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PAPER

Conformational, steric and electronic effects on the site- and chemoselectivity of the metal-catalyzed reaction of *N*-bis(trimethylsilyl)methyl, *N*-(2-indolyl)-methyl α-diazoamides†

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The Rh(II)- and Cu(II)-catalyzed reactions of *N*-bis(trimethylsilyl)methyl, *N*-(2-indolyl)methyl α-diazoamides are investigated to delineate how conformational, steric and electronic factors influence the site- and chemoselectivity of the metallocarbenoid reaction. The *N*-bis(trimethylsilyl)methyl (*N*-BTMSM) group is found to be essential in promoting the metallocarbenoid reaction at the *N*-(2-indolyl)methyl moiety as well as providing subtle but effective conformational influence about the amide N–C_α sigma bond in diazoamides carrying an N–C_α alkoxymethyl side-chain, to afford excellent site- and chemoselectivity. In general, the metal-catalyzed reactions are found to favor metallocarbenoid addition to the indole C(2)–C(3) double bond over C–H insertion to give cyclopropanated products (tetracyclic γ-lactams); however, chemoselectivity is also affected by steric effects, as revealed in the *N*-[2-(3-methylindolyl)]methyl diazoamides, and to some extent by the nature of the catalyst employed, as seen in the N–C_α-alkoxymethyl diazoamides. The tetracyclic γ-lactams are found to rearrange to give good to high yields of the tricyclic indole derivatives under the metallocarbenoid reaction conditions or under acidic conditions. The propensity of the tetracyclic γ-lactams to undergo rearrangement is found to be dependent on the nature of the α-substituent on the original diazo carbon and the indole N-substituent.

Introduction

The indole nucleus is an important structural motif found in many naturally occurring usually biologically active compounds, in therapeutically relevant molecules, and in agrochemicals.[1] The synthesis of these molecules relies on the availability of appropriately functionalized indole derivatives, which has engendered intensive efforts directed at developing methods for the functionalization of indoles. The most common functionalization sites are at the indole nitrogen, C(2)- and C(3)-positions. The electrophilic aromatic substitution reaction[2a] is the most widely used method of introducing substituent groups into the indole ring. In particular, Friedel–Crafts-type alkylation reactions,[2b] promoted by homogeneous and heterogeneous Brønsted acids, Lewis acids and, more recently, by organocatalysts[2c] (usually amine-based catalysts), have received much attention. At the same time, the metal-catalyzed functionalization of indoles is also an area of intensive investigation, wherein Pd-catalyzed reactions have featured prominently in these studies.[3]

The metal-catalyzed reaction of indoles with α-diazocarbonyl compounds is a useful method for the introduction of substituents into the indole nucleus.[4] Both inter- and intramolecular reactions have been explored. The metal-catalyzed intermolecular reaction of indole and its derivatives with α-diazocarbonyl compounds in the presence of either copper [*e.g.* Cu bronze, Cu(acac)$_2$, Cu(OTf)$_2$] or Rh(II) [*e.g.* $Rh_2(OAc)_4$, Rh_2(*S*-DOSP)$_4$] catalysts has been extensively investigated, and several characteristics have been noted. It is generally found that products arising from C(3) alkylation are preferred over C(2) alkylation,[5] but the latter products are formed if the indole C(3) is substituted.[6] Indole N–H insertion to give N-alkylated products is found to be in competition with C-alkylation, but the formation of N-alkylation products is also dependent on the type of α-diazocarbonyl compound and catalyst that are used.[7] An interesting exception

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†Electronic supplementary information (ESI) available: Experimental procedures and data for **6a,b**; **7a–c**; **8a–c**; **9a–d**, **10a–h**, **18c**, **18e**, **18f (20f)**, **18g**, **19d**, **19g**, **19h**, **20c–e**, **22a–c**, **23a–e**, **26**, **27**, **29**, **30a–c**, **31a–d**, **32b,d**, **33b** **34**, **36**, **39**, **40**, **41b**. Copies of ^{1}H and ^{13}C NMR spectra for compounds **10–17**, **18c**, **18e**, **18f (20f)**, **18g**, **19d,g,h**, **20c–e**, **22a–c**, **23a–d**, **24a**, **24c (25c)**, **24e**, **25a**, **26**, **27**, **29**, **30a–c**, **31a,c**, **32b, d**, **33b**, **34**, **36**, **39**, **40** and **41b**; crystallographic data and CIF files for compounds **19h** and **34**. CCDC 691157 and 863240. For ESI and crystallographic data in CIF or other electronic formats see DOI: 10.1039/c2ob25103e

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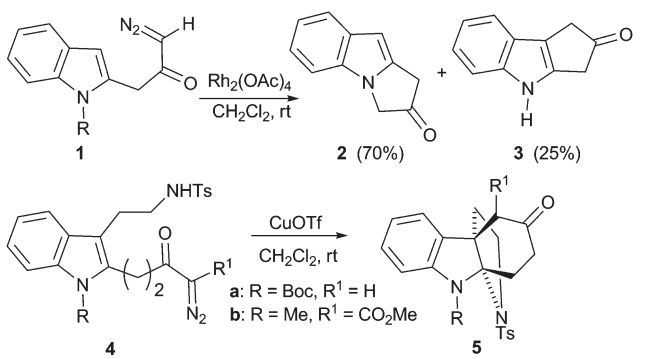
to this trend has been observed recently wherein a Ru(II)-catalyzed reaction of indole with α-diazoarylacetates selectively gave the C(2) alkylation product, and N-alkylation products were not detected.[8] For indoles with an N-electron withdrawing group (*e.g.* Ac, Aroyl, Boc), stable cyclopropanecarboxylate intermediates were obtained by reaction with ethyl or methyl diazoacetate catalyzed by copper.[9] Interestingly, double cyclopropanation of the benzene unit of the indole was observed when *N*-Boc-2 (or 3)-methylindole was treated with methyl α-diazo-(4-bromophenyl)acetate, a donor–acceptor diazocarbonyl compound, in the presence of Rh_2(*S*-DOSP)$_4$ as the catalyst.[10]

The formation of C-alkylation products is generally believed to follow a pathway involving cyclopropanation and ring scission of the unstable cyclopropane intermediates;[6b,c,8] however, there is also evidence which supports a pathway involving zwitterionic intermediates.[5,10]

The intramolecular version, in contrast, has received less attention, and most of the studies[11] reported to date involve a metal-catalyzed reaction of indole and its derivatives with diazocarbonyl moieties tethered mainly to the indole-C(3) position. For example, Salim and Capretta,[11a] and Muchowski and co-workers[11b] independently reported the Rh(II)-catalyzed intramolecular reaction of 3-indolyl α-diazoketones wherein formal metallocarbenoid C–H insertion at the indole-C(2) position was observed. Subsequently, Jung described the Rh(II)-catalyzed intramolecular reaction of indole derivatives with a tethered α-diazo ketoester unit at the C(3) position,[11c] which resulted in the formation of tricyclic β-keto esters. In all these examples, the involvement of an unstable cyclopropyl intermediate was implicated enroute to the formation of the tricyclic products; in one case, the intermediacy of a cyclopropyl derivative was observed by ^{1}H NMR.[11a] However, in the case of the Cu(I)-catalyzed intramolecular reaction of an indole derivative bearing a C(3)-tethered 'donor–acceptor'-type diazoamide moiety,[11d] a stable cyclopropyl intermediate was isolated.



(1)

Studies on the metal-catalyzed intramolecular reaction of indoles possessing a C(2)-tethered diazocarbonyl moiety have, so far, been limited. Salim and Capretta showed[11a] that the metal-catalyzed intramolecular reaction of the α-diazoketone **1** gave mainly the N–H insertion product **2** (70%); the tricyclic ketone **3** (25%), formed from a formal metallocarbenoid C(3)–H insertion, was a minor product (eqn (1)). Recently, Qin and co-workers reported[11e] the Cu(I)-catalyzed intramolecular reaction of the α-diazoketone **4a** and α-diazo β-ketoester **4b**, which led to the formation of the tetracycles **5a** (42%) and **5b** (81%), respectively. In these latter cases, unstable cyclopropyl intermediates were formed, which underwent *in situ* intramolecular ring-opening by the NHTs (Ts = tosyl) unit to give **5**.

In comparison, the metal-catalyzed intramolecular reaction of an indole or its derivatives with an α-diazo *tertiary* amide moiety tethered to C(2) has not been examined yet. This may be due, in part, to regio- and chemoselectivity issues arising from conformational preferences about the amide N–C(O) unit, which can result in product mixtures and poor yields. Therefore, control of site-selectivity in the metallocarbenoid reaction is an important consideration in this type of reaction, with the aim of promoting metallocarbenoid attack at only one of the two N-substituents.[12]

One such strategy used to improve site-selectivity involved replacing one of the N-substituents of the α-diazo *tertiary* amide moiety with a bulky group (*e.g. tert*-butyl, neopentyl, 4-methoxyphenyl, 2,4,6-trimethylbenzyl, cumyl),[13] which sterically biases the conformational preference about the amide N–C(O) moiety in favor of the metallocarbenoid reaction at the remaining N-substituent. Another strategy involves the use of an N-substituent that is electronically deactivated, such as *N*-(4-nitrophenyl), *N*-(carbalkoxyethyl) or *N*-(benzylchromium tricarbonyl), so that the metallocarbenoid reaction will be directed toward the remaining electron-rich N-substituent.[14] However, there are some limitations noted for these two approaches. For example, the *N*-*tert*-butyl group is susceptible to metallocarbenoid C–H insertion at one of the methyl groups, and is not easy to remove from the lactam products.[15] For the *N*-PMP group, we have found[16] that, in cases where the Rh(II)-carbenoid C–H insertion at the second N-substituent was difficult, due to electronic deactivation and/or steric hindrance at the reaction site, the Rh(II)-carbenoid had preferentially attacked the *N*-PMP group leading to the formation of oxindole derivatives.

