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The Bis(trimethylsilyl)methyl Group as an Effective N-Protecting Group and Site-Selective Control Element in Rhodium(II)-Catalyzed Reaction of Diazoamides

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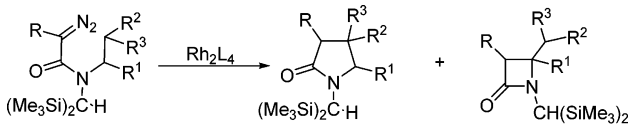
Received May 24, 2005



E.g. R = MeC(O), CO_2Me, H; R^1 = H or Me, R^2 = Me or Ph, R^3 = Me

The intramolecular rhodium(II)−carbenoid-mediated C−H insertion reaction of structurally varied *N*-bis(trimethylsilyl)methyl,*N*-substituted diazoamides is studied. It has been found that in tertiary diazoamides the *N*-bis(trimethylsilyl)methyl (*N*-BTMSM) group is effective for conformational control about the amide N−C(O) bond; C−H insertion occurs at the other N-substituent. In C_α-branched diazoamides, the *N*-BTMSM is found also to exert its influence on the conformational preference about the N−C_α bond, which affects the regioselectivity of the C−H insertion in these systems. In unbranched diazoamides, inherent electronic effects of the N-substituent affect the regio- and chemoselectivity of the reaction; however, in branched diazoamides, electronic effects of the N-substituent and the α-substituent at the carbenoid carbon are subtle, but important in the deciding the eventual outcome of the reaction.

Introduction

α-Diazoamides undergo a number of interesting reactions in the presence of a catalytic amount of dirhodium(II) complexes.[1] Among them, the intramolecular dirhodium(II) carbenoid mediated C−H insertion reaction,[1] cyclopropanation,[2a] and ylide formation/cycloaddition or rearrangement reactions[2b] are the most exploited reactions especially for the preparation of structurally diverse heterocycles. Steric, electronic, and conformational factors inherent in the diazo reactant as well as the nature of Rh(II) catalysts have been shown to play important roles in governing the regio-, chemo-, and stereoselectivity of the transformations.[1] It is also recognized that for acyclic, tertiary α-diazoamides,[1] conformational effects about the amide N−C(O) bond govern site selectivity and, consequently, mixtures of lactam products are usually obtained arising from metallocarbenoid attack at both N-substituents.[3] This complication is especially pronounced in C−H insertion reactions of α-diazoamides.[1]

Two main strategies have been investigated for improving site selectivity in the reactions of tertiary diazoamides. The first approach involves replacing one of the two N-substituents in the tertiary diazoamide with a bulky group[3a,d,4] (e.g., *tert*-butyl, neopentyl, 2,4,6-trimethylbenzyl), which serves to bias the conformational preference about the amide N−C(O) moiety, thereby promoting metallocarbenoid reaction at the remaining N-substituent. This strategy has proved useful but some limitations[5] have been encountered; for example, the

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10.1021/jo051042e CCC: $30.25
Published on Web 09/10/2005

N-tert-butyl is susceptible to metallocarbenoid C−H insertion at one of the methyl groups,[5a] and the removal of the *tert*-butyl group from the lactam product(s) is often difficult.[5b] The second approach involves the use of a group that is electronically deactivated toward C−H insertion thereby favoring metallocarbenoid attack at the remaining N-substituent.[4b,6]

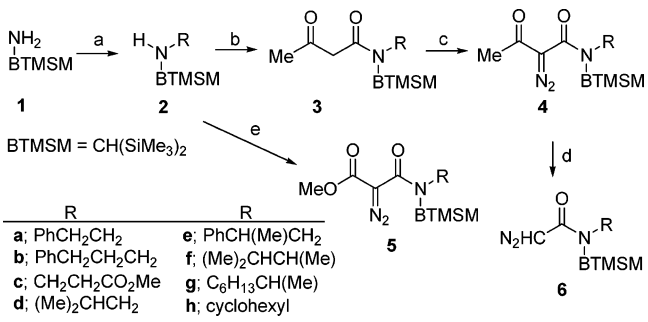
We have reported[7] the successful use of the *p*-methoxyphenyl (PMP) group in Rh(II)-catalyzed C−H insertion reaction of diazoamides wherein preferential metallocarbenoid attack at the N-"alkyl" substituent is observed. However, subsequent studies[8] have revealed that in cases where metallocarbenoid C−H insertion at the N-"alkyl" substituent was difficult due to electronic deactivation and/or steric hindrance at the reaction site, metallocarbenoid attack on the *N*-PMP was favored, which resulted in the formation of oxindole derivatives as major products. Our ongoing interest in achieving control on the site selectivity in the reaction of diazoamides has led us to investigate the Rh(II)-catalyzed reaction of *N*-bis(trimethylsilylmethyl)diazoamides.[9] We wished to determine (1) whether the *N*-bis(trimethylsilyl)methyl (*N*-BTMSM) group would afford effective conformational control about the amide N−C(O) bond thereby improving site-selectivity and (2) whether the *N*-BTMSM group would influence the conformational preference about the N−C_α (sp^3) sigma bond of the second, branched N-substituent. We were encouraged by literature reports[10] on the chemical versatility of the BTMSM group and its use as a N protecting group.[11] Nonetheless, the use of the BTMSM group under metallocarbenoid reaction conditions has not been investigated.

