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# Metal carbene N–H insertion of chiral α,α′-dialkyl α-diazoketones. A novel and concise method for the stereocontrolled synthesis of fully substituted azetidines ☆

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**Abstract**—The syntheses of all *cis* substituted azetidines were accomplished in few steps from L-serine in modest to high yields. The key step was based on a rhodium or copper carbenoid N–H insertion of α,α′-dialkyl-α-diazoketones to furnish *cis*-2,4-dialkyl-azetidin-3-ones as the only observable diastereoisomers.


Azetidine alkaloids are rather rare substances mostly found in nature as sphingosine-like compounds containing an azetidin-3-ol nucleus.[1] Azetidine alkaloids such as penaresidin A and B and penazetidin A were isolated from the marine sponges *Penares* sp.[2a] and *Penares sollasi*,[2b] respectively, and possess remarkable pharmacological activities (Fig. 1). Penaresidin A and B have shown potent actomyosin ATPase-activating activity,[2a] whereas penazetidin A displays protein kinase C inhibitory activity.[2b]

In view of their unique structure and pharmacological properties, there are several reports on the synthesis of these azetidine alkaloids and structural analogues (Fig. 2) in the literature.[3] With the exception of De Kimpe's synthesis,[3l,n] which involves the alkylation of azetidin-3-ones[4] derivatives, all other syntheses of these azetidine containing compounds are based on the cyclization of a suitable 3-amino-1,2-diol intermediate containing all the stereocenters already fixed.

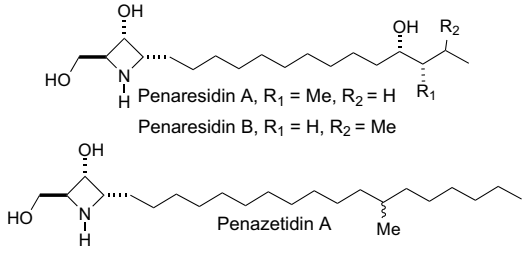


**Figure 1.** Sphingosine type azetidine alkaloids isolated from marine sponges *Penares*.

Herein, we describe our preliminary results toward the synthesis of azetidine containing compounds in few steps from 2,4-dialkyl-azetidin-3-ones, prepared from rhodium or copper carbenoid N–H insertion of α,α′-dialkyl-α-diazoketones.

Metal carbene chemistry has been widely used as an efficient tool in organic chemistry.[5] Although there are many examples in the literature in which rhodium and copper catalysts are employed in N–H insertion reactions of α-diazoketones, few examples describe an intramolecular metal N–H cyclization to form a

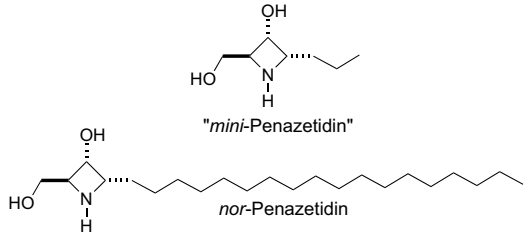


**Figure 2.** Some synthesized azetidine alkaloids analogues.

*Keywords*: Diazo ketones; Metal carbenes; Azetidines.
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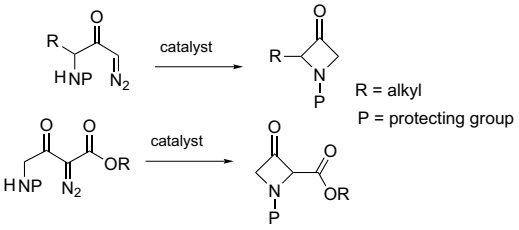



**Scheme 1.** α-Diazoketones employed in the preparation of azetidin-3-ones via metal carbene N–H insertion.

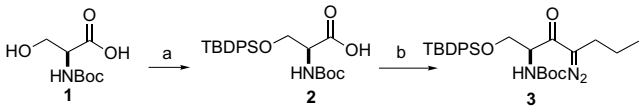
four-membered ring (azetidin-3-ones),[6] and to the best of our knowledge, these are restricted to the preparation of 2-substituted azetidin-3-ones only (Scheme 1).

Moreover, in addition to the synthesis of 2,4-disubstituted azetidin-3-ones, the stereochemical outcome resulting from the carbenoid insertion arising from α,α′-dialkyl-α-diazoketones was also a matter of investigation in our studies.

