Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Organometallic Chemistry 690 (2005) 5636–5646
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

# Asymmetric synthesis of *cis*-2,4-disubstituted azetidin-3-ones from metal carbene chemistry

Antonio Carlos B. Burtoloso, Carlos Roque D. Correia *

*Instituto de Química, Universidade Estadual de Campinas, UNICAMP, C.P. 6154, CEP 13083-970, Campinas, SP, Brazil*

Received 25 May 2005; accepted 4 July 2005
Available online 22 August 2005

**Abstract**

Several chiral *cis*-2,4-disubstituted azetidin-3-ones were prepared as single diastereoisomers from *N*-protected amino acids, employing a highly stereoselective copper carbenoid N–H insertion reaction of diazoketones. These azetidin-3-ones were then converted into fully substituted azetidines in a few steps in good to high yields.


*Keywords:* Metal carbenes; Azetidines; Azetidin-3-ones; N–H insertion; Diazoketones

## 1. Introduction

Among the many nitrogen heterocycles the azetidine compounds are, most probably, the least investigated ones. The literature reports a reasonable number of synthetic methodologies and applications of azetidines, but these figures are still small when compared to other cyclic amines such as pyrrolidines and aziridines. Natural azetidines are rather rare compounds and are found mainly as sphingosine-like compounds, many of which display interesting biological activities [1]. Regarding the synthetic applications of chiral azetidines, the majority of the examples reported have been concentrated in the area of chiral ligands [2]. Studies related to the synthesis of fully substituted azetidines are likewise scarce in the literature and focused mainly in the synthesis of natural azetidines [3]. Most of these studies centered on the preparation of azetidines are based on an intramolecular nucleophilic substitution [4]. In view of the scarcity of methodologies to construct fully-substituted azetidine compounds, new protocols are not only necessary but also highly desirable.

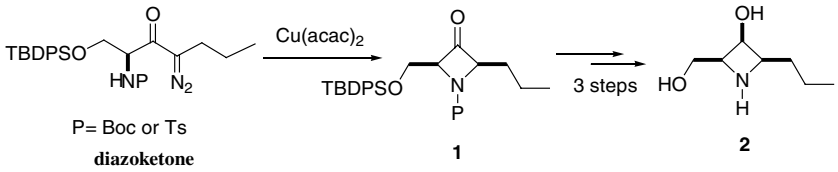
## 2. Discussion

In the last few years [5], we have been engaged in the synthesis of chiral azetidin-3-ones [6] employing metal carbene chemistry as the key synthetic step. In a recent communication [5a], we have shown that the *cis*-2,4-disubstituted azetidin-3-one **1** (Scheme 1), prepared by a new copper catalyzed N–H insertion reaction of diazoketones, could be easily converted to the chiral azetidine **2**, a short sphingosine analogue. These results clearly show that azetidin-3-ones such as **1** are powerful intermediates for the synthesis of fully substituted azetidines in a few steps.

In this paper our aim is several fold: (a) we would like to construct several *cis*-2,4-disubstituted azetidin-3-ones from chiral diazoketones by means of a metal-catalyzed N–H insertion reaction; (b) apply these azetidin-3-ones in the synthesis of fully-substituted azetidines; (c) to understand the stereochemical outcome of these metal-catalyzed N–H insertion reactions; and (d) to evaluate

* Corresponding author.
*E-mail address:* roque@iqm.unicamp.br (C.R.D. Correia).

0022-328X/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2005.07.016

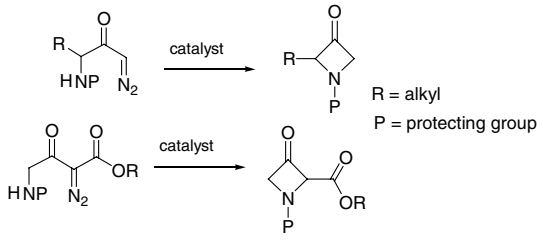



Scheme 1. Synthesis of a small chain sphingosine analogue.

the scope of the methodology with regard to the diastereoselectivity of the N–H insertion reaction.

The synthesis of *cis*-2,4-disubstituted azetidin-3-ones have been previously reported by us [5a], De Kimpe [7] and Kise [8]. The work of De Kimpe and Kise are based on the alkylation of 2-substituted azetidin-3-ones and on the electroreductive intramolecular coupling of iminoesters, respectively.

Metal carbene chemistry has been widely used as an efficient tool in organic chemistry [9]. Despite some examples in the literature using rhodium and copper catalysts in N–H insertion reactions of α-diazoketones to form a four-membered ring (azetidin-3-ones), these efforts have been mainly restricted to the preparation of the structurally simpler 2-substituted azetidin-3-ones [10] (Scheme 2). Therefore, our initial goal was to extend the metal carbene chemistry to the preparation of the more complex 2,4-disubstituted azetidin-3-ones,



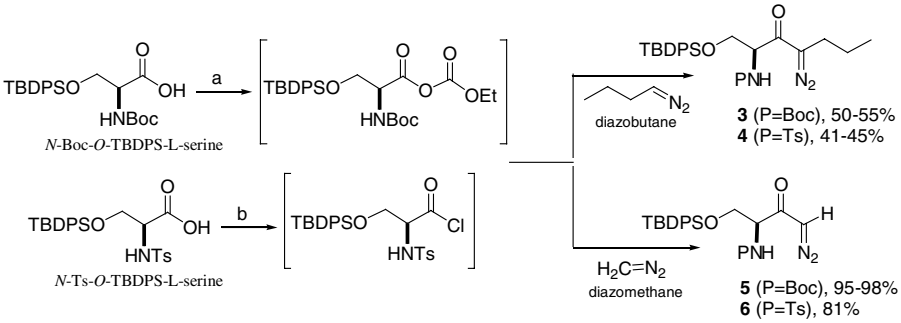

Scheme 2. Insertion reactions for the synthesis of 2-substituted azetidin-3-ones.

employing, α,α′-dialkyl-α-diazoketones as starting materials.

To start with, we prepared the *N*-Boc and *N*-tosyl diazoketones **3** and **4** (Scheme 3) for the N–H insertion reactions. Surprisingly, while diazoketone **3** (*N*-Boc) could be prepared in 50–55% yield by addition of diazobutane [11] to a mixed anhydride [10d,12], the *N*-tosyl diazoketone **4** could not be prepared by the same methodology. However, reaction of diazobutane with the intermediate acyl chloride [10h,12], furnished the *N*-tosyl diazoketone **4** in an overall yield of 41–45%. The moderate yields obtained for these reactions can be ascribed to the lower reactivity of higher diazoalkanes when compared to diazomethane. The superiority of diazomethane was clearly demonstrated when we replaced diazobutane by diazomethane during preparation of diazoketones **5** and **6** (Scheme 3).

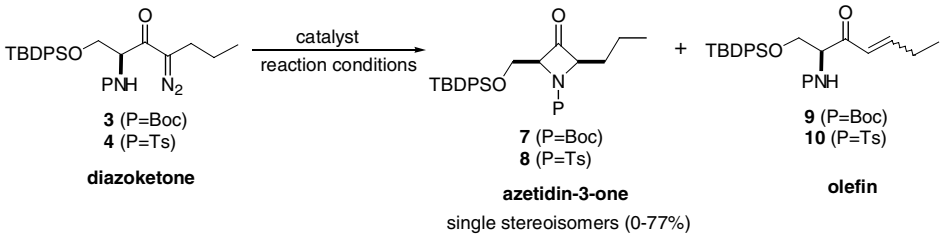
Diazoketones **3** and **4** were then submitted to N–H insertion reactions under several reaction conditions aiming at finding the best experimental protocol to prepare the 2,4-disubstituted azetidin-3-ones (Scheme 4).

The best conditions found for the synthesis of the azetidin-3-ones were obtained when using copper acetylacetonate or copper acetate and the *N*-tosyl diazoketone **4** in refluxing benzene (entries **10**, **11** and **16**, Table 1). It is worth mentioning that in all cases where azetidin-3-ones where isolated only the *cis* stereoisomer was detected. The *cis* stereochemistry was assigned based on nOe experiments and will be discussed in more details below. Together with the *cis*-2,4-disubstituted-azetidin-3-ones,




a: ClCOOEt, $Et_3N$, THF, -21-0°C, 30 min. Then, diazoalkane, 0°C-rt, 2h. b: ClCOCOCl, $CH_2Cl_2$, 0°C-rt, 2h. Then, THF, diazoalkane, 0°C, 2h.