We now report the details[9a] of our studies on the use of the *N*-BTMSM group as a N-protecting group in rhodium(II) catalyzed reactions of diazoamides. We found that the *N*-BTMSM group was effective as a conformational control element for the amide N−C(O) bond in tertiary diazoamides. For N−C_α-branched diazoamides, the *N*-BTMSM group was also able to influence the conformational preference about the amide N−C_α moiety, and this feature as well as electronic effects govern the regioselectivity of the reaction.

Results and Discussion

The diazoamides were prepared by standard procedures as outlined in Scheme 1. The secondary amines (**2**) were prepared either via direct N-alkylation (route A) of **1** with an appropriate bromide or iodide or by reductive amination (route B) of **1** with an appropriate aldehyde or ketone. The overall yield of the amines (**2**) was in the range of 60−80%; the reductive amination route was always more high yielding. In the case of **2c**, its preparation was accomplished efficiently (92%) via the Michael addition (MeOH, rt) of **1** to methyl acrylate. The amines (**2**) were then converted to the acetoacetamides (**3a**−**h**) by reaction with diketene in the presence of a catalytic amount of DMAP. We found that a higher yield of diazoacetoacetamides (**4**) was obtained if compounds **3** were not purified, but used directly in the diazotization step with methanesulfonyl azide (MsN_3). DBU was preferred over Et_3N as the base for these reactions. Good yields (70−80%) of the diazoamides (**4a**−**h**) were obtained.

SCHEME 1. Preparation of Diazoacetamides 4−6



[a] Reagents and conditions: (a) for **1a**,**b** **d**−**h**: (route A) RBr, Na_2CO_3, NaI, DMF, 65 °C or (route B) ketone/aldehyde, Et_2O, $NaBH_4$, MeOH, rt; for **1c**: CH_2=$CHCO_2Me$, MeOH, rt, 24 h; (b) diketene, DMAP, THF; (c) MsN_3, DBU, MeCN; (d) LiOH·H_2O, aq THF or 5% aq KOH, MeCN; (e) MeO_2CCN_2COCl, 2,6-lutidine, CH_2Cl_2, 0 °C.

Deacylation of compounds **4a**,**b**,**d**−**h** was initially accomplished by treating the diazo substrates with LiOH·H_2O (3.5 molar equiv) in aqueous THF[12a] to afford compounds **6a**,**b**,**d**−**h** (60−75% yield). However, it was found that longer reaction time resulted in further hydrolysis of the desired product. An alternative deacylation procedure[12b] involving the use of 5% aqueous KOH in acetonitrile was found to be milder, and afforded higher yields (75−85%) of **6**, although slightly longer reaction times were required.

For the preparation of the α-(carbomethoxy)-α-diazoacetamides (**5a**−**g**), the best route was the direct acylation of the secondary amines (**2**) with methyl diazomalonyl chloride.[13] This provided **5a**−**g** in yields ranging from 70 to 85%. The traditional route involving condensation of **2** with monomethyl malonic acid (DCC, cat. DMAP) to obtain the corresponding α-(carbomethoxy)-acetamides followed by diazo transfer (MsN_3, DBU) gave low overall yields. Although the amide formation step proceeded uneventfully, the diazotization step was problematic; the reaction was plagued by long reaction times, poor conversion and decomposition of both diazo product and starting ester amide. The use of NaH as the base

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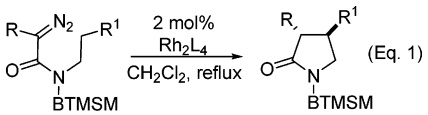
TABLE 1. Rh(II)-Catalyzed Reaction of 4−6(a,b): Regio- and Chemoselectivity

entry	diazoamide	catalyst[a]	γ-lactam: **7**, **8**, or **9**	yield[b] (%)
1	**4a**	$Rh_2(OAc)_4$	**7a**	86
2	**5a**	$Rh_2(OAc)_4$	**8a**	82
3	**5a**	$Rh_2(Piv)_4$	**8a**	94
4	**6a**	$Rh_2(OAc)_4$	**9a**	65[c]
5	**6a**	$Rh_2(cap)_4$	**9a**	75[c]
6	**4b**	$Rh_2(OAc)_4$	**7b**	72
7	**5b**	$Rh_2(OAc)_4$	**8b**	70
8	**6b**	$Rh_2(OAc)_4$	**9b**	82

[a] Reactions were carried out using 2 mol % of Rh(II) catalyst in refluxing CH_2Cl_2. [b] Isolated yield of chromatographically pure **7**, **8**, or **9**. [c] Cycloheptatriene derivative **10** was also isolated. For $Rh_2(OAc)_4$, 33%; for $Rh_2(acam)_4$, 22%.

and dry ether or dry DME as solvent, reaction conditions that have been found[7b] to be effective in other systems, did not alleviate the situation.

