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The rhodium(II)-catalyzed reaction of *N*-bis(trimethylsilylmethyl)diazoamides: steric, electronic and conformational effects

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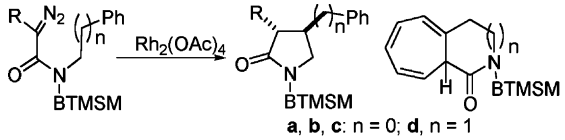
Abstract—The *N*-bis(trimethysilyl)methyl (*N*-BTMSM) group is effective for conformational control about the amide N–C(O) bond in tertiary diazoamides; metallocarbenoid C–H insertion reaction occurs only at the other N-'alkyl' unit. In C_α-unbranched diazoamides, the inherent electronic effects of the N-'alkyl' group influence the regioselectivity of the reaction. The *N*-BTMSM group also influences the conformational preference about the amide N–C_α bond in C_α-branched systems which, in turn, affects the regioselectivity of the reaction; substituent electronic effects are subtle and play subordinate roles. A transition state model to explain the results is proposed.

The intramolecular dirhodium(II) carbenoid C–H insertion reaction of diazocarbonyl compounds is a useful method for the construction of cyclic compounds.[1] This process is useful for the synthesis of β- and γ-lactams when applied to diazoamides. Steric, electronic and conformational factors as well as the nature of the ligands on the Rh(II) catalysts have been shown to play important roles in determining the type of lactam products that are formed.[2] It is also recognized that for tertiary diazoamides, conformational effects about the amide N–C(O) bond can result in metallocarbenoid attack at both N-substituents resulting in product mixtures.[2a–c] Strategies to improve site selectivity, which are based on replacing one of the N-substituents in the tertiary diazoamide with a bulky group (e.g. *t*-butyl[2c]), an electronically deactivated group[2a] or a N-protecting group,[3] have been developed and used with varying degrees of success. In connection with our ongoing interest in this area, we have investigated the Rh(II)-catalyzed reaction of *N*-bis(trimethylsilylmethyl)diazoamides to determine whether the *N*-bis(trimethylsilyl)methyl (*N*-BTMSM)[4] group will be effective for conformational control about (i) the amide N–C(O) bond and (ii) the N–C_α (sp^3) sigma bond of the second N-substituent. We report our preliminary findings in this Letter.

The reaction of compounds **1a–d** catalyzed by $Rh_2(OAc)_4$ (Eq. (1)) was first investigated.[5]



a, **b**, **c**: n = 0; **d**, n = 1

1	**2** (%)	**3** (%)
a; n = 1, R = CO_2Me	82	0
b; n = 1; R = Ac	86	0
c; n = 1, R = H	65	34
d; n = 2, R = H	82	0

(1)

The reactions proceeded efficiently to give good overall, isolated yields of the γ-lactam products. No β-lactam products were detected. Furthermore, the *N*-BTMSM group was not attacked by the reactive metallocarbenoid. For the lactams **2a**,**b**, the relative stereochemistry at C3-C4 was assigned as *trans* on the basis of the vicinal coupling constant of 9 Hz.[2b]

Unlike **1a**,**b**, the reaction of **1c** afforded the γ-lactam **2c** along with the cycloheptatriene derivative **3c** ($n=1$), and in a ratio of 2:1. Treatment of **1c** with the more 'electron-rich'[1] $Rh_2(Cap)_4$ favored more C–H insertion, but the cycloaddition pathway was still significant; the ratio of **2c**:**3c** (combined yield: 97%) was 3.5:1. Moving the phenyl moiety farther by one methylene unit, as in **1d**, resulted in the suppression of the undesired cycloaddition pathway and only the γ-lactam **2d** was formed.

Keywords: C–H insertion; dirhodium(II); diazoamides; conformational; electronic effects; *N*-bis(trimethylsilyl)methyl.

