Metal-catalyzed reaction of *N*-(2-indolyl)methyl, *N*-bis(trimethylsilyl)-methyl diazoamides: an entry into the β-carboline ring system†

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The intramolecular metal-catalyzed reaction of *N*-(2-indolyl)-methyl, *N*-bis(TMS)methyl diazoamides proceeds with high conformational control and chemoselectivity to give cyclopropyl derivatives, which rearrange to β-carboline products.

The tetrahydro-β-carboline and β-carboline ring systems are important structural motifs commonly found in many indole alkaloids and synthetic organic compounds.[1] Many of these substances have interesting and diverse pharmacological activities.[1] Due to the importance of these ring systems, many methods[1–4] have been developed for their construction; the Pictet–Spengler (PS)[3] and Bischler–Napieralski (BN)[4] cyclizations of tryptamine derivatives still remain the methods of choice. However, some limitations in the use of the PS[5a] and BN[5b,c] reactions in synthesis have been noted and there is a need for new methods for the construction of these ring systems.

We were attracted by the possibility of using an intramolecular metallocarbenoid cyclization onto an indole moiety for accessing tetrahydro-β-carbolines (Fig. 1); the method would also serve as an entry to the β-carboline ring system *via* subsequent oxidation of the tetrahydro-β-carboline products. Unlike the extensively studied intermolecular reactions of indole and its derivatives with diazo reactants,[6] intramolecular processes[7] have received less attention. Most studies involved metal-catalyzed reaction of indoles with diazocarbonyl moieties tethered mainly to the C_3-position,[7] which yielded products arising from formal metallocarbenoid C–H insertion at C_2; however, in a case where a donor–acceptor diazoamide was involved cyclopropanation of the indole C_2–C_3 double bond was observed.[7b] There are only two reported examples of the metal-catalyzed intramolecular reaction of an indole with a diazoketone moiety tethered to C_2,[7a,e] which gave mainly the N–H insertion product; metallocarbenoid attack at C_3 was a minor pathway.

We tested the metallocarbenoid mediated reaction of *N*-bis(trimethylsilyl)methyl (*N*-BTMSM) diazoamides[8] of type **1** (Fig. 1, R′ = $CH_2(TMS)_2$, R = R″ = H or substituent). We were interested in ascertaining the chemoselectivity of the metallocarbenoid reaction, and especially that in branched systems. Further, intramolecular reaction of indoles with acceptor-type diazoamides attached to the C_2-position have not yet been investigated. Herein we report our preliminary findings in this investigation.

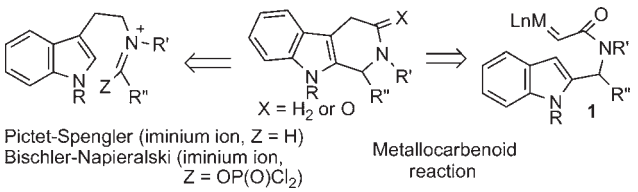
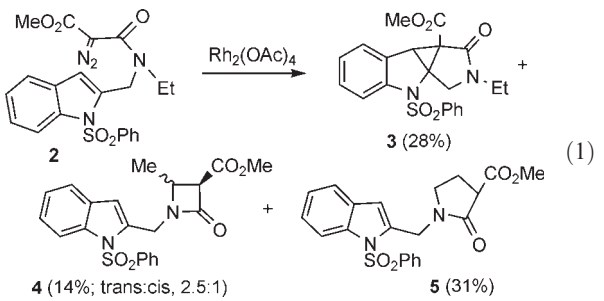


Fig. 1 Approaches to the tetrahydro-β-carboline framework.



We have found that the reactions proceeded *via* the formation of cyclopropanated intermediates; formation of the cyclopropyl derivatives was more dependent on the electronic effects of substituents of the diazoamides than of the metal catalysts. The *N*-BTMSM moiety is essential for enhancing chemoselectivity *via* conformational control about the amide unit and the N–C_α bond in branched systems.