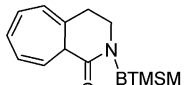
The Rh(II)-catalyzed reaction of the diazoamides **4**−**6a**,**b** (eq 1) was first examined to assess whether the *N*-BTMSM group would be tolerated by the reactive Rh(II)−carbenoid and to determine the regio- and chemoselectivity of the reaction. The results are summarized in Table 1.



4; R = MeC(O)
5; R = CO_2Me
6; R = H

a; R^1 = Ph
b; R^1 = CH_2Ph

7; R = MeC(O)
8; R = CO_2Me
9; R = H



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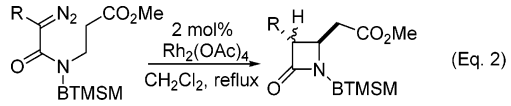
The reactions proceeded efficiently to give good overall, isolated yields of the γ-lactam products **7**, **8**, or **9**. With **5a**, the use of $Rh_2(Piv)_4$ (Piv = $(Me)_3CCO_{2-}$ ligand) gave a higher yield of **8a** but provided the same regio- and chemoselectivity achieved with $Rh_2(OAc)_4$ (compare entries 2 and 3). No β-lactam products were detected in these reactions. Although the *N*-BTMSM unit has a methine C−H bond, we were pleased to find that it was not attacked by the reactive metallocarbenoid, and this is likely due to the steric shielding of the methine C−H bond by both trimethylsilyl groups.

Similarly, there was no product arising from C−H insertion into any of the six methyl groups of the two trimethylsilyl moieties. For the lactams **7a** and **8a**, the relative stereochemistry at C2−C3 was assigned as *trans* on the basis of the vicinal coupling constant of 9 Hz.[7a]

Unlike **4a** and **5a** the $Rh_2(OAc)_4$-catalyzed reaction of **6a** (entries 4 and 5) afforded a readily separable mixture of the γ-lactam **9a** and the cycloheptatriene derivative **10**, and in a ratio of 2:1. With the more "electron-rich" $Rh_2(Cap)_4$ (Cap = caprolactamate ligand), **6a** gave compounds **9a** and **10** in 97% yield, and with a modest improvement on the chemoselectivity for γ-lactam formation; the ratio of **9a/10** was 3.3:1. In the reaction of the homologous diazoamides **4**−**6b** (entries 6−8) regio- and chemoselectivity was excellent, which led only to γ-lactam products **7**−**9b**. In the case of **6b** (entry 8), moving the phenyl unit farther by one methylene unit resulted in the complete suppression of the undesired cycloaddition pathway.

We next studied the $Rh_2(OAc)_4$-catalyzed reaction of diazo compounds **4c** and **5c** (eq 2). It has been shown[14]



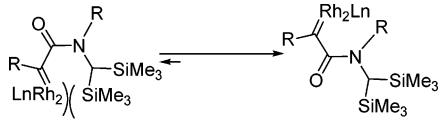
4c; R = Me(CO)
5c; R = CO_2Me

11, R = MeC(O), H = β
12, R = CO_2Me, H = α/β

that an electron-withdrawing carbalkoxy group deactivates α and, to a lesser extent, β C−H bonds toward metallocarbenoid insertion. We[7a] and others[4b] have also shown that the Rh(II)-catalyzed reaction of diazoamides possessing a *N*-(carboalkoxyethyl) substituent yielded products that had arisen from metallocarbenoid insertion into C−H bonds α and β to the carboalkoxy moiety and from the carbonyl ylide derived from the interception of the metallocarbenoid by the carbonyl oxygen of the ester moiety.

For **4c** and **5c**, the Rh(II)−carbenoid C−H insertion occurred exclusively at the electron-rich amide N-activated β-C−H bond to give **11** (71%) and **12** (82%) in very good yields. Neither the γ-lactam nor the dihydro[1,4]-oxazepin-3-one derivative, which would be formed via a carbonyl ylide intermediate, was detected. Compound **11** was obtained only as the *trans*[7a] diastereomer whereas **12** was obtained as a 2:1 mixture of *cis*-[7a] and *trans*-diastereomers. It is likely that in the case of **11**, the electron-withdrawing acetyl group caused the C-3 proton to be more acidic which facilitated epimerization at C-3, under the reaction conditions,[15] to form the thermodynamically more stable *trans* product.

The combined results from the reaction of **4a**−**c**, **5a**−**c**, and **6a**,**b** suggest that the *N*-BTMSM group has a strong bias on the conformation about the amide N−C(O) bond (Figure 1) that is also advantageous; the preferred amide rotamer is **13′**, which has the *N*-BTMSM group and the amide carbonyl moiety positioned *syn* to each other. This then places the reactive Rh(II)−carbenoid center closer to the R group for a facile C−H insertion reaction.



13 **13'**

FIGURE 1. Preferred conformation about the *N*-BTMSM amide unit.