We previously reported[17] that the metallocarbenoid mediated reaction of *N*-bis(trimethylsilyl)methylamine (*N*-BTMSM) diazoamides proceeded efficiently with good to excellent regio- and chemoselectivity and had attributed the latter results to the conformational control about the amide N–C(O) bond that was afforded by the *N*-BTMSM moiety. Furthermore, we also noted another role, albeit subtle, that the *N*-BTMSM group had played in influencing the conformational preference about the amide N–C_α sigma bond in systems carrying two substituents at the carbon α to the amide nitrogen (hereafter referred to as N–C_α-branched). To further explore the scope of the metallocarbenoid reactions of *N*-BTMSM diazoamides, we have investigated the reaction of *N*-BTMSM, *N*-(2-indolyl) diazoamides. We were interested in determining: (a) the effectiveness of the *N*-BTMSM group as a conformational control element in these systems and (b) the influence of electronic effects of: (i) the α-substituent on the carbenoid carbon, (ii) the indole N-substituent and (iii) the metal catalysts on the regio- and chemoselectivity in the reaction. Here, we detail the results from our studies.[18]

We have found that the use of the *N*-BTMSM moiety was essential for encouraging the metallocarbenoid reaction to occur mainly at the indolyl moiety *via* its conformational influence on the amide unit in both N–C_α-unbranched and N–C_α-branched systems. Our results indicate that in the present system, the cyclopropanation pathway is followed even when the C(3) position of the indolyl unit is substituted. The cyclopropyl

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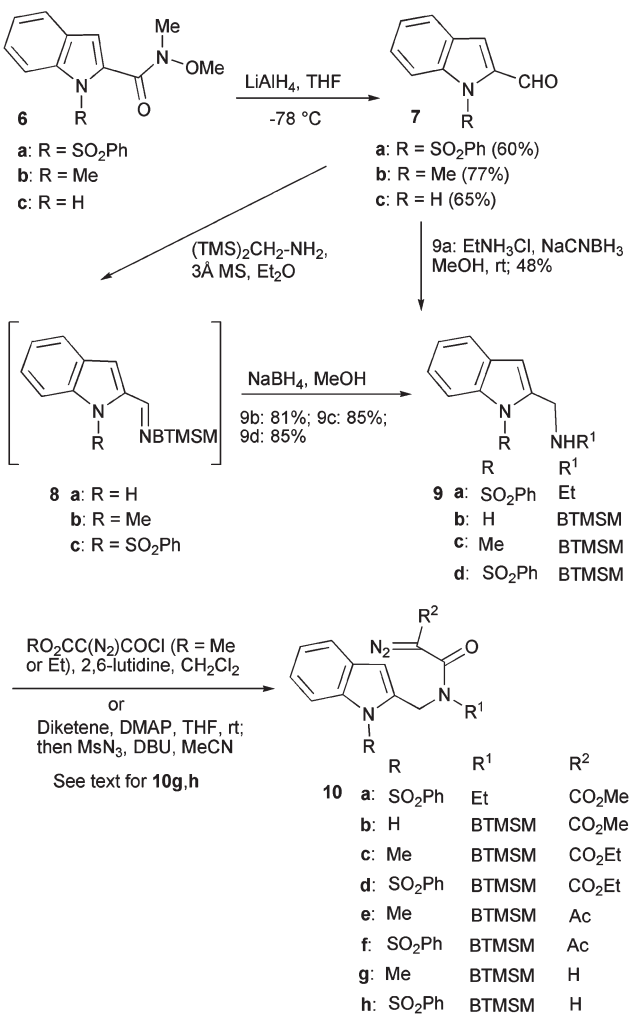
intermediates were generally stable and amenable to isolation, but in some cases rearrangement of the tetracyclic γ-lactams to give the tricyclic products under the metallocarbenoid reaction conditions was observed.

Results and discussion

The chemistry of the *N*-BTMSM, *N*-(2-indolyl) diazoamides **10** was first investigated and they were readily prepared from 2-indolylmethylamines **9** as shown in Scheme 1. The known[19a] *N*, *O*-dimethyl-2-indolecarboxamide **6c** was subjected to *N*-phenylsulfonylation[19b] ($PhSO_2Cl$, KOBu-*t*, cat. 18-C-6) and *N*-methylation[19c] (MeI, NaH) to provide amides **6a** and **b**,[19d] respectively. Reduction of **6a–c** with $LiAlH_4$ at −78 °C gave the corresponding 2-indolecarbaldehydes **7a**,[20a] **7b**,[20b] and **7c**,[20c] which were then subjected to reductive amination to obtain amines **9**. Thus, one-pot reductive amination[21] of **7a** with ethylammonium chloride gave **9a**. For the preparation of the *N*-bis(trimethylsilyl)methylamine (*N*-BTMSM) derivatives **9b–d** it was found that condensation of **7a–c** with $(TMS)_2CHNH_2$ to form the stable *N*-BTMSM imines, **8a–c**, followed by $NaBH_4$ reduction gave better yields of **9b–d** compared to a one-pot procedure.

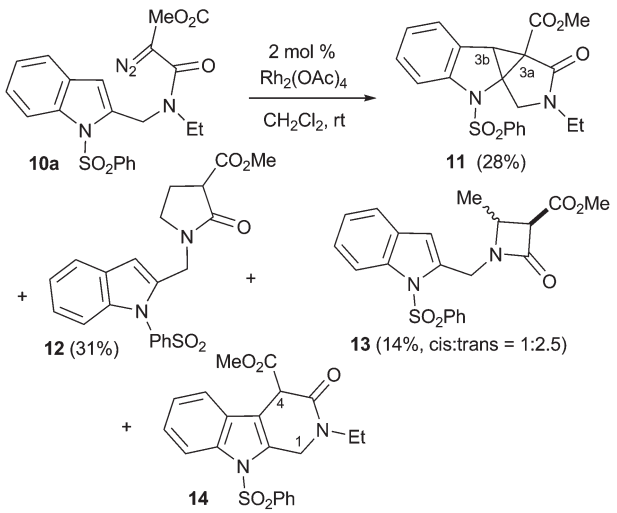


Scheme 1 Preparation of diazoamides **10a–h**.

Acylation of the *N*-BTMSM amines **9a–d** with either methyl or ethyl diazomalonyl chloride[17b,22] gave the diazoamides **10a–d** in good yields (70–80%). The α-acetyl substituted diazoamides **10e,f** were obtained *via* treatment of **9c,d** with diketene followed by the diazotization of the resulting crude acetoacetamides[17c] with MsN_3[23] (71–79% yield over two steps). Subsequent deacylation of **10e,f**, using 5% aq KOH in MeCN, gave the diazoamides **10g,h** in yields ranging from 81–90%.

Metal-catalyzed reaction of *N*-BTMSM indolyl diazoamides 10

Studies of the metal-catalyzed reactions began with compounds **10a** (eqn (2)) and **10b** (eqn (3)). For diazoamide **10a** the derived Rh(II)-carbenoid can, in principle, be involved in (i) a formal C–H insertion reaction at the indole-C(3) position, resulting in a tricyclic product, (ii) C–H insertion reaction at the indolylmethylene position to form a β-lactam, and (iii) at the *N*-ethyl group to form β- and γ-lactam products. In the case of **10b**, the Rh(II)-carbenoid can also react at the indolic N–H site in addition to the indolylmethyl moiety and *N*-BTMSM methine and one of the $SiMe_3$ groups. Therefore, a comparison of the results from these two reactions should allow an assessment of whether the *N*-BTMSM group is effective in influencing the site-selectivity in the reactions of the diazoamides.



(2)

The exposure of **10a**[24a] to $Rh_2(OAc)_4$ gave (73% combined yield) the readily separable tetracyclic γ-lactam **11**, the γ-lactam **12** and the β-lactam **13**[24b] in a ratio of 2 : 2.2 : 1 (eqn (2)). Compound **11** had resulted from metallocarbenoid addition to the indole C(2)–C(3) double bond, and the two lactams **12** and **13** were formed *via* Rh(II)-carbenoid insertion into the methyl and methylene units of the *N*-ethyl moiety. More interestingly, the results indicated that the preferred reaction site for the metallocarbenoid was at the *N*-ethyl unit, as reflected by the higher combined yield of **12** and **13** (44%), compared to a yield of 28% for **11**. Furthermore, cyclopropane ring scission of the tetracyclic γ-lactam **11** occurred to give the tricyclic indole derivative **14**

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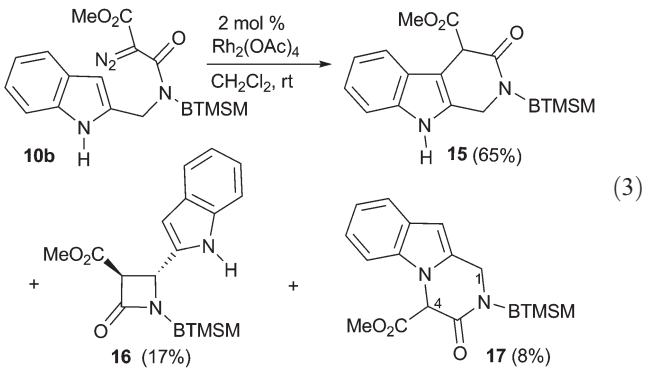
when a $CDCl_3$ solution of **11** was left to stand at room temperature for 24 h.



(3)

Next, the $Rh_2(OAc)_4$-catalyzed reaction of *N*-BTMSM diazoamide **10b** was studied (eqn (3)). Interestingly, in this case, the tricycle **15** was formed as the major product in 65% yield. Although the reactive Rh(II)-carbenoid had the opportunity to insert into the indole N–H bond to form the pyridazine derivative **17**, its isolated yield was only 8%. In fact, the formation of β-lactam **16** was preferred over **17**. The other product that was formed was the imine **8a** (10%) which was derived *via* a hydride-transfer based mechanism.[12b,25] It is noteworthy that there were no products arising from Rh(II)-carbenoid C–H insertion at the *N*-BTMSM methine or at the methyl of one of the $SiMe_3$ groups.