First, we compared the $Rh_2(OAc)_4$-catalyzed reaction of the diazoamides **2** and **6** (eqns (1) and (2)) to assess whether the *N*-BTMSM group is essential in promoting Rh(II)-carbenoid reaction at the indole moiety. The reaction of **2** (eqn (1)) yielded cyclopropanated compound **3**, corresponding to metallocarbenoid addition to the indole C_2–C_3 double bond, as the minor product. Compound **3** was found to be unstable in solution ($CDCl_3$) and rearranged (24 h), *via* cyclopropyl ring opening, to the corresponding β-carboline **3′**.[9] Lactams **4** and **5**, resulting from C–H insertion at the *N*-ethyl moiety, represented the major components. The formation of **5** was unexpected as it involved insertion into a less reactive primary C–H bond. For the diazoamide **6** (eqn (2)), the use of the *N*-BTMSM group was effective in promoting Rh(II)-carbenoid reaction at the indole unit to afford the tricycle **7** in 65% yield; the β-lactam **8** arising from insertion into the benzylic C–H bond was also obtained in

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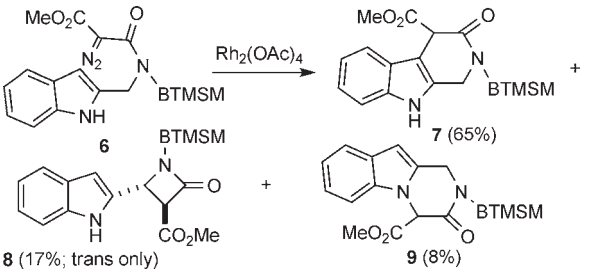
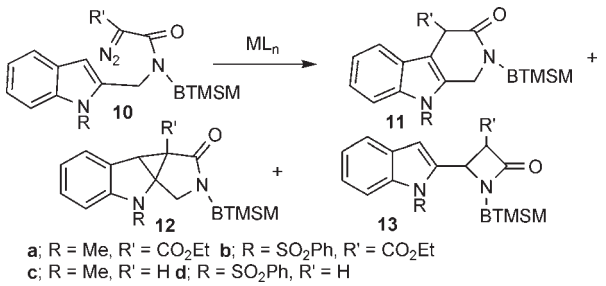
† Electronic supplementary information (ESI) available: Experimental data and H and C NMR data for compounds **3**, **3′**, **5**, **7**, **9**, **11**, **11c**, **12**, **15**, **16**, **17**, **19**, **20** and **21**. CCDC reference number 691157. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b809890e

17% yield. It is noteworthy that the indole NH insertion product **9** was formed only as a minor product (8%).



(2)

It is useful to compare this result with that reported[7e] for the $Rh_2(OAc)_4$-catalyzed reaction of 2-(3-diazo-2-oxopropyl)indole wherein the indole NH insertion product was greatly preferred over the C_3–H formal insertion product. No products corresponding to Rh(II)–carbenoid C–H insertion into the BTMSM moiety of **6** were detected.



(3)

Encouraged by the preceeding results, we examined the influence of electronic effects on the product outcome of the reaction. The diazoamides **10a–d** were prepared and evaluated against Rh(II) and Cu(II) catalysts (eqn (3)), and the results are collected in Table 1. It is clear that the type of products obtained is dependent on both the nature of the indole N-substituent and the diazoamide moiety. Thus, for the diazomalonamide **10a** metallocarbenoid cyclization leads to the preferential formation of the carboline **11a** (entries 1–4); however, with **10b**, the tetracycle **12b** was obtained (entries 5–7). For the reaction of **10c,d**, only the tetracycles **12c,d** were formed, and in high yields. Interestingly, it was found that a $CDCl_3$ solution of the tetracycle **12c** rearranged to **11c**,[9] as was the case observed for **3**.

Table 1 Metal-catalyzed reaction of **10a–d**[a]

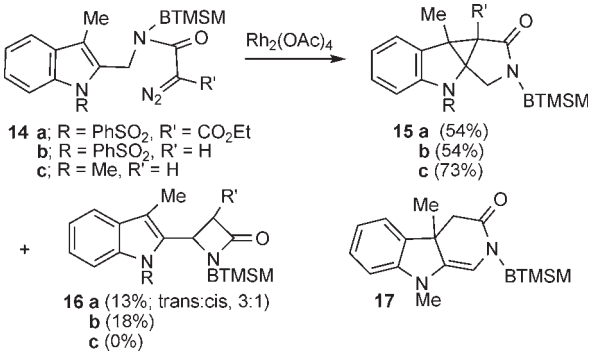
			Isolated yield (%)		
Entry	Diazoamide	Catalyst	**11**	**12**	**13**
1	**10a**	$Rh_2(OAc)_4$	89	nd	nd
2	**10a**	$Rh_2(tfa)_4$	63	nd	10[b]
3	**10a**	$Cu(hfacac)_2$	78	nd	nd
4	**10a**	$Cu(acac)_2$	87	nd	nd
5	**10b**	$Rh_2(OAc)_4$	nd	59	20[c]
6	**10b**	$Rh_2(tfa)_4$	nd	32	28[d]
7	**10b**	$Cu(hfacac)_2$	nd	61	nd
8	**10c**	$Rh_2(OAc)_4$	nd	95	nd
9	**10d**	$Rh_2(OAc)_4$	nd	87	nd