To further define the scope and limitations of the *N*-BTMSM diazoamides in intramolecular C−H insertion reactions, we investigated structurally more varied *N*-BTMSM diazoamides **4d**−**h**, **5d**,**g**, and **6d**−**h** to determine steric, conformational, and electronic effects on regio- and chemoselectivity. Specifically, compounds **4d**,**f**,

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TABLE 2. Rh(II)-Catalyzed Reaction of 4d−f, 5d, and 6d−f

entry	diazo-amide	catalyst[a]	combined yield[b] (%)	relative yield (%) γ/β lactams	**16e/20e**
1	**4d**	$Rh_2(OAc)_4$	87	**14d/17d**, 100:0	
2	**4d**	$Rh_2(acam)_4$	64[c]	**14d/17d**, 100:0	
3	**5d**	$Rh_2(OAc)_4$	75	**15d/18d**, 100:0	
4	**5d**	$Rh_2(acam)_4$	71[c]	**15d/18d**, 100:0	
5	**6d**	$Rh_2(OAc)_4$	94	**16d/19d**, 100:0	
6	**6d**	$Rh_2(acam)_4$	71	**16d/19d**, 100:0	
7	**6e**	$Rh_2(OAc)_4$	98		68:32
8	**6e**	$Rh_2(acam)_4$	88		53:47
9	**4f**	$Rh_2(OAc)_4$	78[d]	**14f/17f**, 67:33[e]	
10	**4f**	$Rh_2(acam)_4$	57[c,d]	**14f/17f**, 67:33[e]	
11	**6f**	$Rh_2(OAc)_4$	72	**16f/19f**, 100:0	
12	**6f**	$Rh_2(acam)_4$	78	**16f/19f**, 100:0	

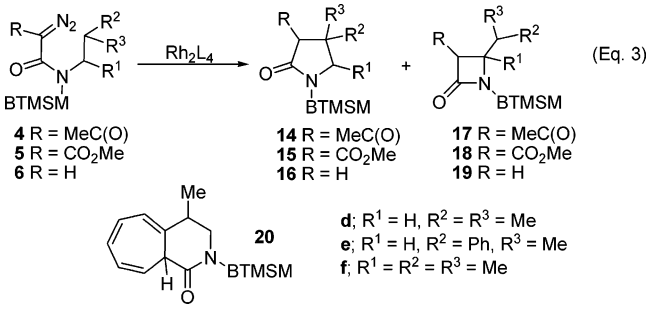
[a] Reactions were carried out using 2 mol % of Rh(II) catalyst in refluxing CH_2Cl_2. [b] Yield of chromatographically pure products. [c] With $Rh_2(acam)_4$, reaction was incomplete in this case and product yield was based on recovered starting material. [d] γ-lactam (**14f**) and β-lactam (**17f**) were obtained as inseparable mixtures of diastereomers. The IR spectrum showed the characteristic ν(C=O) for the β-lactam at 1741 cm^{-1} and for the γ-lactam at 1676 cm^{-1}. [e] The ratio of **14f/17f** was based on the integration of the H-3 singlet at δ 3.55 (**17f**) and at δ 3.14, 3.15 (**14f**).

TABLE 3. Rh(II)-Catalyzed Reaction of 4g−6g

entry	diazoamide	catalyst[a]	combined yield[b] (%)	relative yield[c] (%)
1	**4g**	$Rh_2(OAc)_4$	87	**21**[f]/**24**,[h] 21:79
2	**4g**	$Rh_2(acam)_4$	72[d,e]	**21**[f]/**24**,[h] 27:73
3	**5g**	$Rh_2(OAc)_4$	65	**22**[f]/**25**,[h] 25:75
4	**6g**	$Rh_2(OAc)_4$	85	**23**[g]/**26**, 100:0
5	**6g**	$Rh_2(acam)_4$	94	**23**[g]/**26**, 100:0

[a] Reactions were carried out using 2 mol % of Rh(II) catalyst in refluxing CH_2Cl_2. [b] Yield of chromatographically pure products. [c] Relative yields were calculated based on weight ratio of isolated γ-lactams (**21**−**23**) and β-lactams (**24**−**26**). [d] Starting material was not recovered. [e] Each of the γ- and β-lactam products, **21**, **22** and **24**, **25**, respectively, was obtained as an inseparable mixture of diastereomers. [f] Due to the complexity of the ^{1}H NMR spectra, the ratio of the diastereomers was not determined. [g] The ratio of *cis*-**23**/*trans*-**23**, based on the integration of the H-5 multiplet at δ 3.31−3.51 (*cis*) and δ3.05−3.24 (*trans*), was 1:1 for $Rh_2(OAc)_4$ and 1:3 for $Rh_2(acam)_4$. [h] Ratio of *cis*-**24**/*trans*-**24** dastereomers was 1:4 and was based on the integration ratio of the H-3 singlet at δ 3.65 (*cis*) and δ 3.57 (*trans*). Ratio of *cis*-**25**/*trans*-**25** was 1:2 and was based on the integration ratio of the H-3 singlet at δ 3.57 (*cis*) and δ 3.55 (*trans*).

5d, and **6d**−**f** were designed to examine electronic effects on Rh(II)−carbenoid insertion reaction between tertiary and secondary C−H bonds and between tertiary C−H bonds,[16] respectively. Diazoamides **4**−**6g** and **4h**, **6h** will permit the assessment of electronic effects on metallocarbenoid insertion into secondary and amide N-activated, tertiary C−H bonds. Further, the outcome of the Rh(II)-catalyzed reaction of these compounds should also allow us to ascertain whether the *N*-BTMSM group has any influence on the conformational preference about the amide N−C("alkyl") σ bond, which may affect the regioselectivity of the C−H insertion reactions. The results from the Rh(II)-catalyzed reaction of **4d**,**f**, **5d**, and **6d**−**f** (eq 3) are collected in Table 2.