Together, the results from the reaction of **10a** (eqn (2)) and **10b** (eqn (3)) provided strong support for the notion that the *N*-BTMSM group is effective in influencing the conformational preference about the amide N–C(O) unit. Thus, for **10b**, it is reasonable to suggest that the preferred reaction conformer corresponds to the one where the larger *N*-BTMSM substituent is located *syn* to the less sterically demanding amide carbonyl group, and the smaller indolylmethyl moiety is oriented towards the reactive Rh(II)-carbenoid (Fig. 1).

Informed by the results from the reactions of **10a,b**, we subjected the other N–C_α-unbranched diazoamides **10c–h** to different Rh(II) and Cu(II) catalysts with the aim of defining how electronic effects from the *N*-substituted indole ring, the α-substituent on the metallocarbenoid carbon and the nature of the catalysts would influence the chemoselectivity of the reaction. The results from this study are shown in Table 1.

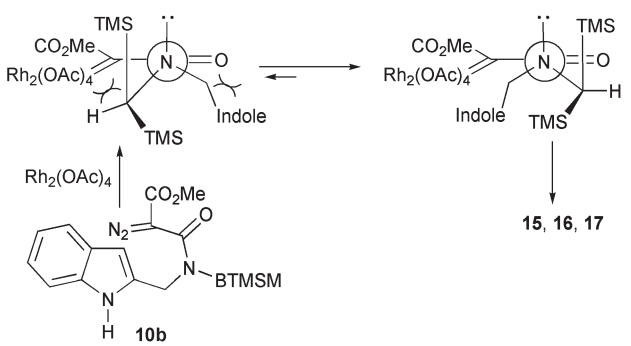
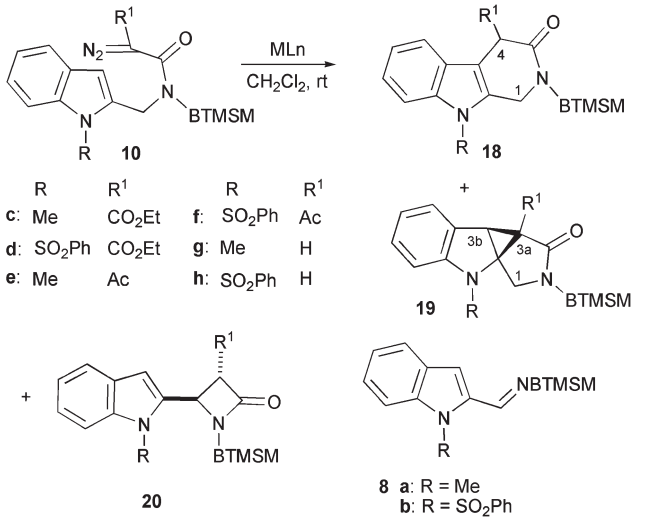


Fig. 1 Conformational preference about the *N*-BTMSM amide unit in **10b**.

Table 1 Rh(II)- and Cu(II)-catalyzed reactions of diazoamides **10c–h**[a]



Entry	Diazo **10**	Catalyst	Yield[b] (%)	Relative yield[c] (%) **18**	**19**	**20**[d]
1	**c**	$Rh_2(OAc)_4$	89	100	0	0
2	**c**	$Rh_2(tfa)_4$	73	86	0	14[e]
3	**c**	$Cu(hfacac)_2$	78	100	0	0
4	**c**	$Cu(acac)_2$	87	100	0	0
5	**d**	$Rh_2(OAc)_4$	79	0	75	25[f]
6	**d**	$Rh_2(tfa)_4$	60	0	53	47[g]
7	**d**	$Cu(hfacac)_2$	61	0	100	0
8	**e**	$Rh_2(OAc)_4$	40	50	0	50[f]
9	**f**	$Rh_2(OAc)_4$	41	27	0	73[f]
10	**g**	$Rh_2(OAc)_4$	95	0	100	0
11	**h**	$Rh_2(OAc)_4$	87	0	100	0

[a] 2 mol% Rh(II) or 4 mol% Cu(II) catalyst, dry CH_2Cl_2, rt. [b] Combined yield of **18**, **19**, **20**. [c] The imine product **8b** or **c** was also obtained: entry 1: 8% **8b**; entry 2: 6% **8b**; entries 3 and 4: **8b** not detected; entry 5: <1% **8c**; entry 6: 8% **8c**; entry 7: **8c** not detected; entry 8: 21% **8b**; entry 9: 7% **8c**; entries 10 and 11: **8b,c** not detected. [d] The relative stereochemistry at C(3) and C(4) was assigned based on the J_{vic}: for the *cis*-diastereomer, $J_{H\text{-}3,H\text{-}4}$ = 2.2 Hz; for the *trans*-diastereomer, $J_{H\text{-}3,H\text{-}4}$ = 5.7 Hz. [e] *cis*-Diastereomer. [f] *trans*-Diastereomer. [g] *cis* : *trans* = 1 : 1 based on the weight of the isolated products.

In general, the preferred reaction pathway for the reactive metallocarbenoid is addition to the indole C(2)–C(3) double bond to give either the tricyclic indole derivative **18** or the tetracyclic γ-lactam **19**.[26] Metallocarbenoid insertion into the indolylmethylene C–H bond to form the β-lactam **20** represented the only competitive pathway. In some of the reactions, a minor amount of the imines **8b** or **c** (with the exception of **10e**, entry 8) was also obtained (Table 1, footnote c), whose formation appeared to be dependent on the starting diazoamide structure and the nature of the catalyst; imines **8b,c** tend to be formed when Rh(II) catalysts are used but not with Cu(II) catalysts.

The influence of the indole N-substituent and the type of catalyst on the chemoselectivity of the reaction was revealed in the reactions of the diazomalonamides **10c,d**. Thus, the $Rh_2(OAc)_4$-catalyzed reaction of **10c** resulted in Rh(II)-carbenoid cyclopropanation of the indole C(2)–C(3) double bond followed by *in situ* ring opening of the cyclopropyl moiety to give the tricycle **18c** in 89% yield (entry 1). No β-lactam product **20c** was

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detected. The use of the more electrophilic $Rh_2(tfa)_4$ catalyst, on the other hand, led to an erosion of chemoselectivity (entry 2); although the tricyclic product was still obtained as the major product, there was a significant increase in the yield of the β-lactam **20c**. Interestingly, it was found that both the Cu(hfacac)$_2$ and Cu(acac)$_2$-catalyzed reactions of **10c** gave only **18c**. The nature of the ligand on the Cu(II) complex was found to have little effect on the chemoselectivity of the reaction except on the yield of **18c**; a higher yield of 87% was realized with Cu(acac)$_2$ compared to a yield of 78% with Cu(hfacac)$_2$.

The composite results from the reactions of the α-diazomalonamides **10c,d** showed several useful trends. The formation of the tricycle **18** and the tetracyclic γ-lactam **19** is found to be dependent on the nature of the indole N-substituent. Cyclopropyl ring opening of the initially formed **19** to give **18** under the reaction conditions is facilitated by an electron-donating indole *N*-methyl substituent, whereas an electron-withdrawing *N*-PhSO$_2$ group afforded stability to the tetracyclic γ-lactam **19**.

It is also evident that the nature of the indole N-substituent has an important influence on the chemoselectivity of the reaction. For example, the Rh(II)-catalyzed reaction of diazoamide **10c** occurred with high chemoselectivity to give the tricyclic product **18c** as the predominant product, whereas with diazoamide **10d** significant amounts of the β-lactam **20d** were obtained (compare entries 1 and 5). A reasonable explanation for the change in the degree of chemoselectivity is the decreased reactivity of the indole C(2)–C(3) double bond. When the indole N-substituent is methyl, this double bond is activated towards metallocarbenoid cyclopropanation to give the tetracyclic γ-lactam **19**, which subsequently rearranges to give the tricycle **18**. However, with an electron-withdrawing indole *N*-PhSO$_2$ group, the reactivity of the indole C(2)–C(3) double bond is decreased, and consequently C–H insertion at the indolylmethylene site to form β-lactam **20** becomes a competitive reaction pathway. The use of the electron-withdrawing $Rh_2(tfa)_4$ promoted the formation of β-lactam **20** and this may be attributed to the increased electrophilicity of the Rh(II)-carbenoid, resulting in lower chemoselectivity (entries 2 and 6). Interestingly, the Cu(II) catalyzed reaction of **10c,d** displayed the same chemoselective preference for the indole moiety (entries 3, 4, 7).

On the basis of the results from the reactions of **10c,d** we chose to use $Rh_2(OAc)_4$ as the catalyst in the reactions of **10e–h**. With **10e,f**, lower chemical yields of **18e,f** and **20e,f** were obtained (entries 8 and 9). Unexpectedly, in the case of **10e**, significant amounts of imine **8c** were also formed, whose yield (21% isolated) equalled that of the β-lactam **20e**. The chemoselectivity of the reaction of **10e,f** was also found to be poorer; the ratio of **18e** : **20e** was 1 : 1 for **10e** and 1 : 3 for **10f**. The products **18e,f** and **20e,f**, especially the former, were found to be somewhat unstable, and purification by chromatography always resulted in low recovery of products due to decomposition on the column. Also, slow degradation of the product was experienced upon isolation and storage.