Scheme 3. Preparation of diazoketones via acyl chlorides and mixed anhydrides.




Scheme 4. Metal catalyzed N–H insertion in the synthesis of 2,4-disubstituted azetidin-3-ones.

Table 1
Conditions evaluated for the metal catalyzed N–H insertion

| Entry | Diazoketone | Catalyst[a] | Conditions[b] | Azetidin-3-one (%)[c] | Olefin (%) (*E*:*Z*[c]) |
|---|---|---|---|---|---|
| 1 | 3 | $Rh_2(OAc)_4$ | $CH_2Cl_2$, 0 °C, 1 h | **7** (~ 35) | **9** (nd)[d] |
| 2 | 3 | $Cu(acac)_2$ | $CH_2Cl_2$, rt, 12 h | Complex mixture | |
| 3 | 4 | $Rh_2(OAc)_4$ | $CH_2Cl_2$, rt, 15 min | **8** (0) | **10** (89) (10:90) |
| 4 | 4 | $Rh_2(OAc)_4$ | $C_6H_6$, rt, 45 min | **8** (0) | **10** (63) (25:75) |
| 5 | 4 | $Rh_2(OAc)_4$ | $C_6H_6$, reflux, 1 min | **8** (0) | **10** (81) (33:67) |
| 6 | 4 | $Rh_2(cap)_4$ | $CH_2Cl_2$, rt, 12 h | **8** (0) | **10** (77) (25:75) |
| 7 | 4 | $Cu(acac)_2$ | $CH_2Cl_2$, rt, 24 h | No reaction | |
| 8 | 4 | $Cu(acac)_2$ | $C_6H_6$, rt, 24 h | **8** (0) | **10** (67) (100:0) |
| 9[e] | 4 | $Cu(acac)_2$ | $C_6H_6$, 60 °C, 45 min | **8** (41) | **10** (35) (70:30) |
| 10 | 4 | $Cu(acac)_2$ | $C_6H_6$, reflux, 1 min | **8** (67) (61)[f] | **10** (22) (66:34) |
| 11[g] | 4 | $Cu(acac)_2$ | $C_6H_6$, reflux, 1 min | **8** (62) | **10** (18) (95:05) |
| 12 | 4 | $Cu(acac)_2$ | PhMe, reflux, 1 min | **8** (traces) | **10** (74) (65:35) |
| 13 | 4 | $Cu(hfacac)_2$ | $CH_2Cl_2$, rt, 12 h | **8** (0) | **10** (80) (70:30) |
| 14 | 4 | $Cu(hfacac)_2$ | $C_6H_6$, rt, 12 h | **8** (0) | **10** (85) (51:49) |
| 15 | 4 | $Cu(hfacac)_2$ | $C_6H_6$, reflux, 1 min | **8** (0) | **10** (90) (64:36) |
| 16 | 4 | $Cu(OAc)_2.H_2O$ | $C_6H_6$, reflux, 1 min | **8** (77) | **10** (17) (67:33) |
| 17 | 4 | $CuCl_2$ | $C_6H_6$, reflux, 1 min | **8** (36) | **10** (60) (82:18) |
| 18 | 4 | $CuBr.SMe_2$ | $C_6H_6$, reflux, 1 min | **8** (21) | **10** (55) (69:31) |

*Abbreviations*. $Cu(acac)_2$: bis(acetylacetonato)copper(II); $Cu(hfacac)_2$: bis(trifluoracetylacetonato)copper(II); $Rh_2(cap)_4$: dirhodium(II) caprolactamate.

[a] $Rh_2(OAc)_4$: 2 mol%, Cu catalysts: 10 mol%.

[b] Catalyst was added in one portion after the desired temperature was attained (except for entry 11[g]). All the reactions were performed in a 0.05 M solution of the diazo compound.

[c] Azetidin-3-one 8 and the olefins have similar $R_f$ and their ratios were determined by $^1$H RMN analysis after filtration of the crude mixture on silica (30% EtOAc/hexane). To assure the validity of the $^1$H RMN analysis, the ratio of the compounds obtained in entry 10 was also determined after separation by flash chromatography[f] (10% EtOAc/hexane).

[d] *E:Z* ratio not determined. The reaction furnished an inseparable mixture of products.

[e] Internal temperature.

[f] Isolated yields (flash chromatography).

[g] Addition of the catalyst as a solution in $CH_2Cl_2$.

two side products were isolated and characterized as the olefins **10a** (*E*) and **10b** (*Z*). Interestingly, the ratio between these two olefins varies greatly according to the reaction conditions, mainly with respect to the catalyst employed. For example, reaction conditions described in entry 8 ($Cu(acac)_2$ as catalyst) furnished exclusive the *E* olefin **10a**, whereas conditions described in entry 3 ($Rh_2(OAc)_4$ as catalyst) provided the *Z* olefin **10b** as the major stereoisomer. A clear trend was observed from these studies: the *Z* olefins predominate under Rh catalysis while copper catalysis favors the *E* olefins. This relationship between the *E:Z* olefin ratio and the metal catalyst employed can be ascribed to the size of these metal catalysts. Fig. 1 illustrates the two possible pathways for the β-hydride elimination leading to the *E* and *Z* olefins. In the Newman projection leading to the *E* olefin (representation A) the alkyl group attached to C2 is placed next to (synperiplanar) the metal catalyst, whereas in the Newman projection leading to the *Z* olefin (representation B) the alkyl group is farther apart from the metal and closer to the OTBDPS group. The active catalyst species for the copper(II) catalysts should be a Cu (I) bearing one ligand [9,13] and comparing its size to that of $Rh_2(OAc)_4$ and $Rh_2(cap)_4$, the Rh catalyst is the bulkiest catalyst. We believe that under Rh catalysis, path B should be the preferred one leading to the *Z* olefins whereas under copper catalysis path A is the main route, therefore leading to the *E* olefins.

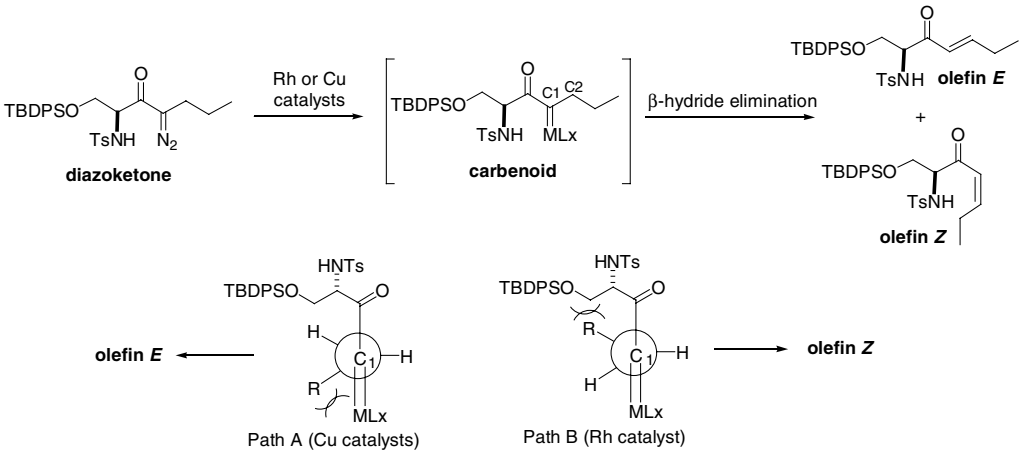
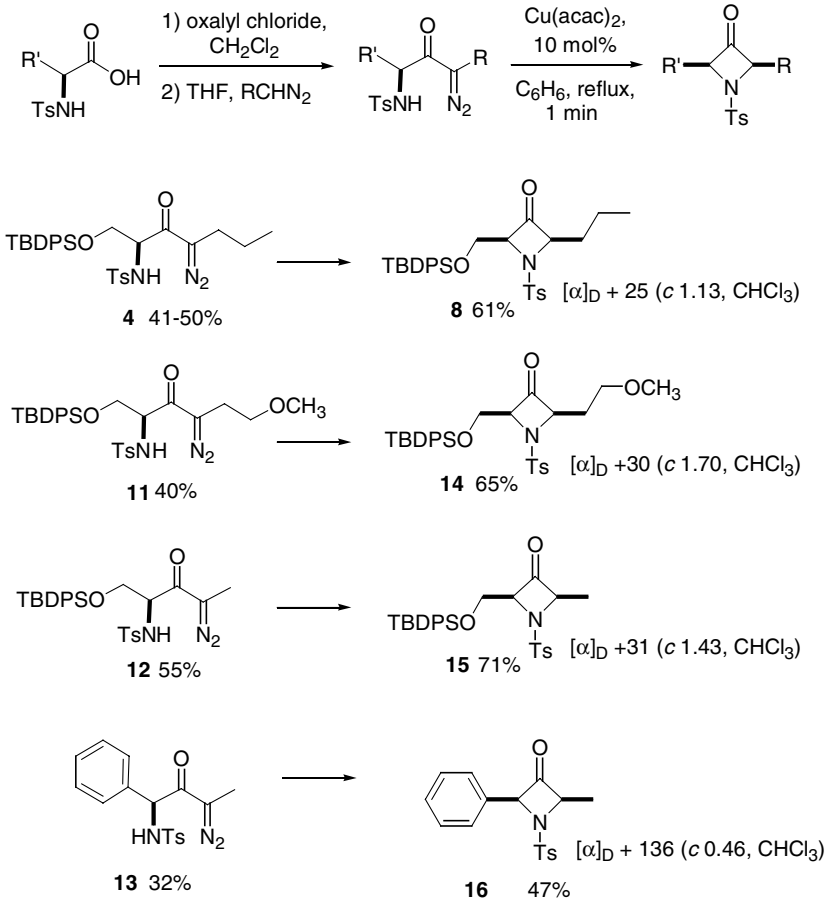