(Eq. 3)

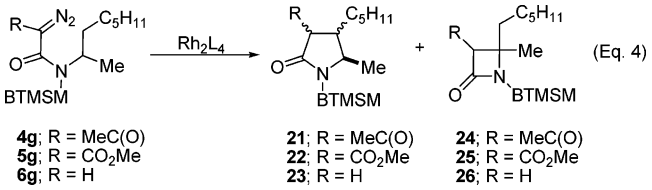
It is clear from Table 2 that the $Rh_2(OAc)_4$-catalyzed reaction of compounds **4d**−**6d** showed a high preference for insertion into the electronically activated tertiary C−H bond[1a,16] to give only the γ-lactams **14d**−**16d** (entries 1, 3, and 5). γ-Lactam formation was also the favored pathway with the more electron-rich, less reactive $Rh_2(acam)_4$ (acam = acetamidate ligand) as catalyst (entries 2, 4, and 6). These results suggest that the nature of the ligand on the Rh(II) catalyst had no influence on the regioselectivity of the reaction. The fact that in all three cases β-lactam products were not detected suggested that regioselectivity was governed mainly by electronic and not steric factors; that is, metallocarbenoid attack occurred preferentially at the electron-rich tertiary C−H bond and steric hindrance at the tertiary site appears not to retard the insertion reaction. In compound **6e** (entries 7 and 8) excellent regioselectivity was still achieved; however, chemoselectivity became an issue. Cyclopropanation of the phenyl moiety was competitive with tertiary C−H insertion in both $Rh_2(OAc)_4$- and $Rh_2(acam)_4$-catalyzed reactions, which resulted in the formation of the γ-lactam **16e** and the cycloheptatriene derivative **20** in high overall yields. These results taken together with the data from **6a** (Table 1, entries 4 and 5) suggest that the Rh(II)−carbenoid wherein the carbenoid carbon is unsubstituted shows a propensity for attack on the phenyl moiety. α-Substituted Rh(II)−carbenoids (Table 1, entries 1−3) do not exhibit this tendency. A reasonable explanation for this is the metallocarbenoid derived from **6e** (or **6a**) is less hindered and when located in close proximity (due to the conformational bias provided by the *N*-BTMSM group, vide supra) to the phenyl moiety would partake in facile cyclopropanation of the phenyl ring. Interestingly, attempted reaction of the acetyl substituted diazoamide **4e** with $Rh_2(OAc)_4$ resulted in a complex mixture of unidentifiable products, and with $Rh_2(acam)_4$, **4e** was recovered (96%) unchanged even after 24 h in refluxing dichloromethane.

In diazoamides **4f** and **6f** (entries 9−12, Table 2) the corresponding Rh(II)−carbenoid can select between two tertiary C−H bonds, one of which is activated by the amide nitrogen. The reaction of **4f** catalyzed by $Rh_2(OAc)_4$ (entry 9) gave metallocarbenoid insertion into both tertiary C−H bonds to give an inseparable, diastereomeric mixture of compounds **14f** and **17f** in a 2:1 ratio. Changing the catalyst to $Rh_2(acam)_4$ (entry 10) had no effect on the regioselectivity of the reaction. The overall yield was, however, modest (57%) due to incomplete reaction even after a prolonged reaction time (>72 h), and starting material (27%) was recovered. On the other hand, the $Rh_2(OAc)_4$- and $Rh_2(acam)_4$-catalyzed reaction of **6f** (entries 11 and 12) gave the γ-lactam **14f** as the sole product. The β-lactam **17f**, which could arise from

(16) Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc*. **1986**, *108*, 7686.

metallocarbenoid insertion into the amide N-activated tertiary C−H bond, was not detected. It is evident that when two competitive pathways for C−H insertion are favorable, the α-substituent at the Rh(II)−carbenoid center has a subtle, but decisive, influence on the regioselectivity of the reaction.

The above C−H insertion results are also nicely complemented by the data from the Rh(II)-catalyzed reaction of compounds **4g**−**6g** (eq 4), which are summarized in Table 3.