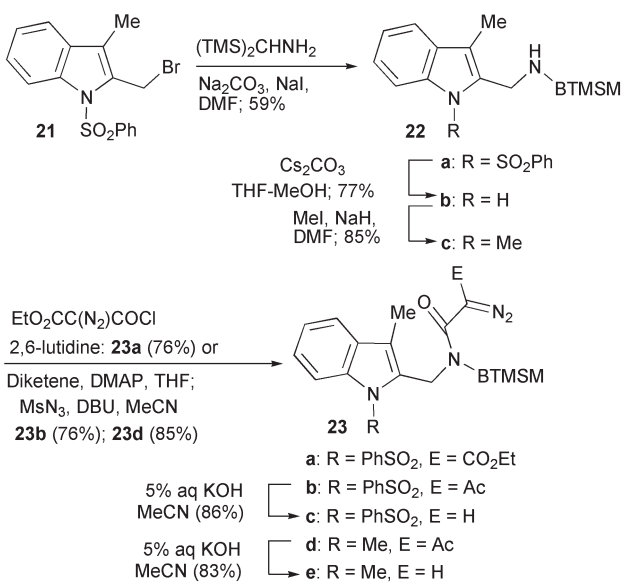
For the α-unsubstituted diazoamides **10g,h** (entries 10, 11), the $Rh_2(OAc)_4$-catalyzed reaction led only to the tetracyclic γ-lactams **19g,h**, in high yields. These results also indicate that metallocarbenoid addition to the indole C(2)–C(3) double bond is highly favored, irrespective of whether the indole nitrogen carries an electron-donating or electron-withdrawing group. Unexpectedly, **19g** did not undergo rearrangement to the tricyclic indole derivative **18g** under the metallocarbenoid reaction conditions. This outcome, when considered together with the result from the reaction of **10c**, suggests that an electron-donating indole N-substituent works in concert with an electron-withdrawing group at C(3a) of the tetracyclic γ-lactam (*e.g.* **19c**) to facilitate the rearrangement to the tricyclic product. However, it should be noted that a $CDCl_3$ solution of **19g**, like **11** (eqn (2)) was also found to rearrange to the tricycle **18g** upon standing at room temperature for 22 h.

Rh(II)-carbenoid reaction of diazoamides 23a,c,e

The interesting results from the reactions of diazoamides **10c–h** led us to investigate whether the chemoselectivity of the reaction would also be affected by steric hindrance at the indole C(2)–C(3) double bond. Steric hindrance at this site could divert metallocarbenoid attack away from the double bond and towards the indolylmethylene site, resulting in higher yields of β-lactam products.

For this study, the 3-methylindolyl diazoamides **23a,c,e** were prepared. Their synthesis began with the preparation of amines **22a,c** as shown in Scheme 2. The known[27a] 2,3-dimethyl-1-(phenylsulfonyl)indole was treated with NBS (cat. benzoyl peroxide) to give crude bromide **21**[27b] which, without further purification, was reacted with $(TMS)_2CHNH_2$ to afford the crude amine **22a** (59% yield over 2 steps). Amine **22c** was prepared *via* base mediated hydrolysis of the *N*-PhSO$_2$ group in **22a** to form **22b**, followed by regioselective indole *N*-methylation. With **22a,c** in hand, the diazoamides **23a,c,e** were prepared in the same manner as was described for the preparation of the diazoamides **10d,g,h** (*vide supra*). We found, however, that the diazoamide **23e** was unstable and therefore was used immediately after purification.

The results from the $Rh_2(OAc)_4$-catalyzed reaction of diazoamides **23a,c,e** are collected in Table 2. Diazoamide **23a** reacted to give the tetracyclic γ-lactam **24a** and β-lactam **25a** in 81%



Scheme 2 Preparation of diazoamides **23a,c,e**.

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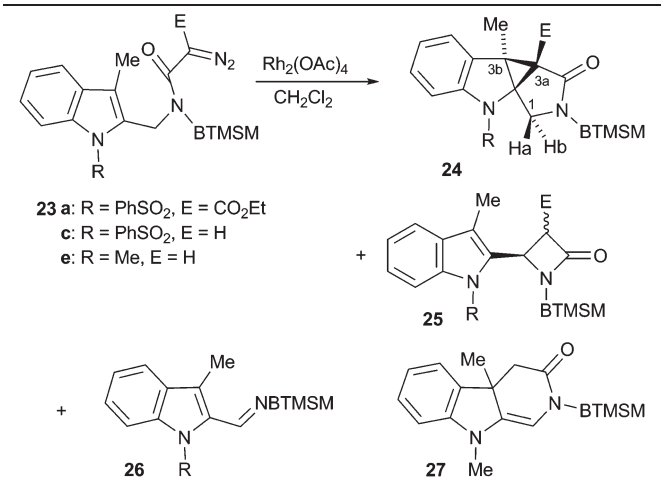
Table 2 Rh(II)-catalyzed reaction of diazoamides **23a,c,e**[a]



Entry	Diazo **23**	Yield[b] (%)	Relative yield (%) **24**	**25**
1	**a**[c]	67	81	19[d]
2	**c**[c]	72	75	25
3	**e**	73	100	0

[a] 2 mol% Rh(II) catalyst, dry CH_2Cl_2, rt. [b] Combined yield of **24** and **25**. [c] The imine **26** was obtained for the reaction of **23a** and **c**: entry 1 : 16%; entry 2 : 4%. [d] The relative stereochemistry at C(3) and C(4) was assigned based on J_{vic}: for the *cis*-diastereomer, $J_{H\text{-}3,H\text{-}4}$ = 2.5 Hz; for the *trans*-diastereomer, $J_{H\text{-}3,H\text{-}4}$ = 5.7 Hz.

and 19% relative yields, respectively. Compound **25a** was obtained as an inseparable mixture of *cis*- and *trans*-diastereomers,[24b] and in a ratio of 1 : 3 based on the integration of the C(4)–H doublet of the *cis* isomer (δ 4.42, $J_{H\text{-}3,H\text{-}4}$ = 2.5 Hz) and of the *trans* isomer (δ 4.20, $J_{H\text{-}3,H\text{-}4}$ = 5.7 Hz). The reaction of **23c** gave an inseparable mixture of **24c** and **25c** in a 72% combined yield; the ratio of **24c** : **25c** was 3 : 1, which was based on the integration of the doublet due to one of the C(1)–hydrogens centered at δ 4.81 in the tetracyclic γ-lactam **24c** and one of the double doublets due to one of the C(3)–Hs centered at δ 3.27 in β-lactam **25c**. For the reaction of **23a** and **c**, the imine product **26** was also obtained (see footnote c, Table 2). With **23e**, only the tetracyclic γ-lactam **24e** was formed in 73% yield.

The structures of the tetracyclic γ-lactams **24a,c,e** were readily characterized based on analysis of the diagnostic ^{1}H NMR signals of the C(1)–H_a,H_b and C(3a)–H_c.[26]

Interestingly, the effect of the metallocarbenoid α-substituent (CO_2Et *vs.* H) on the chemoselectivity of the reaction of diazoamides **23a** and **23c** was minimal, as both reactions afforded very similar ratios of tetracyclic γ-lactam **24** to β-lactam **25**. However, with the α-unsubstituted diazoamides **23c** and **e**, a marked difference in chemoselectivity was observed and this can be attributed to a difference in the electron density of the indole ring as noted earlier (*vide supra*).

It is also instructive to compare the results obtained from the $Rh_2(OAc)_4$-catalyzed reactions of **23a** and **23c** to those from the reactions of **10d** (Table 1, entry 5) and **10h** (Table 1, entry 11), respectively. From the standpoint of the combined yield of the

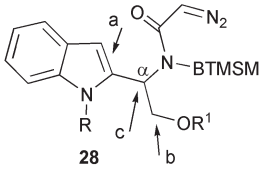


Fig. 2 Potential Rh(II)-carbenoid reaction sites in **28**.

tetracyclic γ-lactam and β-lactam products, **23a** gave a lower yield (67% combined) compared to **10d** (79% combined) but, in the case of **23a**, the imine product **26** (R = $PhSO_2$) was also formed in significantly higher amounts (16%). However, the chemoselectivity of the reaction, as reflected by the ratio of the tetracyclic γ-lactam to β-lactam products, was very similar for **23a** and **10d**. In the case of **23c** and **10h**, there is a difference in product outcome: for **23c**, the β-lactam **25c** and the imine **26** (4%) were formed along with the tetracycle **24c**, whereas for the reaction of **10h**, no β-lactam and imine products were produced. A reasonable explanation for this is that in **23c** the approach of the electrophilic Rh(II)-carbenoid to the indole C(2)–C(3) double bond may be hindered by the C(3)-methyl group, and consequently the metallocarbenoid insertion at the indolylmethylene group leading to the β-lactam **25c**, and hydride abstraction to form imine **26**, occurred at the expense of cyclopropanation of the indole C(2)–C(3) double bond.

As was observed before for the tetracyclic γ-lactams **11** and **19g**, a $CDCl_3$ solution of **24e**, upon standing at rt for 48 h, was converted to a new compound, identified as the tricyclic product **27**. The IR spectrum of **27** showed the characteristic δ-lactam *v* (C=O) at 1630 cm^{-1}, whereas in the precursor **24e**, the carbonyl absorption appeared at 1664 cm^{-1}. In the ^{1}H NMR spectrum, the characteristic signals at δ 3.55 (dd) and δ 3.80 (d) due to the C(1)–methylene hydrogens in **24e** were replaced by a broad singlet at δ 5.22–5.32, which was ascribed to the C(1)–olefinic proton.

Metal-catalyzed reaction of N–C_α-branched *N*-BTMSM indolyl diazoamides

The site-selectivity studies on the metallocarbenoid reactions of diazoamides **10a–h** showed that the *N*-BTMSM group provides useful and effective conformational control about the amide bond, thereby favoring the metallocarbenoid reaction at the indolylmethyl unit. Nonetheless, it is not clear whether this conformational control will be operative in N–C_α-branched diazoamides wherein the α-branch substituent may interfere with conformational preferences, resulting in poor site selectivity. We therefore prepared diazoamides of type **28** to ascertain whether conformational influence about the N–C_α single bond by the *N*-BTMSM moiety is possible. In system **28** (Fig. 2), there are three potential competing sites for the metallocarbenoid reaction: (i) at the indole C(2)–C(3) double bond (path a), (ii) at the methylene C–H bonds adjacent to the methoxymethyleneoxy (*O*-MOM) group (path b) and (iii) at the tertiary α-C–H bond in the indolylmethine group (path c). It is, therefore, of interest to determine which pathway will be preferred and how conformational and electronic factors govern the chemoselectivity of the reaction in diazoamides **28**.

