **8g**, with Zn/Cu couple in hot aq. acetic acid gives 4-(benzylamino)hexan-2-one **17g** *via* a chemoselective reduction of the N–O bond (Scheme 8). The two-step sequence involving nitrone silyl enol ether cycloaddition followed by Zn/Cu couple reduction represents a synthetic alternative to the Mannich reaction.



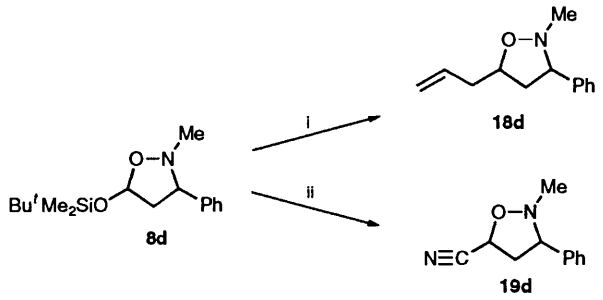
Scheme 8 *Solvent:* i, AcOH

The last topic we wish to discuss are the preliminary results on the most interesting reactions applied to isoxazolidines **8** from a synthetic point of view, since they construct a new carbon–carbon bond. The goal was to add silylated carbon nucleophiles to isoxazolidines **8** in the presence of Lewis acids.[10] Model isoxazolidine **8d** was found to be less reactive than simple acetals, and cross-coupling reactions with allyltrimethylsilane and cyanotrimethylsilane could only be effected in the presence of TMSOTf at 50–75 °C (Scheme 9, Table 5), while other classical Lewis acids like BF_3·OEt_2, ZnI_2, $TiCl_4$ proved to be ineffective. Under these conditions *cis*- and *trans*-**8** undergo a fast equilibration but, unfortunately, no good diastereoselectivity in the formation of the new stereogenic C-5 centre was achieved as a consequence of thermodynamic control. Since the most likely reactive intermediate involved in the coupling reaction corresponds to species **14**, that is the product of the cycloaddition, it is possible to carry out the processes in one

* The formation of a 5-hydroxyisoxazolidine by the lithium enolate of acetaldehyde addition to nitrones has been recently reported,[9] but the reaction seems to be limited to *N*,*C*-diaryl nitrones.

Table 5 TMSOTf-Promoted coupling of compound **8d** with silylated carbon nucleophiles

Run	Nucleophile	Solvent	*T*(°C)	*t*(h)	Product	Yield(%) (*cis*/*trans*)
1	allyltrimethylsilane	$CHCl_3$	75	8	**18d**	60 (45/55)
2	allyltrimethylsilane	toluene	70	5	**18d**	44 (15/85)
3	cyanotrimethylsilane	$CHCl_3$	50	8	**19d**	53 (70/30)



Scheme 9 *Reagents:* i, CH_2=$CHCH_2SiMe_3$, TMSOTf; ii, Me_3SiCN, TMSOTf

pot by exploiting the same TMSOTf to promote both the cycloaddition and the coupling reactions. So, after having stirred *N*-benzylidenemethylamine *N*-oxide with 1.4 mol equiv. of TMSOTf and 1.1 mol equiv. of *tert*-butyl(dimethyl)vinyloxysilane in $CHCl_3$ at 0 °C for 23 h, it is sufficient to add allyltrimethylsilane (3 mol equiv.) and to heat at 60 °C for 7 h. *cis*- and *trans*-2-Methyl-3-phenyl-5-(prop-2-enyl)isoxazolidines (*cis*- and *trans*-**18d**) were formed in the ratio 55:45 and were isolated, after the usual work-up, in 44% overall yield.

Unfortunately, silyl enol ethers cannot be used in TMSOTf-mediated cross-coupling reactions with isoxazolidines **8** since the reaction product is more reactive towards the nucleophile than is substance **8**, and oligomerisation cannot be suppressed.

Conclusions

The cycloaddition of nitrones and silyl enol ethers, when promoted by TMSOTf, takes place at 0 °C or below through a stepwise mechanism which involves a series of silylated intermediates. The final 5-siloxyisoxazolidines, again in the presence of TMSOTf, undergo a further reaction with a different silylated carbon nucleophile at the acetalic C-5 carbon under more drastic conditions (50–70 °C). This makes possible a three-component one-pot coupling process where the same TMSOTf promotes first the 1,3-dipolar cycloaddition of the nitrone and the silyl enol ether, and then the nucleophilic substitution reaction with the second silylated compound.

Besides this interesting approach to a variety of synthetically flexible 3,5-disubstituted isoxazolidines, we have shown that chemoselective reductions of 5-siloxyisoxazolidines leading to Mannich products and *N*-hydroxy-1,3-amino alcohols are possible.