The reaction of **4g** catalyzed by $Rh_2(OAc)_4$ and $Rh_2(acam)_4$ led to diastereomeric mixtures of the γ-lactam **21** and the β-lactam **24** (entries 1 and 2). There was a preference for Rh(II)−carbenoid insertion into the amide N-activated tertiary C−H bond over the secondary C−H bond, and the ratio of **24**/**21** was very similar in both reaction systems and falls in the range 2.7−3.7:1. The reaction of **5g** (entry 3) catalyzed by $Rh_2(OAc)_4$, mirrored the results obtained for **4g**. In contrast to the results for **4g** and **5g**, the exposure of **6g** to both $Rh_2(OAc)_4$ and $Rh_2(acam)_4$ proceeded efficiently to give the γ-lactam **23** as the sole product, and as a mixture of *cis*- and *trans*-diastereomers (entries 4 and 5). A 1:1 ratio of *cis*-**23**/*trans*-**23** was obtained for the $Rh_2(OAc)_4$-catalyzed reaction whereas with $Rh_2(acam)_4$ the ratio of *cis*-**23**/*trans*-**23** was 1:3. This latter outcome indicated that the more "electron-rich" $Rh_2(acam)_4$ catalyst promoted the formation of the *trans*-diastereomer. Neither the γ-lactam that could arise from insertion into the C_α-methyl C−H bond nor the β-lactam **26** that could form from insertion into the amide N-activated tertiary methine C−H bond was detected. This result is the same as that observed for the reaction of **6f** (see Table 2, entries 11 and 12), wherein γ-lactam formation is favored.

The ^{1}H NMR spectra of the diastereomeric mixtures of γ-lactams **21**−**23** (Figure 2), and the β-lactams **24** and **25** (Figure 3) were quite complex. NOE experiments performed on the lactams **23** and β-lactam **24** revealed some interesting structural information. For the γ-lactam **23**, NOE results confirmed the assigned relative stereochemistry of the C_4-pentyl and C_5-methyl substituents. More importantly, the experiments also revealed that the C_5-methyl doublet and the H-5 multiplet in *cis*-**23** and *trans*-**23** had very characteristic chemical shifts. In *cis*-**23**, the C_5-methyl doublet resonated at higher field, centered at δ 1.01 whereas in *trans*-**23**, the C_5-methyl doublet resonated at δ 1.16. The H-5 multiplet in *cis*-**23** appeared at lower field in the range δ 3.39−3.46 but in *trans*-**23**, H-5 resonated at higher field at δ 3.14−3.21. These chemical shifts and in particular the chemical shift of the C_5-methyl doublet was helpful in the analysis of the ^{1}H NMR spectra for **21** and **22**.

In the γ-lactams **21** and **22** (Figure 2) all four diastereomers were detected; the relative stereochemistry of the C_4-pentyl and C_5-methyl groups are *cis* and *trans*

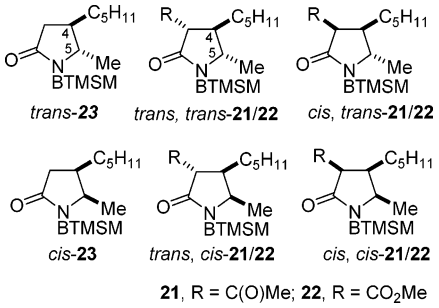


FIGURE 2. γ-Lactams **21**−**23**.

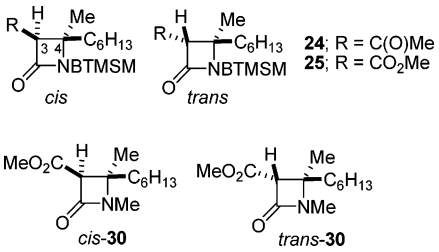


FIGURE 3. β-Lactams **24**, **25**, and **30**.

as indicated by the chemical shift positions of the C_5-methyl doublet for **21** (*cis*, δ 1.02; *trans*, δ1.24) and **22** (*cis*, δ1.04; *trans*, δ1.21). Two doublets were observed, one centered at δ 3.02 (J = 6 Hz), which was attributed to H-3 in the *cis*,*trans*- and *cis*,*cis*-diastereomers and the second was centered at δ3.06 (J = 12 Hz), which was due to H-3 in the *trans*,*trans*- and *trans*,*cis*-diastereomers. In **22**, the H-3 doublet for the *cis*,*trans*- and *cis*,*cis*-diastereomers appeared at δ3.20 (J = 5.0 Hz) and for the *trans*,*trans*- and *trans*,*cis*-diastereomers, the H-3 doublet resonated at δ 3.21 (J = 9.9 Hz).

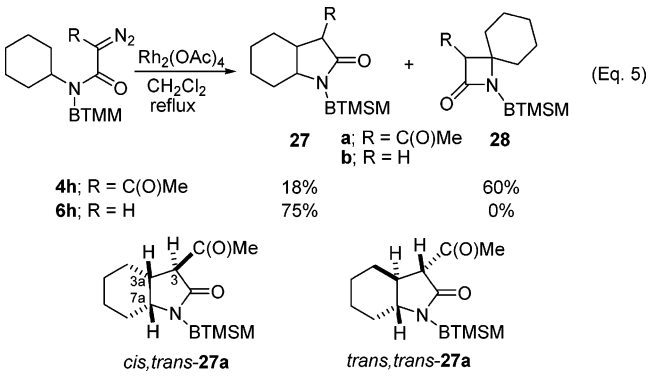
In the case of the β-lactams (Figure 3), NOE experiments were performed on compound **24**. Irradiation of the H-3 singlet at δ 3.65 caused a 2.9% NOE enhancement of the resonance of the C_4-methyl singlet at δ 1.38. On the other hand, irradiation of the H-3 singlet at δ 3.57 only resulted in an enhancement (5%) of the signal of the $C_{1'}$-methylene unit of the C_4-pentyl group, but not the C_4-methyl singlet at δ 1.25. From these results, it was concluded that when the C_4-methyl group was *cis* to the H-3 (δ 3.65) it was deshielded whereas if it was *trans* to the H-3 (δ 3.57) it was shielded.