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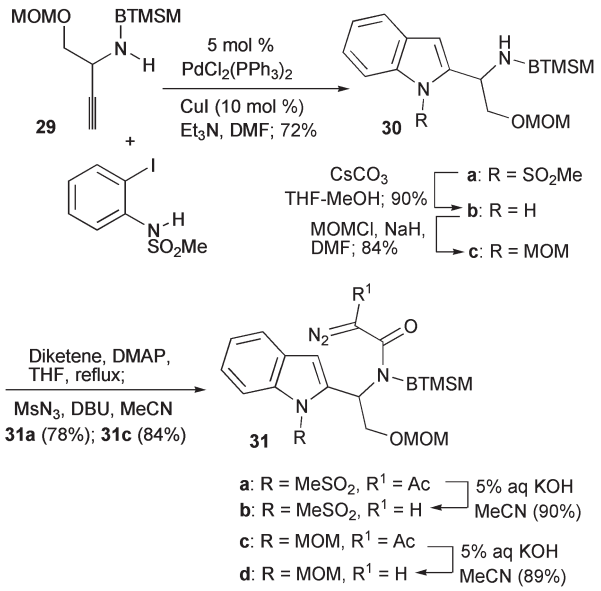


Scheme 3 Preparation of diazoamides **31b,d**.

Synthesis and metal-catalyzed reaction of diazoamides 31b,d

The propargylamine **29** was subjected to a Pd(II)-catalyzed reaction with 2-iodo-*N*-(methanesulfonyl)aniline,[28] to effect a one-pot Sonogashira coupling and cyclization[29a] to obtain the indole amine[29b] **30a** in 72% yield (Scheme 3). It is useful to note that the reaction proceeded quite efficiently without the need for protection of the *N*-BTMSM amino moiety. Subsequent base hydrolysis of the *N*-$MeSO_2$ group gave the indole amine **30b**, which was selectively protected at the indole nitrogen with MOMCl to obtain amine **30c**. The conversion of **30a,c** to the diazoamides **31b,d** employed procedures similar to those described for the preparation of diazoamides **10g,h** and **23b,c** (*vide supra*) except for the acylation step with diketene.

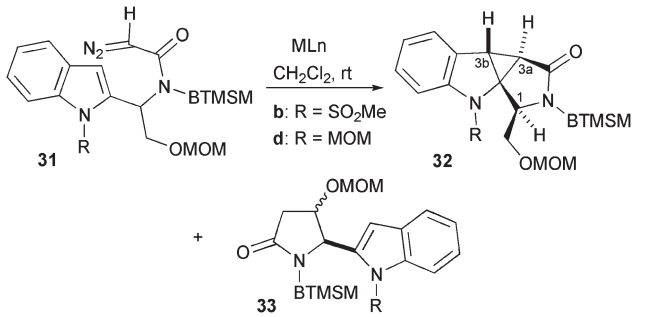
For this step, the reaction was conducted in THF under reflux, as the reaction was found to be slow at rt. The crude acetoacetamide derivatives were then diazotized to provide the corresponding α-diazo acetoacetamides, which were deacylated to give the diazoamides **31b,d** in 70% and 75% overall yields, respectively. Diazoamides **31b,d** were found to be less stable relative to the unbranched diazoamides **10g,h** and **23b** and, therefore, were used immediately after purification by chromatography.

We first studied the metal-catalyzed reaction of **31b** and the results are summarized in Table 3. Both $Rh_2(OAc)_4$ and the less electrophilic $Rh_2(cap)_4$ (entries 1 and 2) provided high chemoselectivity wherein the tetracyclic γ-lactam **32b** is favored over the γ-lactam **33b**. Chemoselectivity, however, was poor with the strongly electron-withdrawing $Rh_2(tfa)_4$, which gave a 1.3 : 1 ratio of **32b** : **33b** (entry 3). A similar outcome (**32b** : **33b** = 1.4 : 1) was also realized with $Cu(hfacac)_2$ (entry 4).

On the other hand, the $Rh_2(OAc)_4$- and $Rh_2(cap)_4$-catalyzed reactions of *N*-(methoxymethyl) diazoamide **31d** proceeded efficiently and with excellent chemoselectivity (entries 5 and 6) to give only the tetracyclic γ-lactam **32d**.

The overall results above indicated that for the reactions of **31b,d**, metallocarbenoid cyclopropanation of the indole C(2)–C(3) double bond was generally preferred. Deactivation of the indole double bond in **31b**, due to the electron-withdrawing *N*-$MeSO_2$ group, allowed γ-lactam formation, *via* metallocarbenoid C–H insertion at the oxymethylene group, to be competitive. The lack of β-lactam formation, which would arise from C–H insertion at the indolylmethine unit, can also be ascribed to preferential insertion at the oxymethylene moiety.

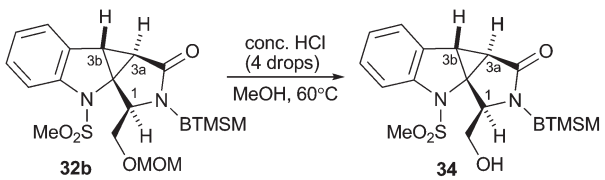
Table 3 Rh(II)- and Cu(II)-catalyzed reactions of diazoamides **31b,d**[a]



Entry	31	Catalyst	Yield[b] (%)	Relative yield[c] (%) 32	33[d,e]
1	**b**	$Rh_2(OAc)_4$	98	82	18[f]
2	**b**	$Rh_2(cap)_4$	91	91	9[f]
3	**b**	$Rh_2(tfa)_4$	69	57	43[g]
4	**b**	$Cu(hfacac)_2$	85	59	41[h]
5	**d**	$Rh_2(OAc)_4$	80	100	0
6	**d**	$Rh_2(cap)_4$	93	100	0

[a] 2 mol% Rh(II) or 4 mol% Cu(II) catalyst, dry CH_2Cl_2, rt. [b] Yield of chromatographically pure products. [c] The relative yield was calculated based on the weight ratio of the isolated products. [d] γ-Lactam **33b** was obtained as separable *cis*- and *trans*-diastereomers. [e] The relative stereochemistry at C(4) and C(5) was assigned based on J_{vic}: for the *cis*-diastereomer, $J_{H\text{-}4,H\text{-}5}$ = 8.5 Hz; for the *trans*-diastereomer, $J_{H\text{-}4,H\text{-}5}$ = 0 Hz. [f] The ratio of *cis* : *trans* was 1 : 1. [g] The ratio of *cis* : *trans* was 1 : 2. [h] Only the *trans*-diastereomer was obtained.

For the reaction of **31b**, it was found that with the three Rh(II) catalysts, a mixture of separable *cis*- and *trans*-**33b** was formed, but with $Cu(hfacac)_2$ only *trans*-**33b** was obtained. The relative stereochemistry at C(4) and C(5) in **33b** was assigned based on the ^1H NMR data. For *trans*-γ-lactam **33b**, the vicinal $J_{H\text{-}4,H\text{-}5}$ was found to be ~0 Hz, which suggested that the dihedral angle between the C(4)–H and C(5)–H was close to 90° and that these hydrogens were *trans* to each other, whereas for *cis*-**33b**, $J_{H\text{-}4,H\text{-}5}$ was 8.5 Hz.



(4)

In order to further confirm the tetracyclic structure of the cyclopropanated product, we decided to recrystallize compound **32b** for X-ray crystallographic analysis, since this product was obtained as a crystalline compound; however, attempts to obtain a single crystal of **32b** failed. Fortuitously, the primary alcohol **34**, obtained *via* treatment of **32b** with acidic methanol at 60 °C (eqn (4)), was highly crystalline and afforded a single crystal for

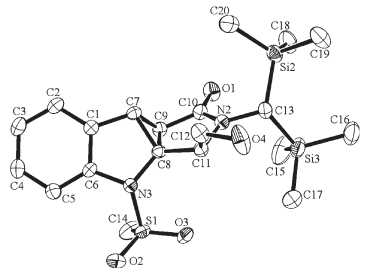


Fig. 3 ORTEP drawing of **34**.

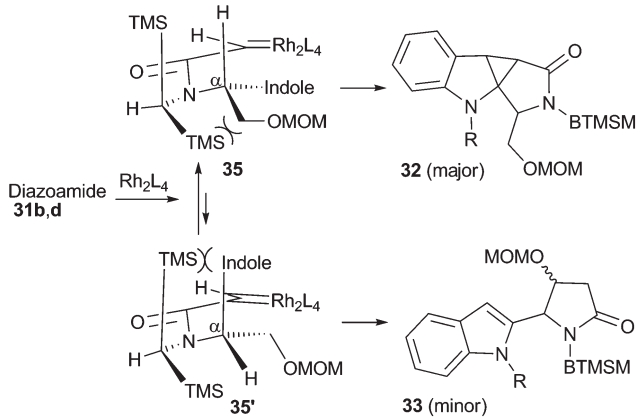


Fig. 4 Preferred conformation about the N–C_α bond of the Rh(II)-carbenoid from **31b,d**.