Fig. 1. Rationale for the β-hydride elimination.

Noteworthy, the above protocol for preparing azetidin-3-ones from *N*-tosyl amino acids does not promote epimerization of the incipient center at C2. Chiral HPLC analyses confirmed the stereochemical integrity of theses azetidin-3-ones [14]. Having established the best conditions for carrying out the synthesis of the diazoketones and their conversion into the corresponding azetidin-3-ones we decided to prepare a number of azetidin-3-ones in order to probe the scope of the methodology. In all the cases examined, the *cis*-azetidin-3-ones **14**–**16** were synthesized in moderate yields as the only observable stereoisomer [15] (Scheme 5).

The *cis* stereochemical outcome observed for the N–H insertion reaction was supported by nOe experiments on azetidin-3-ones **8**, **14**, **15**, **16** (Fig. 2). For azetidin-3-ones **8** and **15** the hydrogens at C2 and C4




Scheme 5. Synthesis of azetidin-3-ones from diazoketones.

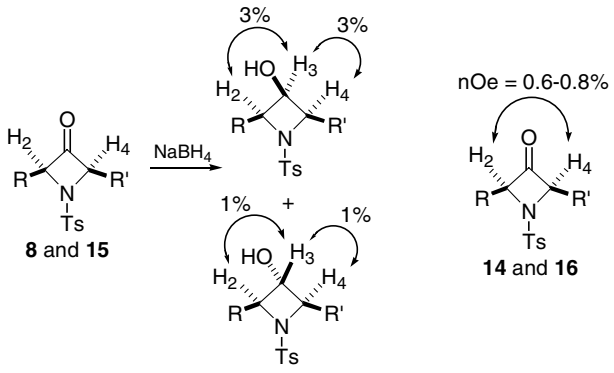


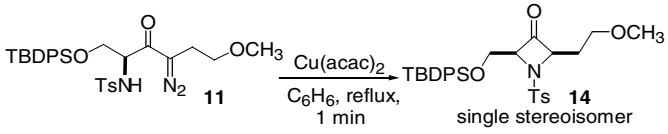

Fig. 2. nOe studies on azetidin-3-ones.

displayed similar chemical shifts and no nOe experiments could be realized. However, nOe experiments carried out on the corresponding alcohols of azetidinones **8** and **15** permitted unambiguous assignments.

The influence of the catalyst loading in the N–H insertion reactions was also investigated (Scheme 6). Varying the catalyst loading from 100 to 5 mol% did not affect the yield of the carbenoid N–H insertion product significantly. However, catalyst loading below 1 mol% caused a drastic decrease in yields.

Despite intense investigations on the mechanism of C–H insertion by rhodium carbenoids [16] the N–H insertions have not been investigated to the same extent and the analogy between these two processes is not straightforward. Nakamura [16c] and co-workers have reported an interesting theoretical study for C–H insertion assuming a concerted but nonsynchronous (three-centered hydride transfer) transition state, whereas a synchronous three-centered concerted transition state was proposed by Doyle et al. [16b]. The N–H insertion deserves a different approach because of the nonbonding electron pair on the nitrogen. The N–H insertion mechanism is still unclear, but a stepwise mechanism involving ylides [9] as well as concerted three or four-centered TS have been proposed [17]. As depicted in Fig. 3, both the concerted three-centered and the ylide process can explain the observed stereochemical outcome. Therefore, a plausible explanation for the interesting *cis* stereochemical outcome can be put forward considering a transition state where both the alkyl group and the bulky $ML_n$ ($Rh_2(OAc)_4$ or $Cu(acac)_2$) are *anti*.

To further demonstrate the synthetic potential of the azetidin-3-ones synthesized in this work, we have constructed the fully-substituted azetidine **19** starting from *N*-Boc-azetidin-3-one **7** or *N*-tosyl-azetidin-3-one **8** (Scheme 7). Introduction of the alcohol functionality at C3 was carried out by reducing azetidin-3-one **7** with $NaBH_4$ at −21 °C in $CH_3OH$. The only detectable diastereoisomer, the all *cis* azetidin-3-ol **17** (*Re* face attack of the hydride at C3), was already expected as the major diastereoisomer, since the *Si* face of the carbonyl in azetidinone **7** was rather congested by the C2 and C4 groups. Previous results from our laboratory and some precedents from the literature [10d] confirm this stereochemical trend. Cleavage of the TBDPS group of **17** with tetrabutylammonium fluoride (TBAF) followed by treatment of the free diol **18** with trifluoroacetic acid furnished the azetidine alkaloid analogue **19** in 71% (over two steps). Starting with *N*-tosyl-azetidin-3-one **8** we carried out the synthesis in a very similar manner. Reduction of **8** with $NaBH_4$ at −21 °C in $CH_3OH$ gave a separable mixture of the *cis* (50%) and *trans* (20%) azetidin-3-ols **20a** and **20b**. After chromatographic separation, cleavage of the tosyl group of **20a** with Na/naphthalene in DME, followed by treatment of the crude amine **21** with tetrabutylammonium fluoride (TBAF) provided (after acidification with trifluoroacetic acid) the azetidine salt **19** in 50% yield (over two steps) (Scheme 7).




| entry | $Cu(acac)_2$ (mol %)[a] | azetidin-3-one[b] (%) |
|---|---|---|
| | | |
| 1 | 100 | 63 |
| 2 | 10 | 64 |
| 3 | 5 | 64 |
| 4 | 1 | 55 |
| 5 | 0.1 | no reaction |

a.The catalyst was added as a solution in 0.65 mL of $CH_2Cl_2$. All the reactions were performed with 0.06 mmol of the diazo compound in 1.2 mL of $C_6H_6$; b. Isolated yield.

Scheme 6. Catalyst loading studies.