On the basis of the diagnostic chemical shift relationship of the C_4-methyl and H-3 resonances observed for **24**, the relative stereochemistry of C_4-methyl group and H-3 in compound **25** was assigned. Thus, in *cis*-**25**, the H-3 singlet appeared at δ 3.57 and the C_4-methyl singlet occurred at δ 1.37, and in *trans*-**25**, the H-3 resonated at δ 3.55 and C_4-methyl singlet appeared at δ 1.24. These results were also in accord with previous studies[17] on 3,4,4-trisubstituted β-lactams **30**, which reported that in *cis*-**30**, the C_4-methyl group resonated at lower field (δ 1.42) and in *trans*-**30**, the C_4-methyl group appeared at higher field (δ 1.29).

We then studied the $Rh_2(OAc)_4$-catalyzed reaction of the geometrically more constrained diazoamides **4h** and **6h** (eq 5). Interestingly, a similar behavior of the met-

(17) Stork, G.; Szajewski, R. P. *J. Am. Chem. Soc.* **1974**, *96*, 5787.

allocarbenoid, as seen in the reactions of **4g**−**6g** (Table 2), was observed.



It was found that the Rh(II)−carbenoid derived from diazoacetamide **6h** showed a propensity for insertion into the secondary C−H bonds of the cyclohexyl unit to give a 75% yield of a mixture of *cis*- and *trans*-**27b**. The ratio of *cis*-**27b**/*trans*-**27b** was 1:1.3 and was based on the integration of the H-7a (ddd) signals centered at δ 2.85 (*trans*) and at δ 3.33 (*cis*). The corresponding spiro β-lactam **28b** was not detected. In contrast, the diazoacetoacetamide **4h** led to the formation of the readily separable γ-lactam **27a** and the spiro β-lactam **28a**; the ratio of **27a/28a** was 1:3.3. Compound **27a** was obtained as an inseparable mixture of two diastereomers. The ^{1}H NMR spectrum of **27a** showed very similar features to the spectrum of **27b** with respect to the H-7a (ddd) resonances, which were observed at δ 2.82 (*trans*) and δ 3.40 (*cis*). The other salient features in the ^{1}H NMR spectrum were the H-3 doublets, one centered at δ 3.04 ($J_{3,3a}$ = 11.9 Hz) and the second signal occurred at δ 3.28 ($J_{3,3a}$ = 8.5 Hz), that showed large vicinal coupling constants which suggested that the H-3 and H-3a hydrogens were *trans* related. On the basis of the ^{1}H NMR data, the two diastereomers were assigned the *cis*,*cis*-**27a** and *trans*,*trans*-**27a** structures. The ratio of *cis*,*cis*-**27a**/*trans*,*trans*-**27a** was 1:1.5 and was based on the integration of the H-7a resonances.

The overall composite results indicate that if the carbon (C_α) directly adjacent to the amide nitrogen atom is unbranched, γ-lactam formation is highly favored (**4**−**5a**,**b**,**d** and **6a**,**b**,**d**,**e**), but the regioselectivity is also subject to the usual electronic effects of the substituent (for example, eq 2, **4c**,**5c** vs Table 2, **4d**−**6d**). However, for the C_α branched systems (**4f**, **6f**, **4g**-**6g**, **4h**, **6h**), the data suggest that the regioselectivity of the reaction is strongly influenced by the conformational preference about the N−C_α σ bond and, to a lesser extent, the electronic effects from the α-substituent at the metallocarbenoid carbon.

The formation of the γ- and β-lactams can be understood by considering the four competing, rapidly interconvertible[18] transition-state conformers **A**, **A′**, **B**, and **B′** (Figure 4). γ-Lactam formation is, in general, a kinetically

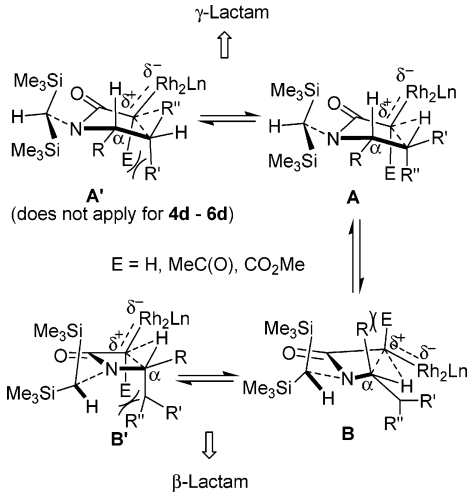


FIGURE 4. Transition-state conformers for formation of γ- and β-lactams.

favored process. It is envisioned that C−H insertion during γ-lactam formation proceeded via the "chairlike" transition states (TS), TS-**A** and TS-**A′**. For β-lactam formation, the five-membered, "envelope-like" transition states, TS-**B** and TS-**B′** are involved. The conformation about the *N*-BTMSM σ bond in each set of the transition states, TS-**A**, **A′** and TS-**B, B′**, was drawn on the basis of AM1 calculations performed on model *N*-BTMSM diazoamides.[19]