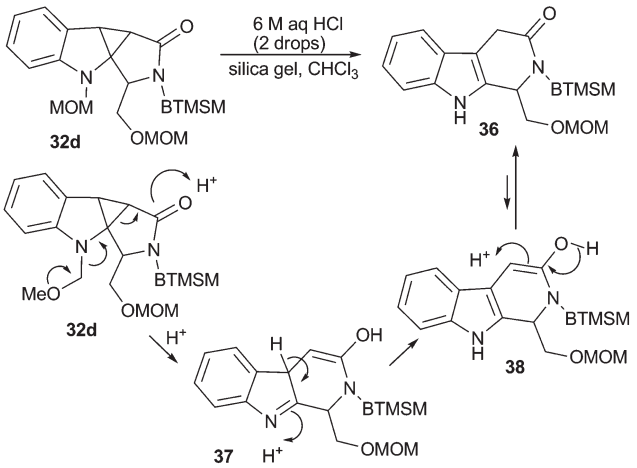
X-ray crystallographic analysis. The X-ray structure of **34**[30] (Fig. 3) clearly shows that the cyclopropyl moiety and the hydroxymethylene group are located on opposite sides of the indoline ring.

The results shown in Table 3 suggest that the *N*-BTMSM group not only provides conformational control about the amide unit but can also exert an influence on the conformational preference about the N–C_α sigma bond. On the basis of the preferred conformation about the amide N–C(O) bond afforded by the *N*-BTMSM moiety (Fig. 1, *vide supra*), the reaction of diazoamides **31a**,**b** is envisaged to proceed *via* the equilibrating reaction conformers **35** and **35′** (Fig. 4), which have resulted from rotation about the N–C_α sigma bond.

The formation of **32** and **33** can be understood if we considered the reactive conformers **35** and **35′** of the Rh(II)-carbenoid intermediate (Fig. 4). In conformer **35**, steric interaction between the $MOMOCH_2$ substituent and one of the TMS units of the *N*-BTMSM group is present, and for **35′** there is steric interaction between the indolyl moiety and the TMS group. It is plausible that the indolyl group–TMS interaction in **35′** is more destabilizing than that of the (relatively smaller) $MOMOCH_2$ group–TMS in **35**. Therefore, the metallocarbenoid reaction occurs preferentially *via* the more stable **35** to give the tetracyclic γ-lactam **32** as the major product. Reaction *via* the less preferred reaction conformer **35′** results in the minor γ-lactam product **33**.

Stability of the tetracyclic γ-lactams

As revealed by the results above, the propensity of the tetracyclic γ-lactams to undergo ring opening at the cyclopropyl moiety under the metallocarbenoid reaction conditions can be related to the indole N-substituent and the nature of the substituent on the diazoamide α-carbon. Thus, tetracyclic γ-lactams derived from indoles bearing an electron-withdrawing *N*-$PhSO_2$ or *N*-$MeSO_2$ group were generally more stable (except for **10f** with an α-acetyl group) whereas tetracyclic γ-lactams derived from indoles possessing an electron donating *N*-Me or *N*-MOM group are stable only when an electron-withdrawing substituent is absent at C(3a). Obviously, relief of ring strain and aromatization of the indole are not sufficient driving forces for rearrangement. Furthermore, it was found that the stability of tetracyclic γ-lactams to the acidic conditions is also related to the indole N-substituent and the nature of the substituent on the diazoamide α-carbon.[31]



Scheme 4 Acid-catalyzed rearrangement of **32d** to **36**.

We therefore investigated the rearrangement of **32d** with the aim of achieving a tandem selective indole *N*-MOM deprotection–rearrangement. Thus, treatment of **32d** with catalytic amounts of 6 M HCl in the presence of silica gel in $CHCl_3$ nicely effected selective hydrolysis of the indole *N*-MOM group and rearrangement of the tetracycle to the tetrahydro-β-carboline **36** in 84% yield (Scheme 4). A likely mechanism for the rearrangement would involve a "push–pull" mechanism wherein protonation of the lactam carbonyl oxygen in **32d** initiates a selective cleavage of the indoline *N*-MOM group and rearrangement to the indolenine (or indolenium) intermediate **37**, which aromatizes to the enol intermediate **38** followed by tautomerization to product **36**.

To gain additional insight into the factors that can influence the ring opening process, we investigated the $BF_3{\cdot}OEt_2$-catalyzed rearrangement of the stable tetracyclic γ-lactams **19h**, **39** and **40** (Scheme 5). We reasoned that coordination of $BF_3{\cdot}OEt_2$ to the lactam carbonyl should render this unit more electron-withdrawing and thus facilitate the tetracyclic γ-lactam to the tricycle rearrangement.

The treatment of **19h** with 20 mol% $BF_3{\cdot}OEt_2$ in 1,2-dichloroethane (DCE), either at rt or 80 °C, did not give the expected tricyclic indole derivative **41a**, but only returned the starting material **19h**. Interestingly, no products that could have resulted from desilylation of the *N*-BTMSM group were detected. The unexpected inertness of **19h** towards $BF_3{\cdot}OEt_2$ led us to consider

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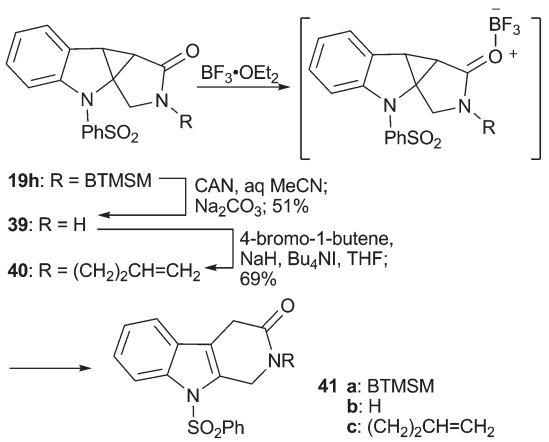

Scheme 5 $BF_3{\cdot}OEt_2$-mediated rearrangement of tetracyclic γ-lactams **19h**, **39** and **40**.

the idea that the *N*-BTMSM group could have sterically shielded the $BF_3{\cdot}OEt_2$ from effectively coordinating to the lactam carbonyl oxygen. To determine if this was the case, the *N*-BTMSM group in **19h** was removed *via* oxidative deprotection (CAN) followed by base hydrolysis (Na_2CO_3) to afford **39** in 51% yield over two steps. Although exposure of **39** to 20 mol% $BF_3{\cdot}OEt_2$ in DCE at rt did not lead to **41b**, we found that upon heating the reaction mixture under reflux for 48 h, **41b** was formed in a respectable yield of 70% (Scheme 5). Interestingly, the *N*-butenyl compound **40**, which was prepared from **39**, behaved similarly to **19h**; that is, no rearrangement to **41c** was observed under the same conditions ($BF_3{\cdot}OEt_2$, DCE, rt or 80 °C). These results suggest that rearrangement is less likely if an N-substituent is present in the γ-lactam moiety of tetracyclic γ-lactams carrying an electron-withdrawing indole-*N*-$PhSO_2$ (or *N*-$MeSO_2$) group.

Conclusion

The above studies on the metal-catalyzed reactions of the *N*-BTMSM indolylmethyl diazoamides have shown that: (1) the use of the *N*-BTMSM group is essential for enhancing site-selectivity *via* its conformational control about the amide N–C(O) unit wherein the metallocarbenoid reaction at the indole moiety is promoted; (2) the *N*-BTMSM group also provided conformational bias about the N–C_α sigma in N–C_α-branched diazoamides, which afforded excellent chemoselectivity in the metallocarbenoid reaction; (3) the chemoselectivity of the reaction was also influenced to some extent by the nature of the catalyst employed, and especially in the N–C_α-branched diazoamides where the use of a less electrophilic catalyst [Rh_2(cap)$_4$] led to excellent chemoselectivity; (4) substitution at the C(3) position of the indole ring had a noticeable steric effect on the chemoselectivity of the reaction; and (5) the electronic effects of the α-substituent at the diazo carbon and the indole N-substituent governed whether the tetracyclic γ-lactams or tricyclic indole derivatives were obtained as major or exclusive products. In this study, our results indicate that cyclopropyl intermediates (tetracyclic-γ-lactams) are formed enroute to the tricyclic indole derivatives.

Experimental section

General experimental details

Melting points are uncorrected. Infrared spectra were recorded either as neat oil or as a film (CH_2Cl_2) on NaCl plates; only diagnostic signals were reported. NMR spectra were recorded at 200 or 300 MHz in deuteriochloroform ($CDCl_3$) unless otherwise noted. The chemical shifts were reported in parts per million (δ) relative to the appropriate reference signal: residual chloroform (δ_H 7.26) singlet for ^{1}H NMR and the $CDCl_3$ triplet centered at δ 77.0 for ^{13}C NMR. Multiplicities of ^{1}H NMR signals were given as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad, and coupling constants (*J*) are given in Hz. High-resolution mass spectral analysis was obtained using either electron-impact (70 ev) or chemical-ionization (NH_3) mode. Reaction progress was monitored by thin-layer chromatography on silica gel 60_{F254} precoated (0.25 mm) on aluminum-backed sheets. Flash chromatography was performed on silica gel 60 Å. Petroleum ether (PE) is the fraction with bp 35–60 °C. Air and moisture sensitive reactions were conducted under a static pressure of Ar. PhMe, CH_2Cl_2 CH_3CN, DMF and DBU were dried by distillation from CaH_2. MeOH and EtOH were dried by distillation from magnesium metal in the presence of catalytic amounts of iodine. THF and Et_2O were dried by distillation from sodium using sodium benzophenone ketyl as indicators. All organic extracts were dried over anhydrous Na_2SO_4. All crude reaction products were purified by flash column chromatography unless noted otherwise.

General procedure for the metal-catalyzed reaction of diazoamides 10. The appropriate rhodium(II) catalyst (2 mol%) or Cu(II) catalyst (4 mol%) was suspended/dissolved in dry CH_2Cl_2 under Ar. A solution of the diazo compound in dry CH_2Cl_2 was added, *via* canula, under Ar to the catalyst suspension/solution either at rt or 40 °C. After the reaction was complete, the solvent was removed *in vacuo*, and the crude mixtures were purified.