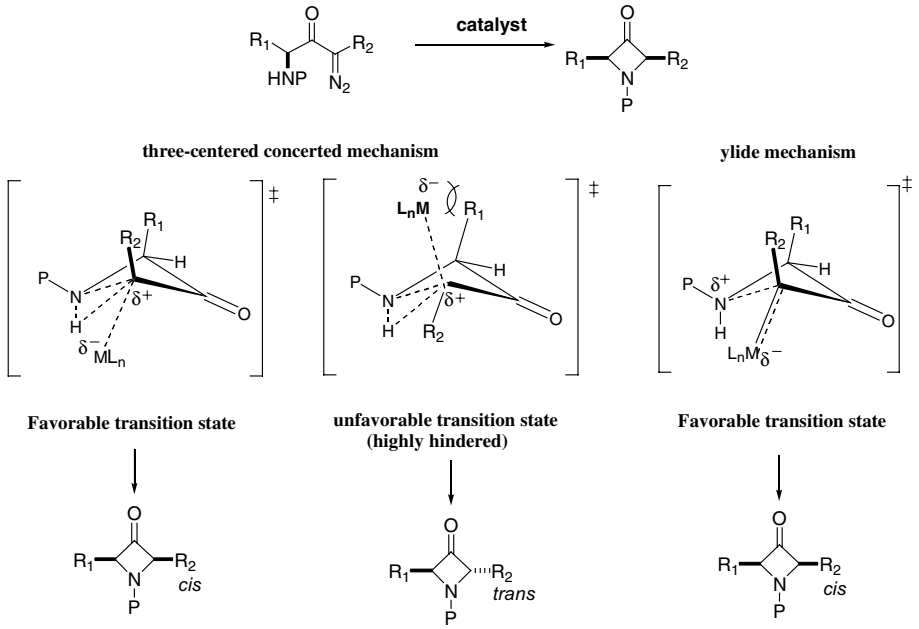
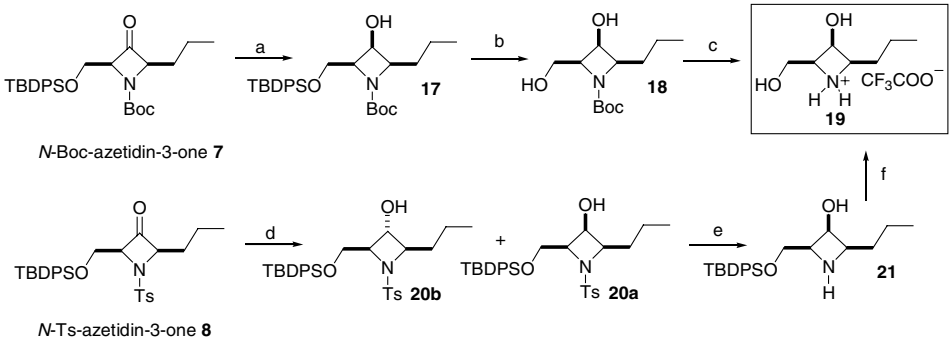



Fig. 3. Rationale for the *cis* stereochemistry.




a: $NaBH_4$, MeOH, -21°C, 30 min (46%). b: TBAF, THF, 0°C-rt, 3h (71%). c: TFA, $CH_2Cl_2$, 0°C, 1h (quantitative). d: $NaBH_4$, MeOH, -21°C, 30 min (50% *cis* and 20% *trans*). e: Na/naphthalene/DME. f: TBAF, THF, 0°C-rt, 3h then, TFA (50%).

Scheme 7. Synthesis of the sphingosine analogue **19**.

The *cis* stereochemistry was confirmed by nOe experiments on azetidin-3-ols **17**, **18** and **20** (Fig. 4). Irradiation at H3 of alcohol **17** showed a nOe with H2 and H4 of 3.0% for each hydrogen, while irradiation of the $CH_2$ at C4, showed a nOe with the secondary hydroxyl of 1.8%. For azetidinol **18**, a nOe was observed involving H2 (1.5%) and H4 (1.4%) when H3 was irradiated, as well as a small nOe (0.5%) involving the hydroxyl group when the methylene of the $CH_2OH$ group was irradiated.

In the case of azetidin-3-ols **20a** and **20b** identical nOe values were observed for H2 and H4 when H3 was irradiated and are strong evidence for the *cis* stereochemistry of the alkyl groups at C2 and C4. The correct stereochemistry for compounds **20a** (*cis, cis*) and **20b** (*trans*, *trans*) were also suggested by the magnitude of the nOe values (3.0% and 1.0%, respectively).

## 3. Conclusion

In summary, we have demonstrated that metal carbenoid insertion of α,α′-dialkyl-α-diazoketones can be a viable and effective tool for the construction of fully substituted azetidines from commercially available amino acids. Chiral *cis*-2,4-disubstituted azetidin-3-ones were readily prepared in just two steps from the protected amino acids by the addition of diazoalkanes followed by a metal catalyzed N–H insertion of the diazoketone formed. The combination of *N*-tosyl diazoketones with

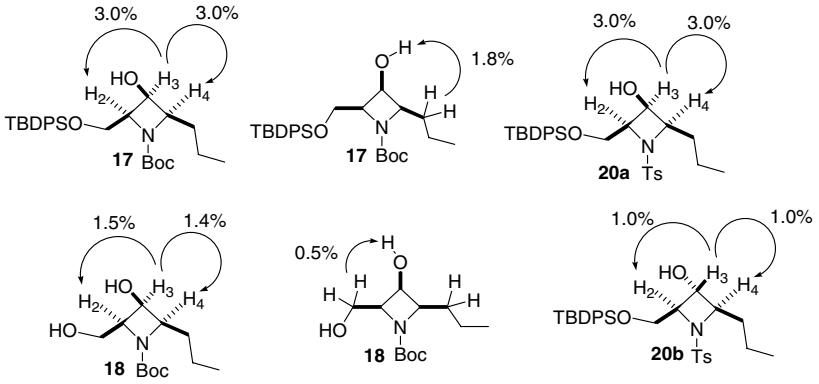



Fig. 4. nOe studies on the synthesized azetidines.

the cheap $Cu(acac)_2$ or $Cu(OAc)_2$ catalysts provided the highest yields for the N–H insertion reactions. The methodology can also be applied to the synthesis of several *cis*-2,4-disubstituted azetidin-3-ones, depending only on the amino acid and diazoalkane employed.

## 4. Experimental

### 4.1. General procedures

Reagents and solvents are commercial grade and were used as supplied, except when specified in the experimental procedure. In the cases where dry solvents were employed, $Et_3N$, DMF and $CH_2Cl_2$ were distilled from calcium hydride and THF were distilled from Na. $Rh_2(OAc)_4$ [18] and $Cu(acac)_2$ [19] were prepared as described in the literature. $^1H$ NMR and $^{13}C$ NMR data were recorded on a Varian Gemini 2000 (7.0 T) or Varian Inova (11.7 T) spectrometer. High resolution mass spectra (HRMS) were measured on a VG Autospec-Micromass spectrometer. IR spectra were obtained on a Thermo-Nicolet IR-200 spectrometer. Optical rotations were measured at 25 °C with a Perkin–Elmer 241 instrument.

### 4.2. General procedure for the protection of N-Boc-L-serine [20] and N-Ts-L-serine [21] with TBDPSCl

To a 4.0 M solution of *N*-protected serine (43.0 mmol) in dry DMF was added 150.5 mmol of imidazole and 53.8 mmol of TBDPSCl. The viscous mixture was stirred for 36 h and then the solvent evaporated in vacuum. Next, water was added to the crude product followed by addition of a 10% solution of citric acid (pH 3.0) under stirring. The product was extracted with $Et_2O$ (3*x*). NaCl was added to the aqueous layer and extracted once again with $Et_2O$. The combined organic layers were dried over anhydrous $Na_2SO_4$, evaporated in vacuum and the residue subjected to column chromatography when necessary.

#### 4.2.1. (S)-N-(tert-butyloxycarbonyl)-O-(tert-butyldiphenylsilyl)-serine

Quantitative yield following the procedure above. White solid, m.p. 147–149 °C. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 7.56$–$7.69$ (m, 4H), 7.32–7.48 (m, 6H), 5.40 (d, $J = 8.8$ Hz, 1H), 4.44 (m, 1H), 4.12 (dd, $J = 10.3$, 2.2 Hz, 1H), 3.91(dd, $J = 10.3$, 2.9 Hz, 1H), 1.45 (s, 9H), 1.04 (s, 9H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 175.4$, 155.3, 135.4, 135.3, 132.7, 132.4, 129.8, 127.7, 80.2, 64.3, 55.4, 28.4, 26.8, 19.4. IR ($cm^{-1}$): 3448, 3277, 3077, 3052, 2964, 2935, 2862, 1724, 1665, 1176, 1113, 703. ESI-MS: 444 (M + 1), 310, 266, 238, 232, 188, 160. HRMS *m*/*z* Calc. for $C_{20}H_{24}NO_4Si$ ($M^+ - OtBu$) 370.1475, Found: 370.1367.