Experimental

^{1}H NMR and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded at 300 and 75 MHz, respectively with a VARIAN GEMINI 300 spectrometer. Chemical shifts are reported in ppm relative to internal standard Me_4Si (δ). NMR spectra of products **8** and **9** are reported in Tables 2 and 3, NMR spectra of isoxazolidines **15**, **18** and **19** are collected in Tables 6 and 7. IR spectra were recorded on Perkin-Elmer PE 682 spectrophotometer. High-resolution mass spectra (HRMS) were obtained using a VG 7070 instrument at 70 eV. Gas chromatographic–mass spectrometric analyses (GCMS) were performed with an HP 5890 cross-linked methyl silicone glass capillary column (0.33 mm film thickness) connected to an HP 5970 quadrupole mass detector. The column temperature was programmed from 50 to 250 °C at 10 °C min^{-1} and was then held at 250 °C for 10 min. The helium carrier gas flow rate was 1 cm^3 min^{-1}. Analytical TLC was performed with Kieselgel 60 F_{254} plates and mixed solvents [cyclohexane (C), diethyl ether (E), ethyl acetate (A)]. Kieselgel 60 (230–400 mesh) was used for flash chromatography. Reactions were performed in oven-dried glassware under an atmosphere of dry argon. Dichloromethane and chloroform were purified before use (water content was 8 ± 1 ppm). All nitrones,[11] *tert*-butyl(dimethyl)vinyloxysilane,[12] *tert*-butyl(diphenyl)vinyloxysilane and trimethyl(1-phenylvinyloxy)silane[13] were prepared according to literature procedures; trimethyl-(1-methylvinyloxy)silane was purchased by Aldrich.

Reaction of N-*Propylidenebenzylamine* N-*Oxide with* tert-*Butyl(dimethyl)vinyloxysilane. General Procedure.*—To a stirred solution of nitrone **1a** (163 mg, 1 mmol) and silyl enol ether **7a** (0.24 g, 1.5 mmol) in dry dichloromethane (8 cm^3) was added drop-by-drop (10 min) a solution of TMSOTf (0.21 cm^3, 1.1 mmol) in dichloromethane (2 cm^3) at −10 °C. After 24 h, the reaction mixture was quenched with saturated aq. $NaHCO_3$ (2 cm^3); the two liquid layers were separated and the aqueous phase was extracted with diethyl ether (3 × 20 cm^3). The combined organic layers were washed with brine (1 cm^3), dried (Na_2SO_4), and evaporated to dryness. Flash chromatography (C–A 98:2) of the residue gave the products *cis*-**8a** (0.1 g, 28%) and *trans*-**8a** (0.2 g, 64%), as pale yellow oil.

cis-2-*Benzyl*-5-(tert-*butyldimethylsiloxy*)-3-*ethylisoxazolidine* cis-**8a** (Found: M$^+$, 321.2128 $C_{18}H_{31}NO_2Si$ requires M, 321.2124); TLC (C–E 85:15) R_f 0.71; *m/z* (%) 321 (M$^+$, 22), 292 (M$^+$ − Et, 10), 264 (M$^+$ − Bu^t, 6), 199 (M$^+$ − $PhCH_2NOH$, 100), 157 (27), 91 (CH_2Ph, 74) and 73 (53).

trans-2-*Benzyl*-5-(tert-*butyldimethylsiloxy*)-3-*ethylisoxazolidine* trans-**8a** (Found: M$^+$, 321.2121); TLC (C–E 85:15) R_f 0.43; *m/z* (%) 321 (M$^+$, 20), 292 (M$^+$ − Et, 11), 264 (M$^+$ − Bu^t, 7), 199 (M$^+$ − $PhCH_2NOH$, 100), 157 (25), 91 (CH_2Ph, 72) and 73 (55).

cis-2-*Benzyl*-5-(tert-*butyldimethylsiloxy*)-3-*isopropylisoxazolidine* cis-**8b**. Purified by flash chromatography (C–E 96:4) as a clear oil (Found: M$^+$, 335.2278. $C_{19}H_{33}NO_2Si$ requires M, 335.2280); TLC (C–E 85:15) R_f 0.73; *m/z* (%) 335 (M$^+$, 11), 292 (M$^+$ − Pr^i, 52), 278 (M$^+$ − Bu^t, 8), 250 (18), 213 (M$^+$ − $PhCH_2NOH$, 33), 171 (10), 91 (CH_2Ph, 100), 75 (18) and 73 (30).

trans-2-*Benzyl*-5-(tert-*butyldimethylsiloxy*)-3-*isopropylisoxazolidine* trans-**8b**. Purified by flash chromatography (C–E 96:4) as a clear oil (Found: M$^+$, 335.2280); TLC (C–E 85:15) R_f 0.43; *m/z* (%) 335 (M$^+$, 13), 292 (M$^+$ − Pr^i, 50), 278 (M$^+$ − Bu^t, 10), 250 (17), 213 (M$^+$ − $PhCH_2NOH$, 31), 171 (9), 91 (CH_2Ph, 100), 75 (18) and 73 (28).

cis-2-*Benzyl*-3-(tert-*butyl*)-5-(tert-*butyldimethylsiloxy*)*isoxazolidine cis*-**8c**. Purified by flash chromatography (C–E 99:1) as an oil (Found: M$^+$, 349.2442. $C_{20}H_{35}NO_2Si$ requires M, 349.2437); TLC (C–E 85:15) R_f 0.86; *m/z* (%) 349 (M$^+$, 2), 292 (M$^+$ − Bu^t, 94), 250 (8), 160 (10), 91 (CH_2Ph, 100), 75 (15) and 73 (19).

trans-2-*Benzyl*-3-(tert-*butyl*)-5-(tert-*butyldimethylsiloxy*)-*isoxazolidine* trans-**8c**. Purified by flash chromatography (C–E 99:1) as an oil (Found: M$^+$, 349.2439); TLC (C–E 85:15) R_f 0.76; *m/z* (%) 349 (M$^+$, 2), 292 (M$^+$ − Bu^t, 90), 250 (7), 160 (11), 91 (CH_2Ph, 100), 75 (14) and 73 (20).