$Rh_2(OAc)_4$-catalyzed reaction of α-diazoamides 10a,b. Diazoamides **10a,b** were treated with $Rh_2(OAc)_4$ according to the general procedure. It was found that the reaction of diazoamide **10a** was complete at rt within 72 h. In the case of **10b**, the reaction was found to be much slower and there was a significant amount of starting **10b** after 3 h at rt as judged by TLC; the reaction was brought to completion by heating the mixture at reflux for 6 h.

Methyl 2-ethyl-2,3,3b,8-tetrahydro-3-oxo-8-(phenylsulfonyl)-pyrrolo[3′,4′ : 1,3]cycloprop[1,2-b]indol-3a(1*H*)-carboxylate (11). Chromatography: 1 : 1 v/v PE–EtOAc; yield: 28%. Pale yellow solid; IR (film) 1734, 1694 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.18 (t, 3 H, J = 7.3 Hz), 3.09 (s, 3 H), 3.15 (s, 1 H), 3.35 (dq, 1 H, J = 14.2, 7.3 Hz), 3.55 (dq, 1 H, J = 14.2, 7.3 Hz), 3.74 (d, 1 H, J = 10.9 Hz), 4.82 (d, 1 H, J = 10.9 Hz), 7.06–7.14 (m, 1 H), 7.29–7.39 (m, 2 H), 7.45–7.54 (m, 2 H, 7.56–7.64 (m, 1 H), 7.71 (d, 1 H, J = 7.7 Hz), 7.85–7.94 (m, 2 H).

Methyl 1-[(1-phenylsulfonylindol-2-yl)methyl]-2-pyrrolidinone-3-carboxylate (12). Chromatography: 1 : 1 v/v PE–EtOAc; yield: 31%. Colorless oil; IR (film) 1741, 1696 cm^{-1}; ^{1}H NMR (300 MHz) δ 2.25–2.40 (m, 1 H), 2.41–2.54 (m, 1 H), 3.45

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(ddd, 1 H, J = 8.2, 8.2, 5.8 Hz), 3.53 (dd, 1 H, J = 9.2, 7.3 Hz), 3.66 (ddd, 1 H, J = 8.2, 8.2, 5.8 Hz), 3.81 (s, 3 H), 4.88 (d, 1 H, J = 16.2 Hz), 4.98 (d, 1 H, J = 16.2 Hz), 6.53 (s, 1 H), 7.18–7.34 (m, 2 H), 7.38–7.46 (m, 3 H), 7.48–7.57 (m, 1 H), 7.74–7.83 (m, 2 H), 8.12 (d, 1 H, J = 8.6 Hz); ^{13}C NMR (75 MHz) δ 22.5, 41.5, 46.0, 48.0, 52.9, 110.6, 114.6, 114.7, 120.9, 124.0, 124.8, 126.2, 129.3, 134.0, 135.3, 137.2, 138.2, 170.0, 170.8; HRMS (EI) calcd for $C_{21}H_{20}N_2O_5S$ (M^+) 412.1093, found 412.1095.

***cis*-Methyl 1-[(1-phenylsulfonylindol-2-yl)methyl]-4-methyl-2-azetidinone-3-carboxylate (*cis*-13).** Chromatography: 1 : 1 v/v PE–EtOAc; yield: 4%. Colorless oil; IR (film) 1768, 1734 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.29 (d, 3 H, J = 5.9 Hz), 3.76 (s, 3 H), 4.03–4.08 (m, 2 H), 4.68 (d, 1 H, J = 17.2 Hz), 4.85 (d, 1 H, J = 17.2 Hz), 6.65 (s, 1H), 7.20–7.30 (m, 2 H), 7.35–7.55 (m, 4 H), 7.69–7.71(m, 2 H), 8.10 (d, 1 H, J = 8.4 Hz); HRMS (EI) calcd for $C_{21}H_{20}N_2O_5S$ (M^+) 412.1093, found 412.1089.

***trans*-Methyl 1-[(1-phenylsulfonylindol-2-yl)methyl]-4-methyl-2-azetidinone-3-carboxylate (*trans*-13).** Chromatography: 1 : 1 v/v PE–EtOAc; yield: 10%. Colorless oil; IR (film) 1769, 1734 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.35 (d, 3 H, J = 6.3 Hz), 3.66 (d, 1 H, J = 2.2 Hz), 3.77 (s, 3 H), 4.10–4.15 (m, 1 H), 4.65 (d, 1 H, J = 17.8 Hz), 4.90 (d, 1 H, J = 17.8 Hz), 6.74 (s, 1 H), 7.20–7.30 (m, 2 H), 7.35–7.55 (m, 4 H), 7.69–7.71 (m, 2 H), 8.10 (d, 1 H, J = 8.4 Hz); ^{13}C NMR (75 MHz) δ 17.6, 38.8, 51.9, 52.9, 61.4, 111.5, 114.8, 121.3, 124.2, 125.1, 126.5, 129.7, 134.0, 135.0, 138.8, 164.8, 167.8; HRMS (EI) calcd for $C_{21}H_{20}N_2O_5S$ (M^+) 412.1093, found 412.1089.

4-Carbomethoxy-2-ethyl-9-phenylsulfonyl-4,9-dihydro-1*H*-pyrido[3,4-*b*]indol-3(2*H*)-one (14). Compound **14** was formed upon standing a solution of **11** (8 mg) in $CDCl_3$ overnight. After purification using PE–EtOAc (1 : 1) as the eluent, a pale yellow powder (8 mg, 100%) was obtained, mp 177–180 °C; IR (film) 1744, 1653 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.29 (t, 3 H, J = 6.5 Hz), 3.70 (s, 3 H), 3.60–3.78 (m, 2 H), 4.68 (t, 1 H, J = 4.0 Hz), 4.88 (d, 1 H, J = 18.6, 4.0 Hz), 4.98 (d, 1 H, J = 18.6, 4.0 Hz), 7.29 (dd, 1 H, J = 8.2, 1.3 Hz), 7.36 (ddd, 1 H, J = 8.6, 8.2, 1.3 Hz), 7.45–7.52 (m, 3 H), 7.52–7.60 (m, 1 H), 7.75–7.82 (m, 2 H), 8.06–8.11 (m, 1 H); ^{13}C NMR (75 MHz) δ 12.1, 43.5, 46.5, 48.0, 53.1, 113.9, 114.8, 119.2, 125.0, 126.0, 127.1, 127.8, 129.0, 130.0, 134.6, 136.8, 138.2, 163.0, 169.0; HRMS (EI) calcd for $C_{21}H_{20}N_2O_5S$ (M^+) 412.1093, found 412.1089.

2-[Bis(trimethylsilyl)methyl]-4-carbomethoxy-4,9-dihydro-1*H*-pyrido[3,4-*b*]indol-3(2*H*)-one (15). Chromatography: 7 : 1 v/v PE–EtOAc; yield: 65%. Pale yellow solid, mp 209–210 °C; IR (film) 3456, 1740, 1614 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.05–0.15 (br s, 9 H), 0.15–0.25 (br s, 9 H), 1.75–1.90 (br s, 1 H), 3.68 (s, 3 H), 4.45–4.57 (m, 1 H), 4.73–4.90 (m, 2 H), 7.11–7.17 (m, 1 H), 7.22 (ddd, 1 H, J = 6.9, 6.9, 1.5 Hz), 7.32–7.37 (m, 1 H), 7.58 (d, 1 H, J = 7.7 Hz), 8.06–8.15 (br s, 1 H); ^{13}C NMR (75 MHz) δ 0.0, 48.1, 49.0, 51.2, 52.5, 106.0, 111.1, 119.0, 120.8, 123.1, 125.5, 127.9, 137.2, 163.8, 170.2; HRMS (EI) calcd for $C_{20}H_{30}N_2O_3Si_2$ (M^+) 402.1795, found 402.1786.

Methyl 1-[bis(trimethylsilyl)methyl]-4-(1*H*-indol-2-yl)-2-azetidinone-3-carboxylate (16). Chromatography: 7 : 1 v/v PE–EtOAc; yield: 17%. White solid, mp 167–169 °C; IR (film) 3453, 1756, 1734 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.17 (s, 9 H), 0.18 (s, 9 H), 2.12 (s, 1 H), 3.77 (s, 3 H), 4.12 (d, 1 H, J = 2.5 Hz), 4.99 (d, 1 H, J = 2.5 Hz), 6.61 (br d, 1 H, J = 2.5 Hz), 7.14 (ddd, 1 H, J = 8.1, 7.4, 0.9 Hz), 7.20–7.28 (m, 1 H), 7.35–7.42 (m, 1 H), 7.61 (d, 1 H, J = 8.1 Hz), 8.30–8.38 (br s, 1 H); ^{13}C NMR (75 MHz) δ −0.1, 0.1, 38.9, 52.6, 54.5, 60.5, 104.5, 111.2, 120.5, 120.7, 123.1, 127.8, 132.4, 136.6, 161.5, 167.6; HRMS (EI) calcd for $C_{20}H_{30}N_2O_3Si_2$ (M^+) 402.1795, found 402.1809.

Methyl 2-[bis(trimethylsilyl)methyl]-1,2,3,4-tetrahydro-3-oxo-pyrazino[1,2-*a*]indole-4-carboxylate (17). Chromatography: 7 : 1 v/v PE–EtOAc; yield: 8%. White foam; IR (film) 1734, 1655 cm^{-1}; ^{1}H NMR (CD_3CN, 300 MHz) δ −0.05–0.25 (br s, 18 H), 3.71 (s, 3 H), 3.92–4.10 (br s, 1 H), 4.59 (d, 1 H, J = 16.5 Hz), 4.90 (br d, 1 H, J = 16.5 Hz), 5.60–5.81 (br s, 1 H), 6.31–6.57 (br s, 1 H), 7.12 (ddd, 1 H, J = 7.7, 7.7, 1.3 Hz), 7.17 (ddd, 1 H, J = 7.7, 7.7, 1.3 Hz), 7.27–7.42 (br s, 1 H), 7.58 (br d, 1 H, J = 7.7 Hz); HRMS (EI) calcd for $C_{20}H_{30}N_2O_3Si_2$ (M^+) 402.1795, found 402.1800.