#### 4.2.2. (S)-N-(p-toluene-sulphonyl)-O-(tert-butyldiphenylsilyl)-serine

70–90% yield after column chromatography, 5% MeOH/chloroform as eluent. Colorless amorphous solid. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 7.18$–$7.72$ (14H, Ar), 5.53 (d, $J = 8.1$ Hz, 1H), 3.95–4.08 (m, 2H), 3.78 (dd, $J = 9.5$, 3.7 Hz, 1H), 2.36 (s, 3H), 0.95 (s, 9H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 174.1$, 143.6, 136.7, 135.3, 132.1, 132.0, 129.9, 129.5, 127.7, 126.9, 64.8, 57.1, 26.8, 21.6, 19.3. IR ($cm^{-1}$): 3277, 2929, 2856, 1727, 1427, 1427, 1334, 1163, 1112. HRMS *m*/*z* Calc. for $C_{22}H_{22}NO_5SSi$ ($M^+ - tBu$) 440.0988, Found: 440.1084.

### 4.3. General procedure for the preparation of diazoketones

#### 4.3.1. Procedure A (via mixed anhydride)

To a solution of the *N*-Boc amino acid (3.41 mmol) in 17 ml of dry THF was added 3.75 mmol of dry $Et_3N$. The solution was then cooled to −21 °C and 3.75 mmol of ethyl chloroformate was added dropwise. The reaction flask was then allowed to warm to 0 °C. After stirring for 30 min at 0 °C, a solution of freshly prepared diazoalkane in ether was added (excess) and the stirring continued for 2 h at room temperature. After this time

the solution was concentrated in vacuum and the crude product purified by flash column chromatography.

#### 4.3.2. (2S)-2-(N-tert-butyloxycarbonyl)-amino-1-tert-butyldiphenylsilyloxy-4-diazo-heptan-3-one (**3**)

Purified by flash column chromatography (10% ethyl acetate/hexane with 1% of $Et_3N$), yellowish oil (50%). $^1H$ NMR (300 MHz, $C_6D_6$, 70 °C): $\delta = 7.64$–$7.80$ (m, 4H), 7.19–7.28 (m, 6H), 5.34 (m, 1H, NH), 4.84 (m, 1H, CH), 3.86 (d, $J = 6.1$ Hz, 2H), 2.02–2.12 (m, 2H), 1.00–1.52 (2s-18H, 1m-2H), 0.70 (t, $J = 7.3$ Hz, 3H). IR ($cm^{-1}$): 3350, 3072, 3052, 2964, 2930, 2867, 2085, 1714, 1636, 1113, 707. ESI-MS: 510 (M + 1), 342, 304, 287, 226, 220. HRMS *m/z* Calc. for $C_{24}H_{31}NO_4Si$ ($M^+ - N_2$, -isobutene) 425.2022, Found: 425.2086.

### 4.4. Procedure B (via acyl chloride)

To a solution of the *N*-tosyl amino acid (1.13 mmol) in 6.0 ml of dry $CH_2Cl_2$ at 0 °C was added 1.36 mmol of oxalyl chloride (1.2 equiv.), followed by one drop of dry DMF. After 2 h of stirring at room temperature, the solvent was evaporated in vacuum and 6.0 ml of dry THF was added to the pale yellow oil. The resulting solution was cooled to 0 °C and a freshly prepared solution of the diazoalkane in ether was added (2 equiv. or more). After stirring for 1 h at 0 °C, the solution was concentrated in vacuum and the crude product purified by flash column chromatography.

#### 4.4.1. (2S)-2-(N-p-toluene-sulphonyl)-amino-1-tert-butyldiphenylsilyloxy-4-diazo-heptan-3-one (**4**)

Purified by flash column chromatography (20% ethyl acetate/hexane with 1% of $Et_3N$), pale yellow oil (41–45% yield). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta =$ 7.24–7.72 (14H, Ar), 5.55 (d, $J = 8.9$ Hz, 1H, NH), 4.20–4.30 (m, 1H, CH), 3.77 (dd, $J = 5.2$, 9.8 Hz, 1H), 3.62 (m, 1H), 2.41 (s, 3H), 2.04–2.17 (m, 2H), 1.29 (m, 2H), 1.01 (s, 9H), 0.84 (t, $J = 7.3$ Hz, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta = 189.8$, 143.7, 136.8, 135.4, 132.2 (2s), 129.9 (2s), 129.6, 127.8 (2s), 127.0, 68.5, 65.4, 57.2, 26.6, 24.5, 21.4, 20.2, 19.0, 13.2. IR ($cm^{-1}$): 3253, 2959, 2930, 2859, 2078, 1616, 1164, 1112, 1091, 702. HRMS *m/z* Calc. for $C_{26}H_{28}NO_4SSi$ ($M^+ - N_2$,-*t*Bu) 478.1508, Found: 478.1587.

#### 4.4.2. (2S)-2-(N-p-toluene-sulphonyl)-amino-1-tert-butyldiphenylsilyloxy-4-diazo-pentan-3-one (**12**)

Purified by flash column chromatography (20% ethyl acetate/hexane containing 1% of $Et_3N$) (55% yield), pale yellow oil. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 7.20$–$7.72$ (m, 14H), 5.46 (d, $J = 8.8$ Hz, 1H), 4.24 (m, 1H), 3.74 (m, 1H), 3.58 (m, 1H), 2.41 (s, 3H), 1.75 (s,3H), 0.99 (s, 9H). $^{13}C$ NMR (75 MHz, $C_6D_6$): $\delta = 190.0$, 142.9, 138.4, 135.8, 135.2, 130.2, 129.5, 128.1, 127.4, 65.6, 57.4, 27.0, 21.2, 19.4, 8.1. IR ($cm^{-1}$): 3227, 3072, 3043, 2927, 2855, 2081, 1616, 1164, 1111, 1091, 702. HRMS *m/z* Calc. for $C_{28}H_{33}N_3O_4SSi$ 535.1961, Found: 535.1982.

#### 4.4.3. (2S)-2-(N-p-toluene-sulphonyl)-amino-1-tert-butyldiphenylsilyloxy-4-diazo-6-methoxy-hexan-3-one (**11**)

Purified by flash column chromatography (3% ethyl acetate/chloroform) (35–40% yield), pale yellow oil. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 7.20$–$7.78$ (m, 14H), 5.48 (d, $J = 8.8$ Hz, 1H), 4.26 (ddd, $J = 9.2$, 8.8, 4.9 Hz, 1H), 3.74 (dd, $J = 9.2$, 4.9 Hz, 1H), 3.60 (br t, $J = 9.2$ Hz, 1H), 3.29 (m, 2H), 3.22 (s, 3H), 2.41 (s, 3H), 2.39 (m, 2H), 0.99 (s, 9H). $^{13}C$ NMR (75 Hz, $CDCl_3$): $\delta = 189.5$, 143.6, 135.4, 132.2, 130.0, 129.9, 129.5, 127.8, 127.7, 127.1, 70.3, 67.7, 65.4, 58.7, 57.2, 26.7, 23.5, 21.6, 19.1. IR ($cm^{-1}$): 3233, 3069, 2930, 2858, 2088, 1616, 1351, 1164, 1112, 1091, 733, 702. HRMS *m/z* Calc. for $C_{26}H_{28}NO_5SSi$ ($M^+ - N_2$,-*t*Bu) 494.1457, Found: 494.1490.

#### 4.4.4. (1S)-1-(N-p-toluene-sulphonyl)-amino-3-diazo-1-phenyl-butan-2-one (**13**)

In this case, 1.5 equiv. of oxalyl chloride were used instead of 1.2. Purified by flash column chromatography (30% ethyl acetate/hexane containing 1% of $Et_3N$) (32% yield), pale yellow oil. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 7.49$ (d, $J = 8.1$ Hz, 2H), 7.04–7.30 (m, 7H), 6.16 (broad d, 1H), 5.21 (d, $J = 6.6$ Hz, 1H), 2.35 (s, 3H), 1.83 (s, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 188.0$, 143.0, 137.3, 129.1, 128.5, 127.8, 126.8, 62.9, 61.0, 21.5, 8.3. IR ($cm^{-1}$): 3358, 3257, 3060, 2929, 2083, 1611, 1351, 1165. HRMS *m/z* Calc. for $C_{17}H_{17}N_3O_3S$ 343.0991, Found: 343.0992.

### 4.5. General procedure for the preparation of N-tosyl azetidin-3-ones

0.63 mmol of diazoketone was dissolved in 13 ml of benzene and the yellow solution heated to reflux. Next, 10 mol% of $Cu(acac)_2$ was added in portions to the reaction turning the reaction mixture from yellow to brown immediately, with vigorous liberation of nitrogen. *CAUTION: liberation of nitrogen can be quite violent and large scale reactions (more than 10 mmols) should be carried out in a large reaction flask to permit nitrogen liberation* (open system). After one minute, the reaction was cooled, the solvent evaporated, and the crude product purified by *flash* column chromatography to furnish the corresponding azetidin-3-one.