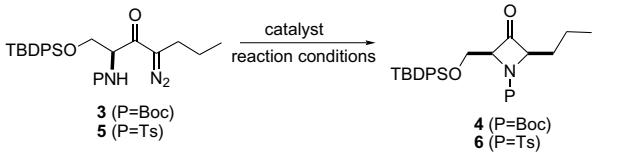
We started by preparing the α,α′-dialkyl-α-diazoketone **3** from L-serine as described in Scheme 2. The synthesis of diazoketone **3** involved the appropriate protection of *N*-Boc serine[7] and addition of diazobutane to a mixed anhydride of carboxylic acid **2**. The diazoketone **3** was obtained with an overall yield of 50–55%.

The diazoketone **3**, was then submitted to rhodium carbenoid N–H insertion reaction in the presence of rhodium acetate $Rh_2(OAc)_4$ (1 mol%) in $CH_2Cl_2$ at 0 °C for 1 h to furnish a single diastereomeric azetidin-3-one, identified as the *cis*-azetidin-3-one **4**, in a somewhat modest yield of 35%.[8] The modest yield obtained in the cyclization step can be ascribed to the formation of 3-furanones in competition with O–Si and N–H insertion and other side products.

Aiming at improving the yield for N–H insertion reaction, we then started a study employing different diazoketones and copper-acetylacetonate ($Cu(acac)_2$) as an alternative catalyst. Best results (45–61% in the cyclization step) were obtained after the combination of the copper catalyst (5–10 mol%) and a *N*-tosyl diazoketone[9] (see table in Scheme 3). *N*-Tosyl diazoketone **5** was prepared from *N*-tosyl serine[10] in a way similar to that described in Scheme 2 in comparable yields. In the case of *N*-tosyl diazoketone **5** an acyl chloride was used instead of a mixed anhydride for the reaction with diazobutane.




**Scheme 2.** Preparation of diazoketone **3** from *N*-Boc serine. a: Imidazole, DMF (4 M solution), TBDPSCl, rt, 36 h, quantitative; b: (1) ClCOOEt, $Et_3N$, THF, −20 °C; (2) diazobutane in $Et_2O$, 0 °C to rt, 50–55%.

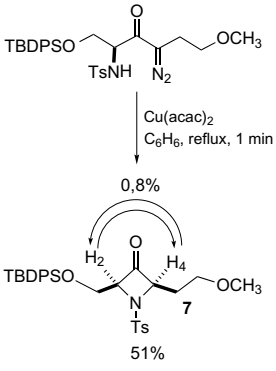



| Diazoketone | Catalyst | conditions | Product (%) |
|---|---|---|---|
| **3** | $Rh_2(OAc)_4$ | $CH_2Cl_2$, 0°C, 1h | **4** (35) |
| **3** | $Cu(acac)_2$ | $CH_2Cl_2$, rt, 12h | complex mixture |
| **5** | $Rh_2(OAc)_4$ | $CH_2Cl_2$, rt, 1h | **6** (0) |
| **5** | $Cu(acac)_2$ | $CH_2Cl_2$, rt, 2h | no reaction |
| **5** | $Cu(acac)_2$ | $C_6H_6$, 50°C, 5 min | **6** (45) |
| **5** | $Cu(acac)_2$ | $C_6H_6$, Δ, 1 min | **6** (61) |

**Scheme 3.** The synthesis of the azetidin-3-ones **4** and **6** from α-diazoketone **3** and **5** employing different catalysts.

The *cis* stereochemistry outcome observed for the cyclization reaction was strongly suggested by NOE experiments of the reduced azetidin-3-ones **4** and **6**. Since the hydrogens at C2 and C4 of these azetidin-3-ones have almost identical chemical shifts, NOE experiments could not be carried out directly on **4** and **6**. To circumvent this problem and to provide convincing evidence of the *cis* cyclization process described above, we synthesized the azetidin-3-one **7** (Scheme 4). Azetidinone **7** showed distinguishable chemical shifts for H2 and H4. Irradiation of H2 in azetidinone **7** showed a NOE with H4 of 0.8%, whereas irradiation of the H4, showed a NOE with H2 of 0.8% (Scheme 4).