cis-5-(tert-*Butyldimethylsiloxy*)-2-*methyl*-3-*phenylisoxazolidine* cis-**8d**. Purified by flash chromatography (C–E 95:5) as a pale yellow oil (Found: M$^+$, 293.1810. $C_{16}H_{27}NO_2Si$ requires M, 293.1811); TLC (C–E 85:15) R_f 0.67; *m/z* (%) 293 (M$^+$, 7), 247 (M$^+$ − CH_3NOH, 100), 205 (43), 135 [$CH_3N(O)CHPh$, 6], 134 [$CH_3N(O)CPh$, 18], 132 (16), 105 (18), 91 (CH_2Ph, 28), 75 (19), 73 (80) and 41 (7).

trans-5-(tert-*Butyldimethylsiloxy*)-2-*methyl*-3-*phenylisoxazolidine* trans-**8d**. Purified by flash chromatography (C–E 95:5) as a pale yellow oil (Found: M$^+$, 293.1806); TLC (C–E 85:15) R_f 0.37; *m/z* (%) 293 (M$^+$, 6), 247 (M$^+$ − CH_3NOH, 100), 205 (45), 135 [$CH_3N(O)CHPh$, 4], 134 [$CH_3N(O)CPh$, 19], 132 (18), 105 (18), 91 (CH_2Ph, 30), 75 (17) and 73 (78).

cis-2-*Benzyl*-5-(tert-*butyldimethylsiloxy*)-3-(2-*methylprop*-1-

enyl)isoxazolidine cis-**8e**. Purified by flash chromatography (C–E 95:5) as a pale yellow oil (Found: M^+, 347.2283. $C_{20}H_{33}NO_2Si$ requires M, 347.2280); TLC (C–E 80:20) R_f 0.85; *m/z* (%) 347 (M^+, 6), 290 ($M^+ - Bu^t$, 2), 226 (18), 225 ($M^+ - PhCH_2NOH$, 92), 208 (17), 174 (22), 91 (CH_2Ph, 100), 75 (44) and 73 (68).

trans-2-*Benzyl*-5-(tert-*butyldimethylsiloxy*)-3-(2-*methylprop*-1-*enyl*)*isoxazolidine* trans-**8e**. Purified by flash chromatography (C–E 95:5) as a pale yellow oil (Found: M^+, 347.2276); TLC (C–E 80:20) R_f 0.57; *m/z* (%) 347 (M^+, 5), 226 (17), 225 ($M^+ - PhCH_2NOH$, 90), 208 (16), 174 (23), 103 (11), 91 (CH_2Ph, 100), 75 (42) and 73 (70).

cis-2-*Benzyl*-5-(tert-*butyldiphenylsiloxy*)-3-*ethylisoxazolidine* cis-**8f**. Purified by flash chromatography (C–E 96:4) as a pale yellow oil (Found: M^+, 445.2440. $C_{28}H_{35}NO_2Si$ requires M, 445.2437); TLC (C–E 90:10) R_f 0.58; *m/z* (%) 445 (M^+, 11), 388 ($M^+ - Bu^t$, 17), 323 ($M^+ - PhCH_2NOH$, 65), 254 (14), 199 (100), 197 (26), 135 (64), 91 (CH_2Ph, 98), 77 (Ph, 23) and 75 (44).

trans-2-*Benzyl*-5-(tert-*butyldiphenylsiloxy*)-3-*ethylisoxazolidine* trans-**8f**. Purified by flash chromatography (C–E 96:4) as a pale yellow oil (Found: M^+, 445.2432); TLC (C–E 90:10) R_f 0.25; *m/z* (%) 445 (M^+, 10), 338 ($M^+ - Bu^t$, 18), 323 ($M^+ - PhCH_2NOH$, 65), 254 (13), 199 (99), 197 (27), 137 (20), 135 (60), 91 (CH_2Ph, 100), 77 (Ph, 20) and 75 (42).

cis-2-*Benzyl*-3-*ethyl*-5-*methyl*-5-(*trimethylsiloxy*)*isoxazolidine* cis-**8g**. Purified by flash chromatography (C–E 98:2) as a pale yellow oil (Found: C, 65.4; H, 9.2; N, 4.7. $C_{16}H_{27}NO_2Si$ requires C, 65.5; H, 9.3; N, 4.8%); TLC (C–E 80:20) R_f 0.75; *m/z* (%) 293 (M^+, 14), 171 ($PhCH_2NOH$, 100), 130 (7), 91 (CH_2Ph, 68), 82 (9), 75 (12), 73 (32) and 43 (8).

trans-2-*Benzyl*-3-*ethyl*-5-*methyl*-5-(*trimethylsiloxy*)*isoxazolidine* trans-**8g**. Purified by flash chromatography (C–E 98:2) as a pale yellow oil (Found: C, 65.4; H, 9.2; N, 4.7 %); TLC (C–E 80:20) R_f 0.39; *m/z* (%) 293 (M^+, 12), 171 ($PhCH_2NOH$, 100), 130 (4), 91 (CH_2Ph, 70), 82 (8), 75 (14), 73 (34) and 43 (7).