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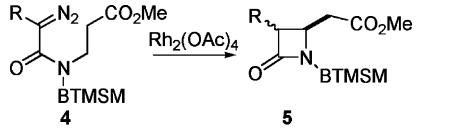
We then studied the $Rh_2(OAc)_4$-catalyzed reaction of diazo compounds **4a**,**b** (Eq. (2)). It has been shown[6] that the electron-withdrawing carbalkoxy group deactivates α and β C–H bonds towards metallocarbenoid insertion. However, the Rh(II)-catalyzed reaction of diazoamides possessing a *N*-(carbalkoxyethyl) substituent was found to give products which had arisen from metallocarbenoid insertion into C–H bonds α and β to the carbalkoxy moiety and from the carbonyl ylide derived from the interception of the metallocarbenoid by the carbonyl oxygen of the ester moiety.[2c]



4 **5**

a; R = CO_2Me 82% (cis: trans; 1.9:1)

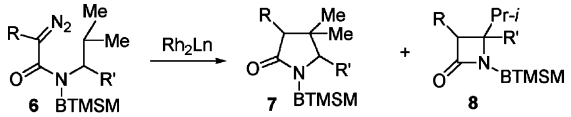
b; R = MeC(=O) 71% (trans) (2)

In **4a**,**b** metallocarbenoid C–H insertion occurred exclusively at the electronically activated[2] β-C–H bond to give **5a**,**b** in very good yields. Neither the corresponding γ-lactam nor the dihydro[1,4]oxazepin-3-one derivative which would be formed via a carbonyl ylide intermediate was detected. Again, the *N*-BTMSM group was not attacked by the metallocarbenoid. Compound **5a** was obtained as a 2:1 mixture of *cis* and *trans* ($J_{cis}=5$ Hz, $J_{trans}=1.9$ Hz)[2b] diastereomers whereas **5b** was obtained only as the *trans* diastereomer. It is likely that in the latter case epimerization at C-3 had occurred under the reaction conditions to afford the thermodynamically more stable *trans* product.

The results from compounds **1** and **4** revealed that metallocarbenoid reaction preferentially occurred at the *N*-'alkyl' substituent and not at the *N*-BTMSM group. This suggested that the *N*-BTMSM group has a strong bias on the conformation about the amide N–C(O)bond; the preferred amide rotamer is the one with the *N*-BTMSM group and the amide carbonyl moiety *syn* to each other.

Next, we investigated the C–H insertion reaction in diazoamides **6**, **9**, and **12**. Compounds **6a**–**e** were designed to examine electronic effects on metallocarbenoid insertion reaction between tertiary and secondary C–H bonds (**6a**,**b**,**c**) and between tertiary C–H bonds (**6d**,**e**). Compounds **9** and **12** will permit the assessment of electronic effects on metallocarbenoid insertion into secondary and tertiary C–H bonds. These compounds should also allow us to determine whether the *N*-BTMSM group has any influence on the conformational preference about the amide N–C('alkyl') sigma bond, which may affect the regio- and site-selectivity of the C–H insertion reactions in **6**, **9** and **12**.

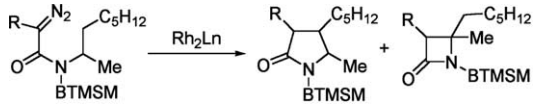
For the $Rh_2(OAc)_4$-catalyzed reaction of **6a**–**c** (Eq. (3) and Table 1), preferential metallocarbenoid insertion into the tertiary C–H bond to give only the γ-lactams **7a**–**c** was observed. Identical results were obtained with the more electron rich $Rh_2(acam)_4$. The reaction of **6d**,**e**, with $Rh_2(OAc)_4$ revealed the subtle influence of the α-substituent at the carbenoid center; with **6d**, only the γ-lactam **7d** was formed, whereas with **6e** a 2:1 ratio of an inseparable diastereomeric mixtures of **7e**:**8e** was produced and in a combined yield of 78%. The γ-lactam that could arise from insertion into the electronically less favorable methyl C–H bond was not detected.



6 **7** **8**

a; R = R' = H; **b**; R = Ac, R' = H;**c**; R = CO_2Me, R' = H;
d, R = H, R' = Me; **e**; R = Ac, R' = Me (3)

The above C–H insertion results are nicely complemented by the data from the reaction of compound **9** (Eq. (4)). The reaction of **9a** with $Rh_2(OAc)_4$ led only to the γ-lactam product **10a**, which arose from preferential insertion of the metallocarbenoid into the secondary C–H bond. Interestingly, the reaction of **9b**,**c** with $Rh_2(OAc)_4$ indicated that there was increased preference for Rh(II)-carbenoid insertion into the tertiary C–H bond adjacent to the amide nitrogen atom, which produced a mixture of the γ-lactams **10b**,**c** and the β-lactams **11b**,**c**, respectively.[7] For **9b** the ratio of **10b**:**11b** was 1:3.8, whereas for **9c** the ratio of **10c**:**11c** was 1:3.