[a] tfa = trifluoroacetamide; nd = not detected. [b] *Cis* diastereomer. [c] *Trans* diastereomer. [d] *Cis* : *trans* diastereomer, 1 : 1.

The observation of the rearrangement of compounds **3** and **12c** indicated that β-carboline product **7** or **11**, shown in eqn (2) and Table 1, was formed from the corresponding tetracycle, *e.g.*, **12**, *via* ring-opening of the cyclopropyl moiety. With an indole NH or *N*-methyl group, and the presence of an electron-withdrawing α-carboethoxy or -carbomethoxy on the metallocarbenoid carbon, the formation of product **7** or **11** was facilitated. However, the conversion of the tetracycle **12** to **11** can be prevented by using an electron-withdrawing *N*-$PhSO_2$ group (entries 5–7). In contrast, when the metallocarbenoid carbon is unsubstituted, the tetracycle **12** is stable, under the reaction conditions, irrespective of whether the indole N has an electron-donating or electron-withdrawing group (entries 8 and 9).

Further, the chemoselectivity of the reaction of **10a,b** showed some dependence on the type of Rh(II) catalysts used. With **10a**, only the electron-withdrawing $Rh_2(tfa)_4$ led to the formation of the β-lactam **13a**, albeit in low yield (10%, entry 2). In the case of **10b**, a significant amount of the β-lactam **13b** was obtained (entries 5 and 6); the ratio of **12b** : **13b** for $Rh_2(OAc)_4$ was 3 : 1 and **12b** : **13b** for $Rh_2(tfa)_4$ was 1.1 : 1. We attribute the formation of the β-lactam **13** to the enhanced electrophilicity of the diazomalonyl-derived Rh(II)-carbenoid, and the marked increase in yield of **13b** is related to the attenuated reactivity of the indole C_2–C_3 double bond.

The tetracyclic structures of **12b–d** were assigned based on their ^{1}H NMR data,[9] and corroborated *via* an X-ray structure (Fig. 2) of **12d**.[10]



(4)

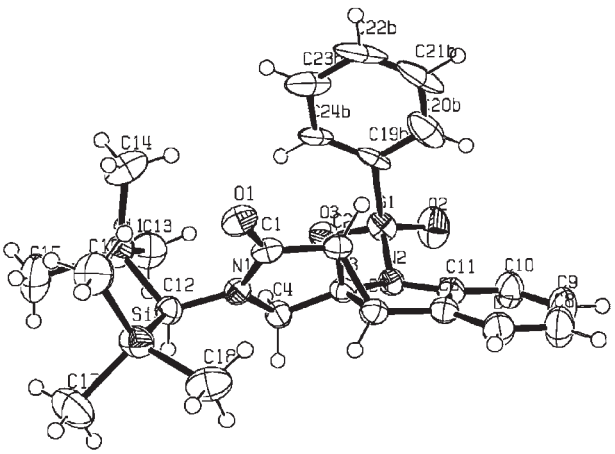
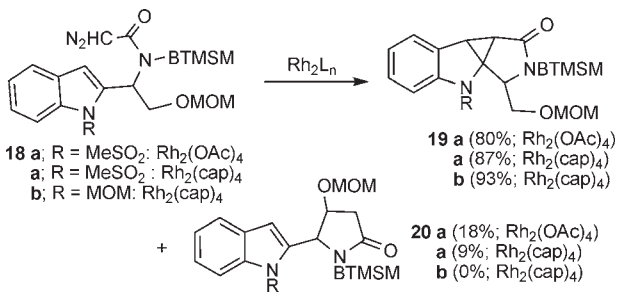


Fig. 2 X-Ray structure of **12d**.