2-*Benzyl*-3-*ethyl*-5-*methyl*-2,3-*dihydroisoxazole* **9g**. Purified by flash chromatography (C–E 98:2) as a pale yellow oil (Found: C, 76.8; H, 8.4; N, 7.0. $C_{13}H_{17}NO$ requires C, 76.8; H, 8.4; N, 6.9%); TLC (C–E 80:20) R_f 0.55; ν_{max}/cm^{-1} 1670 (C=C).

cis-2-*Benzyl*-3-*isopropyl*-5-*methyl*-5-(*trimethylsiloxy*)*isoxazolidine* cis-**8h**. Purified by flash chromatography (C–E 99:1) as a pale yellow oil (Found: C, 66.3; H, 9.5; N, 4.6. $C_{17}H_{29}NO_2Si$ requires C, 66.4; H, 9.5; N, 4.6%); TLC (C–E 85:15) R_f 0.68; *m/z* (%) 307 (M^+, 3), 264 ($M^+ - Pr^i$, 11), 185 ($M^+ - PhCH_2NOH$, 31), 174 (23), 91 (CH_2Ph, 100), 73 (11) and 43 (Pr^i, 6).

trans-2-*Benzyl*-3-*isopropyl*-5-*methyl*-5-(*trimethylsiloxy*)*isoxazolidine* trans-**8h**. Purified by flash chromatography (C–E 99:1) as a pale yellow oil (Found: C, 66.5; H, 9.4; N, 4.6%); TLC (C–E 85:15) R_f 0.52; *m/z* (%) 307 (M^+, 4), 264 ($M^+ - Pr^i$, 10), 185 ($M^+ - PhCH_2NOH$, 33), 174 (21), 91 (CH_2Ph, 100), 73 (11) and 43 (Pr^i, 4).

2-*Benzyl*-3-*isopropyl*-5-*methyl*-2,3-*dihydroisoxazole* **9h**. Purified by flash chromatography (C–E 99:1) as an oil (Found: C, 77.4; H, 8.7; N, 6.5. $C_{14}H_{19}NO$ requires C, 77.4; H, 8.8; N, 6.5%); TLC (C–E 85:15) R_f 0.85; ν_{max}/cm^{-1} 1670 (C=C).

cis-2,5-*Dimethyl*-3-*phenyl*-5-(*trimethylsiloxy*)*isoxazolidine* cis-**8i**. Purified by flash chromatography (C–E 98:2) as a pale yellow oil (Found: C, 63.4; H, 8.7; N, 5.3. $C_{14}H_{23}NO_2Si$ requires C, 63.4; H, 8.7; N, 5.3%); TLC (C–E 85:15) R_f 0.78; *m/z* (%) 265 (M^+, 4), 219 ($M^+ - CH_3NOH$, 100), 146 (11), 134 (13), 91 (5), 75 (18) and 73 (51).

trans-2,5-*Dimethyl*-3-*phenyl*-5-(*trimethylsiloxy*)*isoxazolidine* trans-**8i**. Purified by flash chromatography (C–E 98:2) as a pale yellow oil (Found: C, 63.3; H, 8.7; N, 5.3%); TLC (C–E 85:15) R_f 0.24; *m/z* (%) 265 (M^+, 4), 219 ($M^+ - CH_3NOH$, 100), 146 (15), 134 (11), 91 (4), 75 (14) and 73 (38).

2,5-*Dimethyl*-3-*phenyl*-2,3-*dihydroisoxazole* **9i** Purified by flash chromatography (C–E 98:2) as a pale yellow oil (Found: C, 75.4; H, 7.5; N, 8.1. $C_{11}H_{13}NO$ requires C, 75.4; H, 7.5; N, 8.0%); TLC (C–E 85:15) R_f 0.38; ν_{max}/cm^{-1} 1670 (C=C).

cis-2-*Benzyl*-3-*ethyl*-5-*phenyl*-5-(*trimethylsiloxy*)*isoxazolidine* cis-**8j**. Not isolated. TLC (C–E 85:15) R_f 0.80. NMR signals reported in Tables 1 and 2 are extracted from the spectra of a 2:1 mixture of *cis*-**8j** and **9j**.

trans-2-*Benzyl*-3-*ethyl*-5-*phenyl*-5-(*trimethylsiloxy*)*isoxazolidine* trans-**8j**. Not isolated. TLC (C–E 85:15) R_f 0.61. NMR signals reported in Tables 1 and 2 are extracted from the spectra of a 3:2 mixture of *trans*-**8j** and **9j**.

2-*Benzyl*-3-*ethyl*-5-*phenyl*-2,3-*dihydroisoxazole* **9j**. Purified by flash chromatography (C–E 97:3) as a clear oil (Found: C, 81.4; H, 7.2; N, 5.3 $C_{18}H_{19}NO$ requires C, 81.5; H, 7.2; N, 5.3%); TLC (C–E 85:15) R_f 0.66; ν_{max}/cm^{-1} 1650 (C=C); *m/z* (%) 265 (M^+, 71), 248 (37), 188 ($M^+ - Ph$, 6), 174 ($M^+ - CH_2Ph$, 3), 160 ($M^+ - NCH_2Ph$, 35), 105 (NCH_2Ph, 39), 91 (CH_2Ph, 100), 77 (Ph, 20), 65 (19) and 56 (17).

cis-2-*Benzyl*-3-*isopropyl*-5-*phenyl*-5-(*trimethylsiloxy*)*isoxalidine* cis-**8k**. Not isolated TLC (C–E 85:15) R_f 0.88; NMR signals could not be properly extracted from the spectra of the reaction mixture; *m/z*(%) 369 (M^+, 1.5), 354 ($M^+ - Me$, 2), 326 ($M^+ - Pr^i$, 55), 105 (26), 91 (100) and 77 (14).

trans-2-*Benzyl*-3-*isopropyl*-5-*phenyl*-5-(*trimethylsiloxy*)*isoxazolidine* trans-**8k**. Not isolated TLC (C–E 85:15) R_f 0.80; NMR signals reported in Tables 1 and 2 are extracted from the spectra of a 1:5 mixture of *trans*-**8k** and **9k**; *m/z* (%) 369 (M^+, 2), 354 ($M^+ - CH_3$, 2), 326 ($M^+ - Pr^i$, 58), 248 ($M^+ - PhCH_2NO$, 3), 247 (11), 146 (5), 144 (5), 105 (23), 91 ($PhCH_2$, 100) and 77 (Ph, 12).