This interesting stereochemical outcome was rationalized considering a transition state where both bulk groups, $CH_2OTBDPS$ and $ML_n$ ($Rh_2(OAc)_4$ or $Cu(acac)_2$), are positioned *trans* to each other as illustrated in Figure 3. Despite intense investigation on the mechanism of C–H insertion of rhodium carbenoid,[11] the N–H insertion has not been investigated to the same extent. For C–H insertion, Nakamura[12] et al. have recently reported a complete theoretical study assuming a concerted but nonsynchronous (three-centered hydride transfer) transition state. A synchronous three-centered concerted transition state was proposed by Doyle and co-workers.[11b] The N–H insertion is a quite different case because of the nonbonding electron pair on the N




**Scheme 4.** Synthesis and NOE experiments in azetidin-3-one **7**.

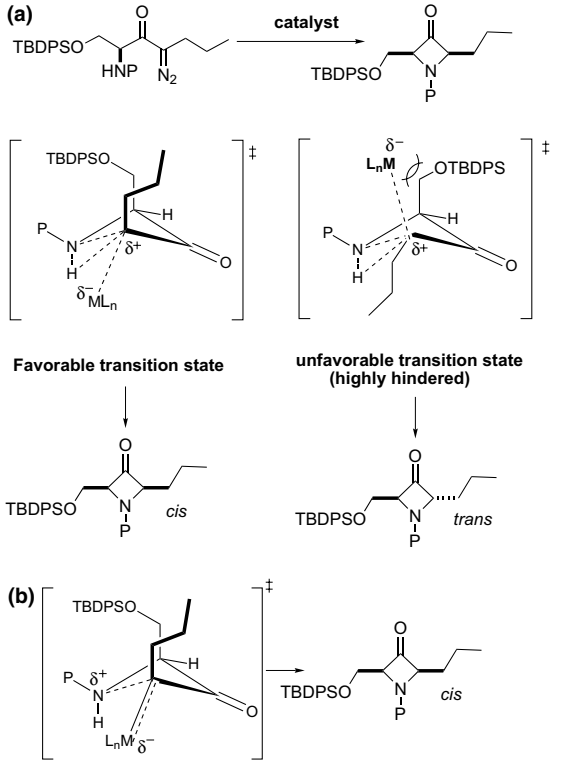



**Figure 3.** (a) Three-centered concerted mechanism for the *cis* and *trans* products in the metal carbene N–H insertion of diazoketones **3** and **5**. (b) Ylide mechanism for the *cis* isomer.

atom. The N–H insertion mechanism is still uncertain, but a stepwise mechanism involving ylides[5] as well as a concerted three/four-centered transition state[13] have been proposed as possible mechanisms. As depicted in Figure 3a and b, both the concerted three-centered and the ylide process can explain the observed stereochemical results.

To construct the fully-substituted azetidine ring, we continued our synthesis with the azetidin-3-one **4**. Introduction of the alcohol functionality at C3 was carried out by reducing azetidin-3-one **4** with $NaBH_4$ at −21 °C in $CH_3OH$ (Scheme 5). The only detectable diastereoisomer, the all *cis* azetidin-3-ol **8** (*Re* face attack of the hydride at C3), was already expected to be the major or the unique diastereoisomer, since the *Si* face of the carbonyl in azetidinone **4** was congested by both C2 and C4 groups. Some other results from the literature[6d] also demonstrate this trend. Cleavage of the TBDPS group of **8** with tetrabutylammonium fluoride (TBAF) followed by treatment of the free diol **9** with trifluoroacetic acid furnished the azetidine alkaloid analogue **10** in 71% over two steps (Scheme 5).

The determination of the *cis*,*cis* stereochemistry was accomplished by NOE experiments of azetidin-3-ols **8** and **9** (Fig. 4). An intense NOE of 6.1% was observed between H3–H4 and H3–H2 when H3 is irradiated, whereas irradiation of the $CH_2$ at C4, permitted the observation of a NOE with the secondary hydroxyl of 1.8%.

For azetidinol **9**, it was observed a NOE with H2 (1.5%) and H4 (1.4%) when H3 was irradiated and a NOE with the secondary hydroxyl group (0.5%) when the $CH_2$ of the $CH_2OH$ group was irradiated.