9		**10**	**11**
a; R = H	$Rh_2(OAc)_4$	85%	0%
	$Rh_2(acam)_4$	94%	0%
b; R = Ac	$Rh_2(OAc)_4$	18%	68%
	$Rh_2(acam)_4$	19%	52%
c; R = CO_2Me	$Rh_2(OAc)_4$	16%	49%

(4)

Furthermore, when **9b** was treated with $Rh_2(acam)_4$ insertion into the tertiary C–H bond was still the preferred pathway; the β-lactam **11b** was obtained as the major product and the ratio of **10b**:**11b** was 1:2.7. This result suggests that the electronic nature of the catalyst

Table 1. Rh(II)-catalyzed reaction of **6**: regioselectivity

Diazo	Rh_2L_4	γ-Lactam%[a]	Diazo	Rh_2L_4	γ-Lactam%[a]
6a	$Rh_2(OAc)_4$	**7a**, 94	**6c**	$Rh_2(OAc)_4$	**7c**, 75
6a	$Rh_2(acam)_4$	**7a**, 71	**6c**	$Rh_2(acam)_4$	**7c**, 57
6b	$Rh_2(OAc)_4$	**7b**, 87	**6d**	$Rh_2(OAc)_4$	**7d**, 70
6b	$Rh_2(acam)_4$	**7b**, 41	**6e**	$Rh_2(OAc)_4$	**7e**,[b] 78

[a] Isolated yields.
[b] Inseparable mixture of γ-lactam **7e** and β-lactam **8e**.

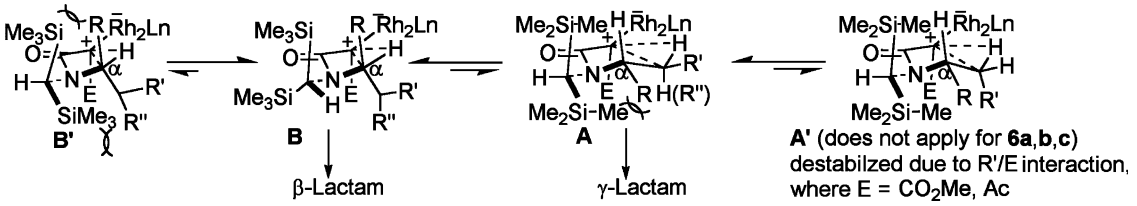
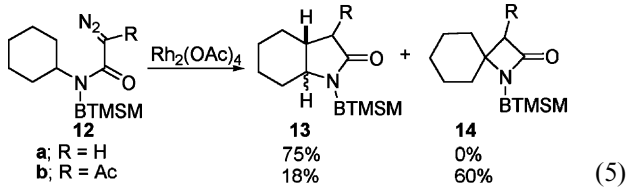


Figure 1. Transition state models for formation of γ- and β-lactams.

has little effect on the regioselectivity of C_α-branched systems. We then studied the $Rh_2(OAc)_4$-catalyzed reaction of the geometrically more constrained diazoamide **12a**,**b** (Eq. (5)). Interestingly, a similar behavior of the metallocarbenoid to that observed for **9a**,**b** was displayed. Thus for **12a**, a high preference for insertion into the secondary (axial and equatorial) C–H bond of the cyclohexyl ring was observed, which resulted in a 75% yield of a 1:1 diastereomeric mixture of *cis*- and *trans*-**13**.



(5)

Insertion into both axial and equatorial bonds in the cyclohexyl ring is well precedented in the literature.[8] For **12b**, however, the spiro β-lactam **14b** was formed as the major product reflecting a high preference for metallocarbenoid attack on the tertiary C–H bond. This outcome is in agreement with the results obtained for the reaction of **9b** (Eq. (4)).