2-*Benzyl*-3-*isopropyl*-5-*phenyl*-2,3-*dihydroisoxazole* **9k**. Purified by flash chromatography (C–E 99:1) as a pale yellow oil (Found: C, 81.8; H, 7.6; N, 5.0. $C_{19}H_{21}NO$ requires C, 81.7; H, 7.6; N, 5.0%); TLC (C–E 85:15) R_f 0.78; ν_{max}/cm^{-1} 1655 (C=C).

Hydrolysis of 2-*Benzyl*-5-(tert-*butyldimethylsiloxy*)-3-*ethylisoxazolidine* cis-**8a** *and* trans-**8a**. *General Procedure*.—To a mixture of *cis*-**8a** and *trans*-**8a** (321 mg, 1 mmol, *cis*:*trans* 1:1) were added TFA (0.5 cm^3, 6.7 mmol) and water (0.3 cm^3) at room temperature. After 3 h the reaction mixture was neutralised with 5 mol dm^{-3} NaOH (1.34 cm^3), then was extracted with $CHCl_3$ (3 × 20 cm^3). The combined organic phases were dried (Na_2SO_4) and the solvent was evaporated off under reduced pressure. The residue was purified by flash chromatography C–E 1:1). 2-Benzyl-3-ethylisoxazolidin-5-ol **15a** (115 mg, 55%, *cis*:*trans* 45:55) was isolated; TLC (C–E 1:1) R_f 0.41; ν_{max}/cm^{-1} 3400br (OH).

2-*Methyl*-3-*phenylisoxazolidin*-5-*ol* **15d**. Hydrolysis of a mixture of *cis*-**8d** and *trans*-**8d** (293 mg, 1 mmol, *cis*:*trans* 6:4) under the same conditions as above gave compound **15d** (135 mg, 76%, *cis*:*trans* 2:1) purified by flash chromatography (C–E 1:1) as a clear oil; TLC (C–E 1:1) R_f 0.20; ν_{max}/cm^{-1} 3400br (OH).

2,5-*Dimethyl*-3-*phenylisoxazolidin*-5-*ol* **15i**. Hydrolysis of *cis*-**8i** and *trans*-**8i** (235 mg, 1 mmol, *cis*:*trans* 55:45) under the same conditions as above afforded compound **15i** (150 mg, 77%, *cis*:*trans* 3:1), purified by flash chromatography (C–E 1:1) as an oil; TLC (C–E 1:1) R_f 0.36; ν_{max}/cm^{-1} 3400br (OH) and 1730; *m/z* (%) 146 ($M^+ - CH_3NOH$, 52), 131 ($CH_3COCH{=}CHPh$, 99), 115 (5), 103 ($M^+ - CH_3NOH - CH_3CO$, 100), 91 (CH_2Ph, 3), 77 (Ph, 56), 74 (7) and 51 (38).

Hydration of 2,5-*Dimethyl*-3-*phenyl*-2,3-*dihydroisoxazole* **9i**.—To a mixture of compound **9i** (170 mg, 1 mmol) and water (0.3 cm^3) was added TFA (0.5 cm^3, 6.7 mmol) at room temperature. After 30 min the reaction mixture was neutralised with saturated aq. $NaHCO_3$ and extracted with diethyl ether (3 × 20 cm^3). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated off under reduced