#### 4.5.1. (2S 4R)-N-(p-toluene-sulphonyl)-2-(tert-butyldiphenylsilyloxymethyl)-4-propyl-azetidin-3-one (**8**)

Purified by flash column chromatography (10% ethyl acetate/hexane) (61% yield), colorless oil. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 7.28$–$7.80$ (14H, Ar), 4.67 (t, $J = 2.5$ Hz, 1H, H2), 4.62 (t, $J = 7.3$ Hz, 1H, H4),

3.78–3.90 (2dd, $J = 11.7$, 2.9 Hz, 2H), 2.44 (s, 3H), 1.92 (q, $J = 7.3$ Hz, 2H), 1.51 (m, 2H), 1.04 (s, 9H), 0.90 (t, $J = 7.3$, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 198.4$, 144.4, 135.4, 132.4 (2s), 129.6 (2s), 128.1, 127.6, 83.2, 83.6, 61.6, 32.2, 26.6, 21.6, 19.2, 18.4, 13.8. IR ($cm^{-1}$): 3075, 2962, 2931, 2856, 1826, 1429, 1350, 1165, 1109, 825, 705. HRMS *m/z* Calc. for $C_{26}H_{28}NO_4SSi$ ($M^+ - t$Bu) 478.1508, Found: 478. 1328.

*4.5.2. (2S) (4E)-2-(N-p-toluene-sulphonyl)-amino-1-tert-butyldiphenylsilyloxy-hept-4-en-3-one (**10a**) (14%)*

$^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.16$–7.74 (14H), 6.85 (dt, $J = 16.1$, 6.2 Hz, 1H), 6.11 (dt, $J = 16.1$, 1.5 Hz, 1H), 5.76 (d, $J = 7.3$ Hz, 1H), 4.19 (m, 1H), 3.91 (dd, $J = 11.0$, 3.7 Hz, 1H), 3.79 (dd, $J = 11.0$, 4.8 Hz, 1H), 2.37 (s, 3H), 2.16 (dq, 7.3, 1.5 Hz, 2H), 1.00 (t, $J = 7.3$ Hz, 3H), 0.97 (s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 194.4$, 151.0, 143.1, 136.9, 132.5, 129.7, 129.4, 127.6, 126.9, 125.2, 64.9, 61.1, 26.8, 25.8, 21.6, 19.3, 12.0. IR ($cm^{-1}$): 3276, 3072, 3039, 2959, 2931, 2857, 1699, 1627, 1427, 1340, 1164, 1112, 1091, 702. HRMS *m/z* Calc. for $C_{30}H_{37}NO_4SSi$ 535.2213, Found: 535.2026.

*4.5.3. (2S) (4Z)-2-(N-p-toluene-sulphonyl)-amino-1-tert-butyldiphenylsilyloxy-hept-4-en-3-one (**10b**) (8%)*

$^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.16$–7.76 (15H), 6.04–6.20 (m, 1H), 5.77 (d, $J = 7.3$ Hz, 1H), 3.74–4.04 (2m, 3H), 2.50 (q, $J = 7.3$ Hz, 2H), 2.38 (s, 3H), 0.95–1.05 (12H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 194.8$, 153.6, 143.2, 135.4, 129.7, 129.5, 127.8, 127.7, 127.6, 127.0, 126.9, 122.6, 64.7, 63.1, 26.8, 23.5, 21.6, 19.3, 13.4. IR ($cm^{-1}$): 3290, 3075, 3048, 2962, 2935, 2863, 1701, 1622, 1426, 1343, 1165, 1113, 1090, 705. ESI-MS: 536 (M + 1), 458, 380, 350.

*4.5.4. (2S 4R)-N-(p-toluene-sulphonyl)-2-(tert-butyldiphenylsilyloxymethyl)-4-methyl-azetidin-3-one (**15**)*

Purified by flash column chromatography (10% ethyl acetate/hexane) (71% yield), colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.76$ (d, $J = 8.1$ Hz, 2H), 7.62–7.72 (m, 5H), 7.30–7.50 (m, 7H), 4.68–4.76 (m, 2H), 3.86 (dd, $J = 12.5$, 2.2 Hz, 1H), 3.81 (dd, $J = 12.5$, 2.2 Hz, 1H), 2.45 (s, 3H), 1.50 (d, $J = 7.3$ Hz, 3H), 1.03 (s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 198.4$, 144.4, 135.4, 132.7, 132.4, 129.8, 129.7, 128.2, 127.6, 83.6, 79.1, 61.4, 26.6, 21.7, 19.2, 15.0. IR ($cm^{-1}$): 3071, 3048, 2958, 2933, 2856, 1822, 1346, 1161, 1116, 956, 708. HRMS *m/z* Calc. for $C_{28}H_{33}NO_4SSi$ 507.1900, Found: 507.1818.

*4.5.5. (2S 4R)-N-(p-toluene-sulphonyl)-2-(tert-butyldiphenylsilyloxymethyl)-4-(methoxy-etane)-azetidin-3-one (**14**)*

Purified by flash column chromatography (20% ethyl acetate/hexane) (65% yield), colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.30$–7.84 (14H, Ar), 4.74 (dd, $J = 7.3$, 5.9 Hz, 1H), 4.63 (t, $J = 2.9$ Hz, 1H), 3.92 (dd, $J = 11.7$, 2.9 Hz, 1H), 3.87 (dd, $J = 11.7$, 2.9 Hz, 1H), 3.48–3.67 (m, 2H), 3.31 (s, 3H), 2.44 (s, 3H), 2.02–2.28 (m, 2H), 1.04 (s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 198.1$, 144.6, 135.5, 132.4, 131.6, 129.8, 129.7, 128.4, 127.6, 84.2, 80.3, 67.3, 61.9, 58.4, 30.1, 26.7, 21.7, 19.4. IR ($cm^{-1}$): 3076, 2924, 2856, 1822, 1354, 1165, 1103, 747, 704. HRMS *m/z* Calc. for $C_{26}H_{28}NO_5SSi$ ($M^+$-$t$Bu) 494.1457, Found: 494.1291.

*4.5.6. (2S 4R)-N-(p-toluene-sulphonyl)-2-(tert-butyldiphenylsilyloxymethyl)-4-phenyl-azetidin-3-one (**16**)*

Purified by flash column chromatography (20% ethyl acetate/hexane) (47% yield), colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.78$ (d, $J = 8.1$ Hz, 2H), 7.30–7.38 (m, 7H), 5.56 (s, 1H), 4.88 (q, $J = 7.3$ Hz, 1H), 2.45 (s, 3H), 1.51 (d, $J = 7.3$Hz, 3H).$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 197.0$, 144.8, 132.4, 132.2, 129.8, 128.7, 128.6, 128.3, 126.3, 84.2, 78.6, 21.7, 16.0. IR ($cm^{-1}$): 3067, 3030, 2931, 2856, 1814, 1346, 1161, 1116, 1093. HRMS *m/z* Calc. for $C_{17}H_{17}NO_3S$ 315.0929, Found: 315.0937.