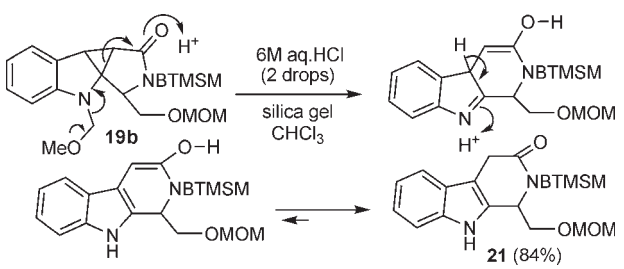
Next, the $Rh_2(OAc)_4$-catalyzed reaction of diazoamides **14** (eqn (4)) was studied to determine whether C_3-substitution would suppress metallocarbenoid addition to the indole C_2–C_3 double bond. We found that the formation of the tetracycle was still the preferred pathway; the diazoamide **14c** gave the highest yield of **15c**. As observed previously (eqn (3); Table 1, entry 5), diazomalonamide **14a** also afforded a small amount of the β-lactam **16a**. Interestingly, with diazoamide **14b** β-lactam formation was now observed, and this outcome is in contrast to the reaction of **10d** (eqn (3); Table 1, entry 9). A plausible explanation is that the C_3-methyl group could have sterically hindered the approach of the less electrophilic Rh(II)-carbenoid, and consequently metallocarbenoid insertion to the benzylic position occurred at the expense of cyclopropanation at the indole C_2–C_3 double bond.

It is useful to note that a $CDCl_3$ solution of tetracycle **15c**, upon standing at room temperature for two days, was converted to the indoline derivative **17**. Its ^{1}H NMR spectrum showed the presence of a broad singlet at δ 5.22–5.32 ascribed to the olefinic proton and the absence of the characteristic signals at δ 3.55 (dd) and δ 3.80 (d) due to the methylene hydrogens adjacent to the amide nitrogen in **15c**. The infrared spectrum of **17** showed the characteristic δ-lactam ν(C═O) at 1630 cm^{-1} whereas in the precursor **15c**, the tetracyclic γ-lactam carbonyl absorption appeared at 1664 cm^{-1}.



(5)

We then directed our attention to diazoamides **18a**[11] and **18b** with branching at the amide N–C_α position (eqn (5)). Both $Rh_2(OAc)_4$- and $Rh_2(cap)_4$-catalyzed reactions of **18a,b** yielded the desired tetracycle **19a,b** in very good yields, providing further evidence for the vital role of the *N*-BTMSM group in ensuring high chemoselectivity *via* conformational control about the amide unit and N–C_α bond. For **18a**, where the indole C_2–C_3 double bond is deactivated by the *N*-$MeSO_2$ group, insertion into a C–H bond α to the MOM ether oxygen, to give **20a**, was observed, but represented only a minor pathway. This minor reaction pathway is suppressed by the use of the less electrophilic $Rh_2(cap)_4$, as was also the case for the reaction of **18b**.



Scheme 1 Acid-catalyzed reaction of **19b**.

To demonstrate that the tetracyclic products are useful synthetic intermediates, compound **19b** was subjected to acid-catalyzed rearrangement of the cyclopropyl moiety to provide the tetrahydro-β-carboline **21** in 84% yield (Scheme 1). It is noteworthy that under these conditions, selective hydrolysis of the indole *N*-MOM group was achieved.

In summary, we have shown that the intramolecular metallocarbenoid reaction of 2-indolyl *N*-BTMSM diazoamides proceeded with high conformational control and chemoselectivity to form cyclopropyl intermediates, which rearranged to give tetrahydro-β-carboline derivatives. The application of this method in alklaoid synthesis is in progress.

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10 Crystal data for **12d** $C_{24}H_{32}N_2O_3SSi_2$, M_r = 484.76, monoclinic, space group $P2_1/c$, a = 16.8073(4), b = 9.1044(2), c = 23.0328(5) Å, β = 131.7160(10)°, V = 2630.86(10) Å^3, T = 173(2) K, Z = 4, D_{calc} = 1.224 Mg m^{-3}, F(000) = 1032, μ = 0.241 mm^{-1}. 40 367 reflections were measured on a Nonius Kappa CCD diffractometer, 4992 were independent ($I > 2\sigma(I)$). Final $R1$ = 0.0403, $wR2$ = 0.0938. CCDC 691157. For crystallographic data in CIF see ESI.
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