Table 6 ^{1}H NMR data for compounds **15**, **18** and **19** at 300 MHz

Compd.	3-H	4-H	5-H	Others
15a[a]	2.57–2.63 (m, *cis*), 3.16 (quintet, *J* 7.2, *trans*)	1.79–1.91 (m, *cis*), 2.03 (ddd, *J* 5.0, 8.4, 12.9, *trans*), 2.38 (ddd, *J* 1.0, 6.6, 12.9, *trans*), 2.57–2.63 (m, *cis*)	5.35 (dd, *J* 0.5, 5.8, *cis*), 5.44 (dd, *J* 1.0, 5.0, *trans*)	0.84 (3 H, t, *J* 7.4, CH_2Me *trans*), 0.88 (3 H, t, *J* 7.4, CH_2Me *cis*), 1.31–1.70 (4 H, m, CH_2Me *cis* + CH_2Me *trans*), 3.40 (2 H, br s, OH *cis* + OH *trans*), 3.73 (1 H, d, *J* 14.0, CH_2Ph *cis*), 4.06 (1 H, d, *J* 14.0, CH_2Ph *cis*), 4.08 (1 H, d, *J* 13.3, CH_2Ph *trans*), 4.17 (1 H, d, *J* 13.3, CH_2Ph *trans*), 7.18–7.38 (10 H, m, Ph *cis* + Ph *trans*)
15d[a]	3.49 (t, *J* 9.0, *cis*), 4.01–4.12 (m, *trans*)	2.33–2.40 (m, *cis*), 2.44–2.60 (m, *trans*), 2.76–2.85 (m, *trans*), 2.72–3.03 (dt, *J* 7.1, 13.6, *cis*)	5.53–5.59 (m, *cis*), 5.61–5.66 (m, *trans*)	2.62 (6 H, s, NMe *cis* + NMe *trans*), 2.76–2.85 (2 H, m, OH *trans* + OH *cis*), 7.29–7.49 (5 H, m, Ph)
15i[a]	3.57 (br t, *J* 8.9, *cis*), 4.15 (dd, *J* 5.8, 12.1, *trans*)	2.28–2.44 (m, *trans*), 2.47 (dd, *J* 9.3, 13.2, *cis*), 2.50–2.70 (m, *trans*), 2.75 (dd, *J* 8.3, 13.2, *cis*)		1.58 (3 H, s, 5-Me *cis*), 1.62 (3 H, s, 5-Me *trans*), 2.61 (6 H, s, NMe *cis* + NMe *trans*), 2.79 (2 H, br s, OH *cis* + OH *trans*), 7.27–7.43 (10 H, m, Ph *cis* + Ph *trans*)
cis-**18d**	3.62 (br t, *J* ~7.5)	2.09 (ddd, *J* 6.9, 9.6, 12.4), 2.77 (dt, *J* 7.3, 12.4)	4.25–4.36 (1 H, m)	2.30–2.50 (1 H, m, 5-CH_2), 2.53–2.68 (1 H, m, 5-CH_2), 2.61 (3 H, s, NMe), 5.05–5.19 (2 H, m, CH_2=), 5.78–5.93 (1 H, m, =CH), 7.23–7.41 (5 H, m, Ph)
trans-**18d**	3.42–3.54 (m)	2.29–2.53 (2 H, m)	4.28–4.39 (m)	2.29–2.53 (2 H, m, 5-CH_2), 2.59 (3 H, s, NMe), 5.06–5.20 (2 H, m, CH_2=), 5.77–5.93 (1 H, m, =CH), 7.23–7.44 (5 H, m, Ph)
cis-**19d**	3.49 (br t, *J* ~8.5)	2.62 (ddd, *J* 3.8, 8.4, 13.0), 3.09 (dt, *J* 8.9, 13.0)	4.86 (dd, *J* 3.8, 8.9)	2.65 (3 H, s, NMe), 7.28–7.51 (5 H, m, Ph)
trans-**19d**	3.92–4.01 (m)	2.79 (dt, *J* 8.0, 12.6), 2.98 (ddd, *J* 4.4, 6.9, 12.6)	4.81–4.94 (m)	2.74 (3 H, s, NMe), 7.28–7.53 (5 H, m, Ph)

[a] *cis*- and *trans*-**15** cannot be separated by flash chromatography. The reported data were obtained from spectra of fractions enriched in one isomer.

pressure. Flash chromatography (C–E 1:1) gave 2,5-dimethyl-3-phenylisoxazolidin-5-ol **15i** (160 mg, 82%, *cis*:*trans* 3:1) as an oil.

Reduction of 2-*Methyl*-3-*phenylisoxazolidin*-5-*ol* **15d**.—To a solution of compound **15d** (270 mg, 1.5 mmol) in methanol (0.8 cm^3) was added $NaBH_4$ (42 mg, 1 mmol) at room temperature. After 2 h the solvent was evaporated off under reduced pressure, saturated aq. $NaHCO_3$ (1 cm^3) was added, and the mixture was extracted with diethyl ether (3 × 10 cm^3). The combined organic phases were evaporated to dryness and the residue was purified by flash chromatography (A–C 7:3) to give 3-(*N*-hydroxy-*N*-methylamino)-3-phenylpropan-1-ol **16d** (250 mg, 92%); TLC (A–C 8:2) R_f 0.28; ν_{max}/cm^{-1} 3300br (OH); *m*/*z* (%) 181 (M^+, 3), 179 ($M^+ - 2$, 1), 163 ($M - H_2O$, 7), 136 (54), 121 (10), 120 (36), 105 (100), 104 (30), 91 (CH_2Ph, 65), 77 (Ph, 32) and 51 (15); δ_H 1.90–2.07 (1 H, m, 2-H), 2.07–2.20 (2 H, br s, NOH + OH), 2.34–2.48 (1 H, m, 2-H), 2.53 (3 H, s, NMe), 3.63–3.82 (3 H, m, 1-H_2 + 3-H) and 7.24–7.39 (5 H, m, ArH); δ_C 35.2 (C-2), 45.6 (MeN), 60.9 (C-3), 72.0 (C-1), 127.7, 128.2 and 128.9 (ArCH) and 138.5 (ArC).

Reduction of 2,5-*Dimethyl*-3-*phenylisoxazolidin*-5-*ol* **15i**.—To a solution of compound **15i** (290 mg, 1.5 mmol) in methanol (0.8 cm^3) was added $NaBH_4$ (42 mg, 1 mmol) at room temperature. After 30 min the solvent was evaporated off under reduced pressure, saturated aq. $NaHCO_3$ (1 cm^3) was added, and the mixture was extracted with diethyl ether (3 × 10 cm^3). The combined organic phases were evaporated to dryness and the residue was purified by flash chromatography (A–C 8:2) to give oily 4-(*N*-hydroxy-*N*-methyl)-4-phenylbutan-2-ol **16i** (250 mg, 85%) as a 1:1 mixture of diastereoisomers on the basis of integrals of methyl signals in the ^{1}H NMR spectrum; ν_{max}/cm^{-1} 3300br (OH); *m*/*z* (%) 193 ($M^+ - 2$, 8), 146 (5), 134 (12), 131 (17), 121 (30), 120 (23), 118 (20), 105 (77), 104 (100), 78 (28) and 77 (52); δ_H 1.20 ($\frac{3}{2}$ H, d, *J* 6.7, 1-H_3), 1.22 ($\frac{3}{2}$ H, d, *J* 6.3, 1-H_3), 1.65–1.75 (1 H, m, 3-H), 2.00–2.14 (2 H, br s, NOH + OH), 2.25–2.40 (1 H, m, 3-H), 2.51 (3 H, s, NMe), 2.54 (3 H, s, NMe), 3.80–3.90 (1 H, m, 4-H), 3.93–4.06 (1 H, m, 2-H) and 7.29–7.40 (5 H, m, ArH); δ_C 23.1 (C-1), 23.8 (C-1), 40.6 (C-3), 41.3 (C-3), 45.0 (MeN), 45.9 (MeN), 65.4 (C-4), 68.6 (C-4), 72.3 (C-2), 127.7, 127.9, 128.1, 128.5, 128.6 and 129.5 (ArCH) and 138.0 (ArC).