To show the applicability of this methodology, we also have synthesized the azetidine compound **10** from *N*-tosylazetidin-3-one **6**. It is worth noticing that during the N–H insertion of diazoketone **5** ($Cu(acac)_2$ as catalyst) to provide **6**, we also observed two side products characterized as the α,β unsaturated ketones **11** and **12** (Scheme 6). Reduction of **6** with $NaBH_4$ at −21 °C in $CH_3OH$ furnished a separable mixture of the *cis* azetidinol **13a** (50%) and *trans* azetidinol **13b** (20%) (Scheme 6). Cleavage of the tosyl group of **13a** with

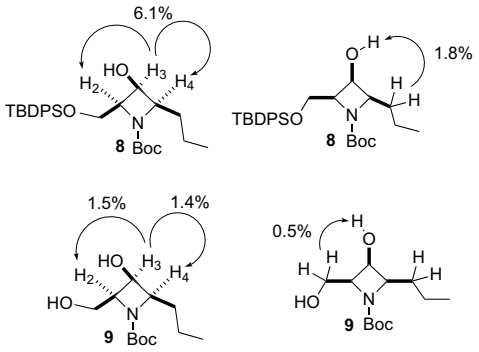
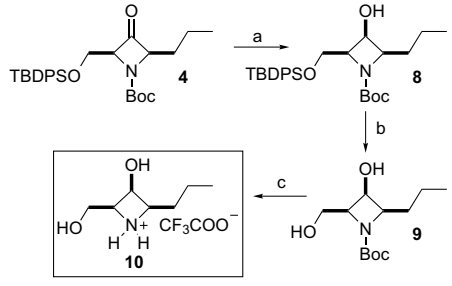
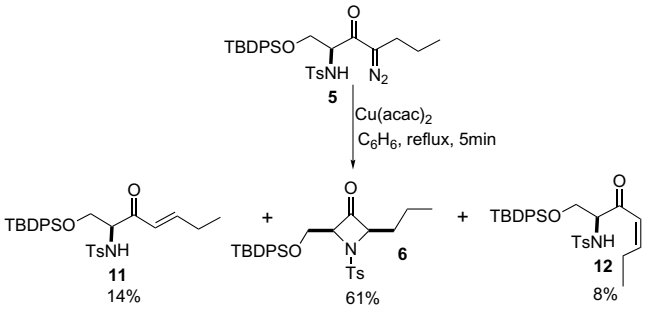


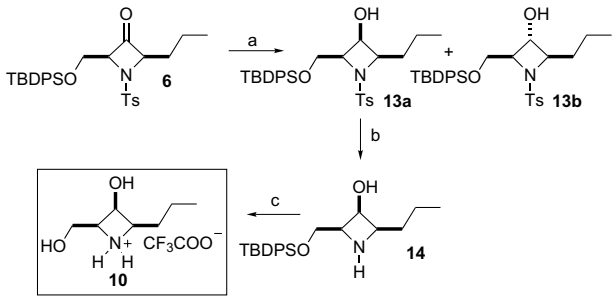

**Figure 4.** NOE experiments on azetidin-3-ols **8** and **9**.




**Scheme 5.** Reduction of azetidin-3-one **4** followed by deprotection. (a) $NaBH_4$, MeOH, −21 °C, 30 min, 46%; (b) TBAF, THF, 0 °C to rt, 1 h, 71%; (c) TFAA, $CH_2Cl_2$, 0 °C, 1 h, quantitative.




**Scheme 6.** Reaction of diazoketone **5** in the presence of $Cu(acac)_2$.




**Scheme 7.** Reduction of azetidinone **6** followed by deprotection. (a) $NaBH_4$, MeOH, −21 °C, 30 min, 70% (*cis* + *trans*); (b) Na/Naphthalene, DME, −78 °C, 1 h; (c) TBAF, THF, rt, 1 h, then ATFA, 50% (two steps).

Na/naphthalene in DME followed by treatment of the crude amine **14** with tetrabutylammonium fluoride (TBAF), furnished, after acidification with trifluoroacetic acid, the azetidine salt **10** in 50% yield[14] after the two steps (Scheme 7).

In summary, we have demonstrated that metal carbenoid insertion of α,α′-dialkyl-α-diazoketones can be a viable and powerful tool for the construction of fully substituted azetidines in few steps from commercially available amino acids. The combination of *N*-tosyl diazoketones with the cheap $Cu(acac)_2$ catalyst provided the best results for the N–H insertion reactions. The use of amino acids other than L-serine and other higher diazoalkanes (to prepare different diazoketones) are under investigation for the construction of other azetidines in our research group.

## Supplementary material

$^1H$ NMR and $^{13}C$ NMR spectroscopic data for compounds **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9**, **15a**, and **15b** and ESI-MS and IV for compounds **2**, **3**, **4**, **7**, **8**, and **9**.