*4.5.7. (2S, 4R)-N-(tert-butyloxycarbonyl)-2-(tert-butyldiphenylsilyloxymethyl)-4-propyl-azetidin-3-one (7)*

609 mg (1.2 mmol) of diazoketone **3** in 24 ml of dry $CH_2Cl_2$ was cooled to 0 °C and 11 mg of $Rh_2(OAc)_4$ (2 mol%) were added. After 1 h, the solvent was removed under vacuum and the crude product purified by flash chromatography (5% ethyl acetate/hexane) to give 223 mg of a mixture of two compounds displaying almost identical Rfs. Reduction of this mixture with $NaBH_4$ in MeOH provided, after flash chromatography, the azetidine-3-ol **17** and the unidentified side product (33 mg). An analytical sample of azetidin-3-one **7** was obtained by oxidation of the azetidin-3-ol **17** with IBX in ethyl acetate under reflux. $^1$H NMR (300 MHz, $C_6D_6$, 70 °C): $\delta = 7.72$–7.83 (m, 4H), 7.18–7.34 (m, 6H), 4.53 (t, $J = 7.3$ Hz, 1H, H4), 4.48 (t, $J = 2.9$ Hz, 1H, H2), 3.98 (dd, $J = 11.7$, 2.9 Hz, 1H), 3.81 (dd, $J = 11.7$, 2.9 Hz, 1H), 2.02 (m, 1H), 1.88 (m, 1H), 1.04–1.64 (2s-18H, m-2H), 0.85 (t, $J = 7.3$, 3H). $^{13}$C NMR (125 MHz, $C_6D_6$): $\delta = 201.4$, 156.5, 135.9, 133.3, 133.1, 130.0, 129.9, 128.1, 82.4, 81.4, 79.7, 61.8, 32.3, 28.2, 26.8, 19.3, 19.1, 13.9. IR ($cm^{-1}$): 3077, 3047, 2969, 2935, 2857, 1826, 1714, 1377, 1113, 712. ESI-MS: 482 (M + 1), 348, 304, 226, 186. HRMS *m/z* Calc. for $C_{28}H_{39}NO_4Si$ 481.2648, Found: 481.2461.

*4.6. Typical procedure for the reduction of azetidin-3-ones*

*4.6.1. (2S, 3S, 4R)-N-(tert-butyloxycarbonyl)-2-(tert-butyldiphenylsilyloxymethyl)-4-propyl-azetidin-3-ol (17)*

102.9 mg (0.21 mmol) of azetidin-3-one **7** was dissolved in 1.0 ml of methanol and the solution was cooled

to −21 °C, followed by the addition of 20 mg of $NaBH_4$. After stirring for 30 min, a 1 M solution of $NaHSO_4$ was added (pH 3.0) and the methanol removed in vacuum. The product was extracted four times with $CH_2Cl_2$ and the combined organic layers dried ($Na_2SO_4$) and concentrated. After purification by flash column chromatography (20% ethyl acetate/hexane), alcohol **17** (47.5 mg) was obtained as a colorless oil in 46% yield. $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.58$–$7.82$ (m, 4H), 7.31–7.54 (m, 6H), 4.68 (dt, $J = 10.3$, 7.3 Hz, 1H, H3) (turns into a triplet, $J = 7{,}3$ Hz, upon addition of $D_2O$), 4.34 (d, $J = 10.3$ Hz, 1H, OH), 4.14–4.30 (m, 2H, H2 and H4), 4,07 (m, 1H), 3.91 (dd, $J = 11.7$, 2.2 Hz, 1H), 1.74–2.00 (m, 2H), 1.26–1.56 (m, 2H), 1.01–1.20 (s, 9H), 0.93 (t, $J = 7.3$ Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 156.7$, 135.3, 135.2, 132.0, 131.7, 129.7, 129.6, 127.6, 127.5, 79.2, 67.3, 66.6 (br), 64.9 (br), 63.4, 30.8, 28.3, 26.8, 19.2, 19.0, 14.2. IR ($cm^{-1}$): 3487, 3082, 2969, 2930, 2857, 1699, 1367, 1123, 707. ESI-MS: 484 (M + 1), 384, 350, 306, 272, 228, 220. HRMS *m*/*z* Calc. for $C_{28}H_{41}NO_4Si$ 483.2805, Found: 483.2695.

#### 4.6.2. (2S, 3S, 4R)-N-(p-toluene-sulfonyl)-2-(tert-butyldiphenylsilyloxymethyl)-4-propyl-azetidin-3-ol (**20a**)

50%, $^1$H NMR (300 MHz, $CDCl_3 + D_2O$): $\delta = 7.24$–$7.84$ (14H, Ar), 4.31 (t, $J = 7.3$ Hz, 1H, H3), 4.11 (dd, $J = 11.7$, 3.7 Hz, 1H), 3.92 (dd, $J = 11.7$, 2.2 Hz, 1H), 3.76–3.88 (m, 2H), 2.44 (s, 3H), 1.76–2.04 (m, 2H), 1.36 (sext., $J = 7.3$ Hz, 2H), 1.10 (s, 9H), 0.92 (t, $J = 7.3$ Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 143.7$, 135.6, 135.4, 132.2 (2s), 131.4, 129.9, 129.4, 128.0, 127.7, 67.7, 66.8, 65.0, 64.0, 30.9, 26.9, 21.7, 19.2, 18.8, 14.2. IR ($cm^{-1}$): 3456, 3071, 3045, 2954, 2931, 2860, 1335, 1158, 1116, 1090, 701. HRMS *m*/*z* Calc. for $C_{26}H_{30}NO_4SSi$ ($M^+$-*t*Bu) 480.1665, Found: 480.1653.

#### 4.6.3. (2S, 3R, 4R)-N-(p-toluene-sulfonyl)-2-(tert-butyldiphenylsilyloxymethyl)-4-propyl-azetidin-3-ol (**20b**)

20%, $^1$H NMR (300 MHz, $CDCl_3 + D_2O$): $\delta = 7.28$–$7.70$ (14H, Ar), 3.97 (t, $J = 5.1$ Hz, 1H, H3), 3.80–3.92 (m, 2H), 3.39–3.51 (m, 2H), 2.44 (s, 3H), 1.80 (m, 1H), 1.63 (m, 1H), 1.36 (m, 2H), 1.08 (s, 9H), 0.92 (t, $J = 7.3$ Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 143.7$, 135.6, 133.2, 132.8, 132.0, 129.6 (2s), 128.2, 127.8, 70.4, 69.1, 63.4, 35.5, 26.9, 21.7, 19.4, 17.4, 14.1. IR ($cm^{-1}$): 3490, 3075, 3052, 2962, 2931, 2860, 1339, 1154, 1112, 705. HRMS *m*/*z* Calc. for $C_{26}H_{30}NO_4SSi$ ($M^+ - t$Bu) 480.1665, Found: 480.1643.

#### 4.6.4. (2S, 3S, 4R)-N-(tert-butyloxycarbonyl)-2-hydroxymethyl-4-propyl-azetidin-3-ol (**18**)

50 μl of a 1.0 M solution of TBAF in THF was added to a stirred solution of 15.6 mg (0.032 mmol) of the azetidin-3-ol **17** in 1.1 ml of THF at 0 °C. The solution was stirred for 3 h followed by evaporation of the solvent and purification of the crude product by flash column chromatography (60% ethyl acetate/hexane). Diol **18** was obtained as a white solid in 71% yield (5.6 mg). $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 4.62$ (q, $J = 7.3$ Hz, 1H, H3), 4.30 (m, 1H, H2), 4.21 (q, $J = 7.3$, 1H, H4), 3.99 (m, 1H), 3.89 (m, 1H), 3.47 (br s, 1H, OH), 2.65 (br s, 1H, OH), 1.18–1.94 (s-9H, 2m, 4H), 0.95 (t, $J = 7.3$ Hz, 3H).$^{13}$C NMR (125 MHz, $CDCl_3$): $\delta = 157.7$, 80.1, 66.7, 66.6, 66.0, 61.5, 30.7, 28.4, 19.2, 14.1. IR ($cm^{-1}$): 3380, 3297, 2974, 2940, 2872, 1680, 1396, 1162. ESI-MS: 246 (M + 1), 190, 172, 154, 146, 128, 116, 111.

#### 4.6.5. (2S, 3S, 4R)-2-hydroxymethyl-3-hydroxy-4-propyl-azetidinium trifluoroacetic salt (**19**)

3.1 mg (0.013 mmol) of diol **18** were dissolved in 0.2 ml of $CH_2Cl_2$ and the resulting solution cooled to 0 °C. Trifluoroacetic acid (0.1 ml) was added to this solution and after 1.5 h the solution was concentrated to dryness. The desired salt was obtained in 99% yield (3.2 mg) as a pure material as analyzed by NMR. $^1$H NMR (300 MHz, $CD_3OD$): $\delta = 4.57$ (t, $J = 5.9$ Hz, 1H, H3), 4.39 (m, 2H, H2 and H4), 3.97 (dd, $J = 12.5$, 8.8 Hz, 1H), 3.83 (dd, $J = 12.5$, 4.4 Hz, 1H), 1.82(q, $J = 7.3$ Hz, 2H), 1.36 (sex, $J = 7.3$ Hz, 2H), 0.99 (t, $J = 7.3$ Hz, 3H). $^{13}$C NMR (75 MHz, $CD_3OD$): $\delta = 67.8$, 65.2, 65.0, 58.7, 29.3, 19.4, 14.2. IR ($cm^{-1}$): 3282 (br), 2969, 2876, 1680, 1196, 1142. ESI-MS: 146 (M + 1), 128, 116, 110, 98, 81, 60. HRMS *m*/*z* Calc. for $C_9H_{16}F_3NO_4$ 259.1031, Found: 259.1052.