The overall composite results suggested that if the carbon (C_α) directly adjacent to the amide nitrogen atom is unbranched, γ-lactam formation is highly favored (**1a**–**d**; **6a**–**c**), but the regioselectivity is subject to the usual electronic effects of the N-substituent and not the α-substituent at the carbenoid center (**4a**,**b** versus **6a**–**c**). However, for the C_α branched systems (**6d**,**e**; **9a**–**c**, **12a**,**b**), the data suggested that the regioselectivity of the reaction is strongly influenced by the conformational preference about the N–C_α sigma bond; the electronic influence of the α-substituent at the carbenoid carbon is subtle but important.

The formation of the γ- and β-lactams can be understood by considering the following 'chair-like' transition state (TS) models (Fig. 1), wherein the Rh–carbenoid bond is aligned parallel to the target C–H sigma bond.[9] Insertion of the carbenoid center into the C–H bond is believed to involve the overlap of the vacant p-orbital of the carbenoid carbon and the target C–H sigma bond.[10] In an unbranched system, C–H insertion proceeds via TS-**A**[11a] to give γ-lactams. Neither the α-substituent at the carbenoid carbon nor the nature of the ligand in the Rh(II) catalyst has an influence on the regioselectivity of the reaction.

When C_α is branched, destabilizing interaction between the *syn* pseudoequatorial R (see TS-**A**) and $SiMe_3$ moiety of the *N*-BTMSM group causes the R group to rotate away and adopt the relatively more stable TS-**B**.[11b] In this TS, the tertiary C–H unit is in the vicinity of the metallocarbenoid. The results from **6d**,**e**, **9a**–**c** and **12a**,**b** suggest that for the α-acetyl and α-carbomethoxy substituted metallocarbenoid, interaction of the more electrophilic carbenoid center with the C–H bonds occur via an earlier[10] TS and therefore the more electron-rich (nucleophilic) tertiary C–H bond is preferentially attacked leading to the formation of the β-lactam as the major product. When the metallocarbenoid center is unsubstituted, the carbenoid carbon is less electrophilic and a later[10] TS is involved. Insertion into the tertiary C–H bond is now enthalpically less favored and the carbenoid reacts via the more kinetically and electronically favored pathway, that is via TS-**A** to preferentially give the γ-lactam.

In summary, we have demonstrated the effectiveness of the *N*-BTMSM group for conformational control about the amide N–C(O) bond in tertiary diazoamides. In C_α-unbranched diazoamides, the regioselectivity of the C–H insertion reaction was influenced by the inherent electronic effects of the N-'alkyl' group, whereas in C_α-branched systems regioselectivity was governed by conformational preference about the amide N–C_α bond as well as by subtle, but important electronic effects of the α-substituent at the carbenoid carbon and the N-'alkyl' group. Further studies are directed at expanding the use of *N*-BTMSM in C_α-branched diazoamides for the synthesis of trisubstituted γ-lactams.