$Rh_2(OAc)_4$-catalyzed reaction of α-diazoamides 23a,c,e. Compounds **23a,c,e** were treated with $Rh_2(OAc)_4$ at rt following the procedure described for the reaction of α-diazoamides **10**. For **23a**, the reaction was complete only after 24 h, but for **23c,e** complete reaction occurred within 10 min.

Ethyl 2-[bis(trimethylsilyl)methyl]-2,3,3b,8-tetrahydro-3b-methyl-3-oxo-8-(phenylsulfonyl)-pyrrolo[3′,4′ : 1,3]cycloprop[1,2-*b*]indol-3*a*(1*H*)-carboxylate (24a). Chromatography: 2 : 1 PE–Et_2O; yield: 54%. Colorless oil; IR (film) 1679, 1730 cm^{-1}; ^{1}H NMR (CD_3CN, 300 MHz) δ 0.17 (s, 18 H), 0.78 (t, 3 H, J = 7.2 Hz), 1.46 (s, 3 H), 2.82–2.94 (br s, 1 H), 3.56–3.68 (m, 2 H), 3.69 (d, 1 H, J = 12.1 Hz), 4.81 (d, 1 H, J = 12.1 Hz), 7.15 (br t, 1 H, J = 7.8 Hz), 7.21–7.30 (m, 1 H), 7.46 (br d, 2 H, J = 8.0 Hz), 7.46 (br t, 2 H, J = 7.8 Hz), 7.65–7.73 (m, 1 H), 7.83–7.92 (m, 2 H); ^{13}C NMR (CD_3CN, 75 MHz) δ 0.0, 11.2, 13.1, 38.6, 39.1, 39.2, 48.1, 60.0, 60.9, 114.9, 124.5, 125.7, 127.2, 128.1, 129.9, 132.8, 134.2, 139.8, 141.9, 163.8, 165.9; HRMS (EI) calcd for $C_{28}H_{38}N_2O_5SSi_2$ (M^+) 570.2040, found 570.2031.

2-[Bis(trimethylsilyl)methyl]-2,3,3b,8-tetrahydro-3b-methyl-3-oxo-8-(phenylsulfonyl)-pyrrolo[3′,4′ : 1,3]cycloprop[1,2-*b*]indol-3*a*(1*H*)-one (24c) and 1-[bis(trimethylsilyl)methyl]-4-(phenylsulfonyl-3-methyl-indol-2-yl)-2-azetidinone (25c). Chromatography: 2 : 1 v/v PE–Et_2O. Compounds **24c** and **25c** were obtained as an inseparable 3 : 1 mixture in 72% combined yield. The ratio of **24c** : **25c** was based on the integration of the doublet due to the H-1′ at δ 4.81 in the tetracyclic γ-lactam **24c** and the double doublet due to the H-3 at δ 3.01 in the β-lactam **25c**. IR (film) 1668, 1737 cm^{-1}; *Tetracyclic γ-lactam* **24c**: ^{1}H NMR (300 MHz) δ 0.27 (s, 9 H), 0.30 (s, 9 H), 0.85 (d, 1 H, J = 1.9 Hz), 1.41 (s, 3 H), 2.85–2.95 (br s, 1 H), 3.65 (dd, 1 H, J = 11.1, 1.9 Hz), 4.81 (d, 1 H, J = 11.1 Hz), 7.10 (ddd, 1 H, J = 8.0, 8.0, 0.6 Hz), 7.68–7.72 (m, 2 H), 7.84 (d, 1 H, J = 11.4 Hz), 7.19–7.62 (m, 5 H, extensive overlap of signals for indole and SO_2Ph hydrogens); ^{13}C NMR (75 MHz) δ 0.6, 0.9, 11.0, 26.9, 34.7, 38.1, 49.8, 53.8, 116.9, 124.1, 124.9, 127.8, 128.1, 129.2, 134.0, 135.0, 135.9, 142.2, 168.2.

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β-lactam **25c**: ^{1}H NMR (300 MHz) δ 0.10 (s, 9 H), 0.20 (s, 9 H), 2.13 (s, 1 H), 2.30 (s, 3 H), 3.01 (dd, 1 H, J = 13.9, 2.8 Hz), 3.27 (dd, 1 H, J = 13.9, 5.6 Hz), 5.61 (dd, 1 H, J = 5.6, 2.8 Hz), 8.21 (d, 1 H, J = 11.4 Hz), 7.19–7.62 (m, 8 H, extensive overlap of signals for indole and SO_2Ph hydrogens); ^{13}C NMR (75 MHz) δ 0.3, 10.0, 30.3, 39.8, 43.4, 115.9, 116.8, 118.8, 124.1, 125.7, 126.1, 127.8, 129.1, 131.7, 132.1, 133.8, 137.3, 167.1.

2-[Bis(trimethylsilyl)methyl]-1,2,3b,8-tetrahydro-3-oxo-3,8-dimethylpyrrolo[3′,4′ : 1,3]cycloprop[1,2-*b*]indol-3(3a*H*)-one (24e). Chromatography: 10 : 1 v/v PE–EtOAc; yield: 73%. White solid, mp 148–150 °C; IR (film) 1664 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.16 (s, 9 H), 0.18 (s, 9 H), 1.21 (d, 1 H, J = 1.8 Hz), 1.54 (s, 3 H), 2.86 (s, 3 H), 3.08–3.18 (br s, 1 H), 3.55(dd, 1 H, J = 11.3, 1.8 Hz), 3.80 (d, 1 H, J = 11.3 Hz), 6.70 (br d, 1 H, J = 7.5 Hz), 6.86 (ddd, 1 H, J = 7.5, 7.5, 0.9 Hz), 7.16 (ddd, 1 H, J = 7.5, 7.5, 0.9 Hz), 7.28 (d, 1 H, J = 7.5 Hz); ^{13}C NMR (75 MHz) δ 1.2, 10.8, 24.0, 34.1, 33.8, 37.2, 47.8, 56.2, 111.0, 120.2, 124.0, 128.0, 134.2, 149.5, 169.2; HRMS (EI) calcd for $C_{20}H_{32}N_2OSi_2$ (M^+) 372.2053, found 372.2054.

Ethyl 1-[bis(trimethylsilyl)methyl]-4-(1-phenylsulfonyl-3-methyl-indol-2-yl)-2-azetidinone-3-carboxylate (25a). Chromatography: 2 : 1 v/v PE–Et_2O; yield: 13%. Compound **25a** was obtained as an inseparable 1 : 3 mixture of *cis*- and *trans*-diastereomers; the *cis* : *trans* ratio was determined based on the integration of the H-4 signal of the β-lactam. IR (film) 1731, 1750 cm^{-1}; ^{1}H NMR (300 MHz, discernible signals for *cis*-diastereomer in square brackets) δ 0.10 (s, 9 H), 0.21 and [0.22] (s, 9 H), [1.06] and 1.33 (t, 3 H, J = 7.3 Hz), [2.12] and 2.18 (s, 1 H), 2.32 and [2.41] (s, 3 H), 4.20 (d, J = 2.5 Hz) and [4.42 (d, J = 5.7 Hz)] (1 H), [3.92–4.02 (m)] and 4.22–4.36 (m) (2 H), [5.90 (d, J = 5.7 Hz)] and 5.94 (d, J = 2.5 Hz) (1 H), 7.27–7.54 (m, extensive overlap of signals for indole and SO_2Ph hydrogens), 7.67–7.75 (m, extensive overlap of signals for indole and SO_2Ph hydrogens), [7.98 (dd, J = 7.7, 1.5 Hz)] and 8.22 (d, J = 8.5 Hz) (1 H); ^{13}C NMR (75 MHz, discernible signals for *cis*-diastereomer in square brackets) δ 0.4 and [0.6], 0.8 and [1.4], 10.6 and [10.7], [14.1] and 14.5, [39.5] and 39.9, 53.1 and [54.5], [59.4] and 60.3, [61.5] and 62.1, [115.1] and 116.1, 119.2 and [119.4], 122.7 and [122.9], [123.9] and 124.3, [125.7] and 126.2, 126.8 and [127.0], [129.2] and 129.3, 130.5 and [131.5], 131.7 and, [133.9] and 134.1, [137.2] and 137.4, 138.2 and [139.1], 162.3 and [163.2], 167.4; HRMS (EI) calcd for $C_{28}H_{38}N_2O_5SSi_2$ (M^+) 570.2040, found 570.2029.

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30 Crystal data for **34**: $C_{20}H_{32}N_2O_4SSi_2$, M_r = 452.72, monoclinic, space group *P*21/*n*, *a* = 9.0478(9), *b* = 18.6125(18), *c* = 14.1521(14) Å, *β* = 96.3590(10)o, *V* = 2368.6(4) Å3, *T* = 193(2) K, *Z* = 4, D_{calc} = 1.270 Mg m^{-3}, *F*(000) = 968, *μ* = 0.265 mm^{-1}. 15 535 reflections were measured on a Nonius Kappa CCD diffractometer, 5381 were independent ($I > 2\sigma(I)$). Final R_1 = 0.0410, wR_2 = 0.1103.
31 Three relatively stable tetracylic γ-lactams **11**, **19g**, and **24e**, which were obtained from the metal-catalyzed reaction of N–Cα-unbranched indolyl diazoamides, rearranged to tricyclic products, **14**, **18g**, and **27**, when stored as $CDCl_3$ solutions. These outcomes were attributed to catalysis by trace amounts of HCl.

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