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## References and notes

1. Kobayashi, J.; Ishibashi, M.; Walchli, M. R.; Yamamura, S.; Ohizumi, Y. *J. Chem. Soc. Heterocycles* **1996**, *42*, 943.
2. (a) Kobayashi, J.; Cheng, J.; Ishibashi, M.; Walchli, M. R.; Yamamura, S.; Ohizumi, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1135; (b) Alvi, K. A.; Jaspars, M.; Crews, P. *Bioorg. Biomed. Chem. Lett.* **1994**, *4*, 2447.
3. For previous synthesis of azetidine alkaloids and analogues, see: (a) Hiraki, T.; Yamagiwa, Y.; Kamikawa, T. *Tetrahedron Lett.* **1995**, *36*, 4841; (b) Takikawa, H.; Maeda, T.; Mori, K. *Tetrahedron Lett.* **1995**, *36*, 7689; (c) Yoda, H.; Oguchi, T.; Takabe, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2113; (d) Yashima, A.; Takikawa, H.; Mori, K. *Liebigs Ann.* **1996**, *7*, 1083; (e) Mori, K. *J. Heterocyclic Chem.* **1996**, *33*, 1497; (f) Yoda, H.; Oguchi, T.; Takabe, K. *Tetrahedron Lett.* **1997**, *38*, 3283; (g) Knapp, S.; Dong, Y. *Tetrahedron Lett.* **1997**, *38*, 3813; (h) Takikawa, H.; Maeda, T.; Seki, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, *2*, 97; (i) Lin, G. Q.; Liu, D. G. *Heterocycles* **1998**, *47*, 337; (j) Lin, G. Q.; Liu, D. G. *Tetrahedron Lett.* **1999**, *40*, 337; (k) Reference 2j cited in 3l; (l) Salgado, A.; Boeykens, M.; Gauthier, C.; Declercq, J.; De Kimpe, N. *Tetrahedron* **2002**, *58*, 2763; (m) Yoda, H.; Uemura, T.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 977; (n) Salgado, A.; Boeykens, M.; Gauthier, C.; Dejaegher, Y.; Verniest, G.; Lopin, C.; Tehrani, K. A.; De Kimpe, N. *Tetrahedron* **2003**, *59*, 2231.
4. Dejaegher, Y.; Kuz'nenok, N. M.; Zvonok, A. M.; De Kimpe, N. *Chem. Rev.* **2002**, *102*, 29.
5. Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: from Cyclopropanes to Ylides*; John Wiley and Sons: New York, 1998.
6. (a) Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223; (b) Emmer, G. *Tetrahedron* **1992**, *48*, 7165; (c) Hanessian, S.; Fu, J.; Chiara, J. L.; Di Fabio, R. *Tetrahedron Lett.* **1993**, *34*, 4157; (d) Podlech, J.; Seebach, D. *Helv. Chim. Acta* **1995**, *78*, 1238; (e) Sengupta, S.; Das, D. *Synth. Commun.* **1998**, *28*, 403; (f) Desai, P.; Aubé, J. *Org. Lett.* **2000**, *2*, 1657; (g) Pusino, A.; Saba, A.; Desole, G. *Gazzeta Chim. Italiana* **1985**, *115*, 33; (h) Wang, J.; Hou, Y.; Wu, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2277.
7. Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.
8. Yields for **4** were initially higher. However, compound **4** was contaminated with small amounts of an undesirable side product, which could not be separated by chromatography. Reduction of **4** to azetidinol **8** with $NaBH_4$ permitted the isolation of this side product (inert to $NaBH_4$ reduction).
9. Typical experimental procedure: 353 mg (0.63 mmol) of diazoketone **5** was dissolved in 13 mL of dry benzene and the yellow solution heated under reflux. Next, 16 mg (10 mol%) of $Cu(acac)_2$ was added to the reaction mixture turning it brown immediately with liberation of nitrogen. After 1 min, the reaction mixture was cooled, the solvent evaporated, and the crude product purified by flash column chromatography (10% ethyl acetate/hexane) to furnish 205.8 mg (61%) of the azetidin-3-one **6**. $^1H$ 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.
10. Craig, D.; Berry, M. B. *Synlett* **1992**, 41.
11. (a) Taber, D. F.; You, K. K.; Rheigold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547; (b) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958; (c) See reference 9 cited in reference 12 below.
12. Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 7181.
13. Davis, F. A.; Yang, B.; Deng, J. *J. Org. Chem.* **2003**, *68*, 5147.
14. Yield not optimized.