Acknowledgements

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3. E.g. (a) *N*-Benzhydryl: Zargoza, F. *Tetrahedron* **1995**, *51*, 8829–8834; (b) *N*-(4-Nitrophenyl): Anada, M.; Hashimoto, S.-i. *Tetrahedron Lett*. **1998**, *39*, 79–82; (c) *N*-(4-Methoxyphenyl): Wee, A. G. H.; Liu, B.-S.; McLeod, D. D. *J. Org. Chem*. **1998**, *63*, 4218–4227.
4. (a) Another interest for developing the use of the *N*-BTMSM group in carbenoid chemistry is that the *N*-BTMSM group has been effectively used as an N-protecting group elsewhere, which suggested that once the desired role of the *N*-BTMSM group has been fulfilled it can be readily removed (cf. Palomo, C.; Aizpurua, J. M.; Legido, M.; Galarza, R.; Deya, P. M.; Dunogues, J.; Picard, J. P.; Ricci, A.; Seconi, G. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 1239–1241) from the lactam product; (b) Deprotection of the *N*-BTMSM group in our lactam products is readily achieved via CAN oxidation/base hydrolysis. Duncan, S., unpublished observations.
5. (a) All reactions were conducted in refluxing dichloromethane and using 2 mol% of Rh(II) catalyst, unless otherwise stated. $Rh_2(acam)_4$: dirhodium(II) tetrakisacetamidate; $Rh_2(Cap)_4$: dirhodium(II) tetrakiscaprolactamate; (b) All new compounds gave satisfactory ^1H, ^{13}C NMR, IR and HRMS data. **7a**: δ_H 3.12 (s, 3H, H_5, $CH(SiMe_3)_2$), 2.20 (s, 2H, H-3), 1.13 (s, 6H, Me), 0.08 (s, 18H, $2SiMe_3$), δ_c 0.14, 28.3, 32.3, 35.1, 45.5, 62.8, 172.7. HRMS: calcd for $C_{13}H_{29}NOSi_2$ 271.1788, found 271.1781. **7d**: δ_H 3.17 (q, 1H, $J=6.2$ Hz, H-5), 2.24–1.86 (m, 3H, H-3, $CH(SiMe_3)_2$), 1.13 (s, 3H, Me), 1.05 (d, 3H, $J=6.2$ Hz, C_5-Me), 0.81 (s, 3H, Me), 0.10 (s, 18H, $2SiMe_3$), δ_C 0.5, 1.0, 14.1, 23.2, 28.5, 38.8, 45.0, 66.2, 172.5. **10a**: δ_H (*cis* diastereomer in brackets): (3.51–3.71) and 3.24–3.05 (m, 1H, H-5), 2.49 (dd, 1H, $J=8.8$, 16.7 Hz, H-3), 2.36–1.68 (m, 3H, H-3, H-4, $CH(SiMe_3)_2$)), 1.51–1.20 (m, 8H, $4CH_2$), 1.15 (d, $J=6.5$ Hz) and [1.10 (d, $J=6.7$ Hz)] (3H, C_5-Me), 0.88 (t, 3H, $J=6.1$ Hz. Me), 0.10 (m, 18H, $2SiMe_3$), δ_C 0.6, 0.8, 13.0, 13.1, 19.3, 22.0, 22.5, 25.6, 27.2, 27.6, 29.6, 30.0, 31.7, 35.0, 35.5, 36.2, 36.5, 37.6, 40.3, 62.8, 172.7. **11b**: δ_H (mixture of diastereomers) 3.65 and 3.55 (s, 1H, H-3), 2.30 (s, 3H, MeC(=O), 1.98 (s, 1H, $CH(SiMe_3)_2$), 1.87–1.08 (m, 13H, $5CH_2$, Me), 0.88 (t, 3H, $J=5.7$ Hz, Me), 0.15 (s, 18H, $2SiMe_3$), δ_C 0.5, 0.6, 14.0, 19.2, 22.5, 23.5, 25.3, 25.7, 29.5, 29.7, 30.9, 31.6, 35.0, 35.4, 40.3, 63.1, 67.4, 68.5, 163.0, 202.5. HRMS: calcd for $C_{19}H_{40}NO_2Si_2$ (M+1) 370.2598, found 370.2537. **14b**: δ_H 3.65 (s, 1H, H-3), 2.31 (s, 3H, MeC(=O)), 2.15–0.95 (m, 11H, $CH(SiMe_3)_2$, $5CH_2$), 0.14 (s, 18H, $2SiMe_3$), δ_C 0.4, 0.6, 23.7, 24.4, 24.6, 30.2, 32.2, 43.6, 35.9, 67.7, 203.1.
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7. Each of the lactams **10** and **11** were obtained as inseparable mixtures of diastereomers.
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11. The conformation about the *N*-BTMSM sigma bond in TS-**A** and TS-**B** is drawn on the basis of AM1 calculations (PC Spartan Pro 6.0.6) performed on model *N*-BTMSM diazoamides. (a) For TS-**A**, we used *N*-BTMSM,*N*-butyl-α-diazoacetamide: ΔH_f (*syn* $[Me_3Si]_2C$-H/amide C=O) = −56.645 kcal mol^{-1} and ΔH_f (*anti* $[Me_3Si]_2C$-H/amide C=O) = −52.805 kcal mol^{-1}. (b) For TS-**B** we used *N*-BTMSM,*N*-(2-pentyl)-α-diazoacetamide: ΔH_f (*syn* $[Me_3Si]_2C$-H/amide C=O) = −53.170 kcal mol^{-1} and ΔH_f (*anti* $[Me_3Si]_2C$-H/amide C=O) = −53.717 kcal mol^{-1}.