Reduction of 2-*Benzyl*-3-*ethyl*-5-*methyl*-5-(*trimethylsiloxy*)-*isoxazolidine* cis-**8g** *and* trans-**8g**.—Copper(II) acetate (10 mg) and Zn dust (325 mg, 5 mmol) were poured into glacial acetic acid (0.8 cm^3) and the solution was stirred for 10 min at room temperature until the blue colour disappeared. To this freshly prepared Zn/Cu couple was added a solution of isoxazolidines **8g** (293 mg, 1 mmol; this reaction is often exothermic) in acetic acid (1.2 cm^3)–water (0.3 cm^3). After 1 h at 60–70 °C the reaction was worked up by addition of 6 mol dm^{-3} NaOH until pH 8 (glass electrode), and extraction with $CHCl_3$ (3 × 20 cm^3). Flash chromatography (C–A 6:4) of the residue afforded 4-(benzylamino)hexan-2-one **17g** (100 mg, 50%) as a yellow oil; TLC (C–A 1:1) R_f 0.20; ν_{max}/cm^{-1} 3700 (NH), 1710 (C=O), 1360 and 1180; δ_H 0.93 (3 H, t, *J* 7.4, 6-H_3), 1.45–1.67 (2 H, m, 5-H_2), 1.90 (1 H, br s, NH), 2.16 (3 H, s, 1-H_3), 2.57 (2 H, d, *J* 6.3, 3-H_2), 3.05 (1 H, quint, *J* 6.3, 4-H), 3.74 (1 H, d, *J* 12.9, CH_2Ph), 3.87 (1 H, d, *J* 12.9, CH_2Ph) and 7.32–7.38 (5 H, m, ArH); δ_C 9.7 (C-6), 26.4 (C-5), 30.6 (C-1), 47.9 (C-3), 50.9 (C-4), 54.6 (CH_2Ph), 126.8, 128.0 and 128.3 (ArCH), 140.4 (ArC) and 206.0 (C-2).

Coupling of Compound **8d** *with Allyltrimethylsilane* (*Table* 5, *Run* 1).—To a solution of *cis*-**8d** and *trans*-**8d** (293 mg, 1.0 mmol) in $CHCl_3$ (13 cm^3) were added allyltrimethylsilane (0.20 cm^3, 1.3 mmol) and TMSOTf (0.212 cm^3, 1.1 mmol) at room temperature. The mixture was stirred at 75 °C for 8 h and quenched with aq. $NaHCO_3$ (2 cm^3); the two liquid layers were separated and the aqueous phase was extracted with diethyl ether (3 × 10 cm^3). The combined organic layers were dried ($MgSO_4$), and evaporated to dryness. Flash chromatography (C–E 99:1) gave *cis*-and *trans*-2-methyl-3-phenyl-5-(prop-2-enyl)isoxazolidine **18d** as an oil (122 mg, 60%, *cis*:*trans* 1:1.3).

Alternatively (Table 5, run 2), to isoxazolidines *cis*-**8d** and *trans*-**8d** (293 mg, 1.0 mmol) dissolved in toluene (20 cm^3) were added, at room temperature, allyltrimethylsilane (0.48 cm^3, 3.0 mmol) and TMSOTf (0.212 cm^3, 1.1 mmol). The mixture was stirred at 70 °C for 5 h and quenched with aq. $NaHCO_3$ (2 cm^3);

Table 7 ^{13}C NMR data for compounds **15**, **18** and **19** at 75 MHz

Compd.	C-3	C-4	C-5	CH_2Ph	Ph	NMe	Others
cis-**15a**[a]	65.4	43.5	95.4	64.6	127.1, 127.2, 128.1, 128.2,		10.8 (CH_2*Me cis*), 26.8 (CH_2Me *cis*)
trans-**15a**[a]	67.2	42.3	97.6	60.6	128.9, 129.1, 136.9, 137.8		11.0 (CH_2*Me trans*), 25.0 (CH_2Me *trans*)
cis-**15i**[a]	74.2	52.8	102.0		127.4, 127.8, 128.0, 128.4,	42.6	25.9 (Me)
trans-**15i**[a]	74.2	51.2	103.3		128.6, 128.8, 137.6, 138.7	42.6	25.9 (Me)
cis-**18d**	73.3	40.4[b]	76.2		127.5, 127.6, 128.6, 139.2	43.7	45.4[b] (5-CH_2), 117.2 (CH_2=), 134.6 (CH=)
trans-**18d**	73.0	38.9[b]	76.1		127.7, 128.6, 129.0, 139.3	43.2	44.5[b] (5-CH_2), 117.4 (CH_2=), 133.9 (CH=)
cis-**19d**	63.7	44.1	72.0		127.8, 128.4, 128.7, 136.9	42.4	119.6 (CN)
trans-**19d**	63.5	43.8	71.9		127.3, 128.3, 128.8, 137.0	44.4	118.2 (CN)

[a] *cis*- and *trans*-**15** cannot be separated by flash chromatography. The reported data were collected from spectra of mixtures enriched in one isomer. Aromatic carbons of *cis*- and *trans*-**15** are collected together. [b] The assignments may have to be interchanged.

the two liquid layers were separated and the aqueous phase was extracted with diethyl ether (3 × 20 cm^3). The combined organic layers were dried ($MgSO_4$), and evaporated to dryness. Flash chromatography of the oily residue gave the products **18d** (90 mg, 44%, *cis*:*trans* 1:5).