#### 4.6.6. (2S, 3S, 4R)-2-hydroxymethyl-3-hydroxy-4-propyl-azetidinium trifluoroacetic salt **19** from **20a**

55.4 mg (0.10 mmol) of *N*-Ts-azetidin-3-ol **20a** were dissolved in 0.5 ml of dry DME and the resulting solution cooled to −78 °C. To this solution was added dropwise a dark-green solution of Na/naphthalene in dry DME (prepared by the addition of 18.0 mg of Na in a 0.5 M solution of naphthalene (125.0 mg) in DME) until the dark-green color persisted. After 30 min, brine was added to the solution and the aqueous phase extracted with ethyl acetate (3*x*). The organic phase was dried ($Na_2SO_4$), concentrated in vacuum and the crude product filtered in a small pad of silica (5% ethyl acetate/hexane to remove naphthalene and then pure ethyl acetate to remove the product). After removal of the ethyl acetate by vacuum, the crude product was dissolved in 4.0 ml of THF and the resulting solution cooled to 0 °C. Next, 1.5 equiv. of a 1.0 M solution of TBAF in THF were added and the solution stirred for 3 h, followed by the addition of trifluoroacetic acid. The solvent was removed in vacuum and the crude product purified by flash column chromatography (50% MeOH/$CHCl_3$), furnishing 13.0 mg of azetidine **19** (50% yield).

## Acknowledgments

We thank FAPESP (Research Supporting Foundation of the State of São Paulo) and CNPq, for financial support and a PhD fellowship.

## Appendix A. Supplementary data

$^{1}H$ NMR, $^{13}C$ NMR and IR spectra for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2005.07.016.

## References

[1] (a) J. Kobayashi, J. Cheng, M. Ishibashi, M.R. Walchli, S. Yamamura, Y.J. Ohizumi, Chem. Soc. Perkin Trans. 1 (1991) 1135;
(b) K.A. Alvi, M. Jaspars, P. Crews, Bioorg. Biomed. Chem. Lett. 4 (1994) 2447.

[2] Some recent examples: (a) A. Marinetti, P. Hubert, J.P. Genêt, Eur. J. Org. Chem. (2000) 1815;
(b) F. Couty, D. Prim, Tetrahedron: Asymmetry 13 (2002) 2619;
(c) G. Guanti, R. Riva, Tetrahedron: Asymmetry 12 (2001) 605;
(d) J. Wilken, S. Erny, S. Wassmann, J. Martens, Tetrahedron: Asymmetry 11 (2000) 2143;
(e) M. Shi, J.K. Jiang, Tetrahedron: Asymmetry 10 (1999) 1673.

[3] (a) T. Hiraki, Y. Yamagiwa, T. Kamikawa, Tetrahedron Lett. 36 (1995) 4841;
(b) H. Takikawa, T. Maeda, K. Mori, Tetrahedron Lett. 36 (1995) 7689;
(c) H. Yoda, T. Oguchi, K. Takabe, Tetrahedron: Asymmetry 7 (1996) 2113;
(d) A. Yashima, H. Takikawa, K. Mori, Liebigs Ann. 7 (1996) 1083;
(e) K. Mori, J. Heterocyclic Chem. 33 (1996) 1497;
(f) H. Yoda, T. Oguchi, K. Takabe, Tetrahedron Lett. 38 (1997) 3283;
(g) S. Knapp, Y. Dong, Tetrahedron Lett. 38 (1997) 3813;
(h) H. Takikawa, T. Maeda, M. Seki, J. Chem. Soc. Perkin Trans. 1 2 (1997) 97;
(i) G.Q. Lin, D.G. Liu, Heterocycles 47 (1998) 337;
(j) G.Q. Lin, D.G. Liu, Tetrahedron Lett. 40 (1999) 337;
(k) H. Yoda, T. Uemura, K. Takabe, Tetrahedron Lett. 44 (2003) 977.

[4] For a review on the synthesis of chiral azetidines, see: F. Couty, G. Evano, D. Prim, Mini-reviews Org. Chem. 1 (2004) 133.

[5] (a) A.C.B. Burtoloso, C.R.D. Correia, Tetrahedron Lett. 45 (2004) 3355;
(b) A.C.B. Burtoloso, C.R.D. Correia, Synlett (2005) 1559.

[6] For a review in the chemistry of azetidin-3-ones, see: Y. Dejaegher, N.M. Kuz'nenok, A.M. Zvonok, N. De Kimpe, Chem. Rev. 102 (2002) 29.

[7] (a) A. Salgado, M. Boeykens, C. Gauthier, J. Declercq, N. De Kimpe, Tetrahedron 58 (2002) 2763;
(b) A. Salgado, M. Boeykens, C. Gauthier, Y. Dejaegher, G. Verniest, C. Lopin, K.A. Tehrani, N. De Kimpe, Tetrahedron 59 (2003) 2231.

[8] N. Kise, H. Ozaki, N. Moriyama, Y. Kitagishi, N. Ueda, J. Am. Chem. Soc. 125 (2003) 11591.

[9] M.P. Doyle, M.A. McKervey, T. Ye, Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: from Cyclopropanes to Ylides, Wiley, New York, 1998.

[10] (a) M.P. Moyer, P.L. Feldman, H. Rapoport, J. Org. Chem. 50 (1985) 5223;
(b) G. Emmer, Tetrahedron 48 (1992) 7165;
(c) S. Hanessian, J. Fu, J.L. Chiara, R. Di Fabio, Tetrahedron Lett. 34 (1993) 4157;
(d) J. Podlech, D. Seebach, Helv. Chim. Acta 78 (1995) 1238;
(e) S. Sengupta, D. Das, Synth. Commun. 28 (1998) 403;
(f) P. Desai, J. Aubé, Org. Lett. 2 (2000) 1657;
(g) A. Pusino, A. Saba, G. Desole, Gazzeta Chimica Italiana 115 (1985) 33;
(h) J. Wang, Y. Hou, P.J. Wu, Chem. Soc. Perkin Trans. 1 (1999) 2277.

[11] J.R. Dyer, R.B. Randall, H.M. Deutsch, J. Org. Chem. 29 (1964) 3423.

[12] T. Ye, A. McKervey, Tetrahedron 48 (1992) 8007.

[13] T. Aratani, Pure Appl. Chem. 57 (1985) 1839.

[14] Racemic and chiral diazo compound **6** (see Scheme 3) were synthesized and submitted to the conditions described in Scheme 4 (entry 10) for the N–H insertion reactions. After HPLC analysis of the respective azetidin-3-ones, we found an enantiomeric excess higher than 99% for the chiral compound, demonstrating that no epimerization had occurred during the two-step reaction.

[15] The results employing $Cu(OAc)_2$ as catalysts (azetidin-3-one 8 (77%) compared with $Cu(acac)_2$ (67%), Scheme 4) are very recent in our laboratory. That is the main reason for using $Cu(acac)_2$ as catalyst in the synthesis of the azetidin-3-ones instead of $Cu(OAc)_2$.

[16] (a) D.F. Taber, K.K. You, A.L. Rheigold, J. Am. Chem. Soc. 118 (1996) 547;
(b) M.P. Doyle, L.J. Westrum, W.N.E. Wolthuis, M.M. See, W.P. Boone, V. Bagheri, M.M. Pearson, J. Am. Chem. Soc. 115 (1993) 958;
(c) E. Nakamura, N. Yoshikai, M. Yamanaka, J. Am. Chem. Soc. 124 (2002) 7181, and references cited therein.

[17] F.A. Davis, B. Yang, J. Deng, J. Org. Chem. 68 (2003) 5147.

[18] G.A. Rampel, P. Legzdins, H. Smith, G. Wilkinson, Inorg. Synth. 13 (1972) 90.

[19] D.P. Graddon, J. Inorg. Nucl. Chem. 14 (1960) 161.

[20] P. Garner, J.M. Park, J. Org. Chem. 52 (1987) 2361.

[21] D. Craig, M.B. Berry, Synlett (1992) 41.