One-pot Synthesis of Compound **18d**.—To a stirred solution of isoxazolidine **8d** [prepared from nitrone **1d** (135 mg, 1 mmol) and silyl enol ether **7a** (0.174 g, 1.1 mmol) in anhydrous chloroform (3 cm^3)] was added drop-by-drop (10 min) a solution of TMSOTf (0.21 cm^3, 1.4 mmol) in chloroform (2 cm^3) at 0 °C. After 23 h was added allyltrimethylsilane (0.6 cm^3, 3 mmol) and the reaction mixture was heated at 60 °C for 7 h before being quenched with saturated aq. $NaHCO_3$ (2 cm^3); the two liquid layers were separated and the aqueous phase was extracted with diethyl ether (3 × 20 cm^3). The combined organic layers were dried (Na_2SO_4), and evaporated to dryness. The residue was chromatographed to give the products **18d** (90 mg, 44%, *cis*:*trans* 55:45) as clear oil.

cis-2-*Methyl*-3-*phenyl*-5-(*prop*-2-*enyl*)*isoxazolidine* cis-**18d** (Found: C, 76.7; H, 8.4; N, 6.9. $C_{13}H_{17}NO$ requires C, 76.8; H, 8.4; N, 6.9%); TLC (C–E 85:15) R_f 0.57; ν_{max}/cm^{-1} 1640 (C=C) and 990 (CH); *m*/*z* (%) 203 (M^+, 26), 174 (56), 160 (46), 136 [PhCHN(CH_3)OH, 57], 135 (19), 134 [PhC=NO(CH_3), 100], 118 (43), 115 (31), 104 (28), 91 ($PhCH_2$, 63), 77 (Ph, 53) and 51 (26).

trans-2-*Methyl*-3-*phenyl*-5-(*prop*-2-*enyl*)*isoxazolidine* trans-**18d** (Found: C, 76.8; H, 8.4; N, 6.9%); TLC (C–E 85:15) R_f 0.46; ν_{max}/cm^{-1} 1640 (C=C) and 985 (CH); *m*/*z* (%) 203 (M^+, 30), 174 (52), 160 (40), 136 [PhCHN(CH_3)OH, 50], 135 (18), 134 [PhC=NO(CH_3), 100], 118 (43), 115 (35), 104 (28), 91 ($PhCH_2$, 70), 77 (Ph, 45) and 51 (26).

Coupling of Compound **8d** *with Cyanotrimethylsilane*.—To a solution of *cis*-**8d** and *trans*-**8d** (293 mg, 1.0 mmol) in $CHCl_3$ (13 cm^3) were added cyanotrimethylsilane (0.173 cm^3, 1.3 mmol) and TMSOTf (0.212 cm^3, 1.1 mmol) at room temperature. The mixture was stirred for 8 h at 50 °C and quenched with saturated aq. $NaHCO_3$ (1 cm^3); the two liquid layers were separated and the aqueous phase was extracted with diethyl ether (3 × 20 cm^3). The combined organic layers were dried (Na_2SO_4), and evaporated to dryness. Flash chromatography (C–E 90:10) of the residue gave the cis- and trans-2-*methyl*-3-*phenylisoxazolidine*-5-*carbonitrile* **19d** (100 mg, 53%, *cis*:*trans* 2.4:1), as a yellow oil.

cis-2-*Methyl*-3-*phenylisoxazolidine*-5-*carbonitrile* cis-**19d** (Found: C, 70.3; H, 6.4; N, 14.9. $C_{11}H_{12}N_2O$ requires C, 70.2; H, 6.4; N, 14.9%); TLC (C–E 65:35) R_f 0.52; ν_{max}/cm^{-1} 2230 (CN); *m*/*z* (%) 188 (M^+, 61), 143 (M − CH_3NO, 41), 142 (17), 135 [PhCHN(O)CH_3, 23], 134 (100), 115 (38), 91 ($PhCH_2$, 17), 77 (Ph, 30) and 51 H (22).

trans-2-*Methyl*-3-*phenylisoxazolidine*-5-*carbonitrile* trans-**19d** (Found: C, 70.2; H, 6.3; N, 14.9%); TLC (C–E 65:35) R_f 0.67; ν_{max}/cm^{-1} 2230 (CN); *m*/*z* (%) 188 (M^+, 57), 143 (M − CH_3NO, 46), 142 (17), 135 [PhCHN(O)CH_3, 28], 134 (100), 116 (38), 115 (42), 91 ($PhCH_2$, 18), 77 (Ph, 37) and 51 (30).

Acknowledgements

We thank Italian CNR (Progetto Finalizzato Chimica Fine 2) for financial support.

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Paper 3/03032F
Received 27*th May* 1993
Accepted 9*th July* 1993