For C−H insertion to occur,[20] the Rh(II)−carbenoid bond was aligned parallel to the target C−H σ bond.[20a] 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 C−H sigma bond.[20b]

The unbranched systems, **4**−**6a**,**b**,**d** and **6e** (Tables 1 and 2), led only to γ-lactam products. In the case of **4**−**6a**,**b**, the results suggest that C−H insertion proceeds preferentially via the energetically more stable TS-**A** (R = H, R′ = Ph or CH_2Ph, R" = H) because R′ occupies the more stable pseudoequatorial position. TS-**A′**, is energetically less preferred due to the pseudoaxial orientation of R′ and the developing 1,3-diaxial interaction between R′ and E (MeC(O) or CO_2Me). For the diazoamides **4**−**6d** and **6e**, insertion occurs *preferentially* at the tertiary C−H bond,[16] which has to involve only TS-**A** (R = H, R′ = Me or Ph, R″ = Me) because in TS-**A′**, R″ = Me and the target C−H bond is oriented away from the Rh(II)-carbenoid carbon. The formation of the corresponding β-lactam products, via TS-**B** and **B′**, is enthalpically less favored due to developing ring and steric strain in these transition states. However, in the case of diazoamides **4c**,**5c** (eq 1) only the β-lactam products (**11** and **12**) were

(18) A Curtin-Hammett scenario is considered here. β-and γ-Lactam product ratios are determined by the difference in the transition state energies ($\Delta\Delta G^{\ddagger}$) between **A** and **A′** for γ-lactam formation, between **B** and **B′** for β-lactam formation and between TS-**A**, **A′** and **B**, **B′** in reactions where both types of lactam products are formed. For a discussion on the Curtin−Hammett principle, see: Seeman, J. I. *Chem. Rev.* **1986**, *86*, 42.

(19) AM1 calculations (PC Spartan Pro 6.06) were performed on model C_α-unbranched and branched *N*-BTMSM diazoamides to determine the minimum energy conformation about the *N*-BTMSM σ bond. For TS-**A**, **A′**, *N*-BTMSM,*N*-butyl-α-diazoacetamide was used: ΔH_f [*syn* $(Me_3Si)_2$CH/amide C=O] = −56.645 kcal mol^{-1} and ΔH_f [*anti* $(Me_3Si)_2$CH/amide C=O] = −52.805 kcal mol^{-1}. For TS-**B**, **B′**, *N*-BTMSM,*N*-(2-pentyl)-α-diazoacetamide was used: ΔH_f [*syn* $(Me_3Si)_2$CH/amide C=O] = −53.170 kcal mol^{-1} and ΔH_f [*anti* $(Me_3Si)_2$CH/amide C=O] = −53.717 kcal mol^{-1}.

(20) (a) Taber, D. F.; You, K. K.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547. (b) Doyle, M. P.; Westrum, L. J.; Wolthius, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958. (c) Nakamura, E.; Yoshikai, N.; Yamanaka. M. *J. Am. Chem. Soc.* **2002**, *124*, 7181.

obtained. This means that TS-**A** and **A′**, which leads to the γ-lactam products, are energetically disfavored since it requires Rh(II)-carbenoid insertion into an electronically deactivated C−H bond. The preferred reaction pathway is via TS-**B** and **B′**, as it involves metallocarbenoid insertion into the more electro-rich amide N-activated C−H bond. This process is energetically favored because of the increased electrophilicity[7a] of the α-acetyl- and α-carbomethoxy-substituted Rh(II)−carbenoid carbon centers. The enhanced electrophilicity of these α-substituted metallocarbenoids causes their interaction with the N-activated C−H bond to occur at a greater distance; that is, TS-**B** and **B′** (R = H, R′ = CO_2Me, R″ = H) may represent earlier transition states (more open TS)[7b] along the reaction coordinate. In this situation, any ring and steric strain emanating from nonbonded interactions in each of the transition states may not be as significant. Further, diazoamide **5c** gave a mixture of *cis*- and *trans*-β-lactams **12**, which lends further support for the involvement of TS-**B** and **B′** during β-lactam formation.

The Rh(II)−carbenoid derived from the diazoamides **4f**, **6f**, **4**−**6g**, **4h**, **6h** (Tables 2 and 3, and eq 5) showed two distinct behaviors. Note that the results obtained for the reaction of the diazoacetamides **6g** and **6h**, and for the α-substituted diazoacetamides **4g**, **4h**, and **5g** are very similar. Therefore, the discussions below will be confined to the representative compounds **6g** and **4g** from each group, respectively.

The diazoacetamides **6f**, **6g** (**6h**) have an amide N-activated, tertiary C−H bond, but Rh(II)−carbenoid insertion is seen to occur at the methine (**6f**, TS: R = R′ = R″ = Me) and methylene (**6g**, TS: R = Me, R′ = C_5H_{11}, R″ = H) C−H bonds to give only the γ-lactams. The Rh(II)−carbenoid intermediate derived from **6f**,**g** is less electrophilic (compared to the α-substituted metallocarbenoids), and therefore, effective interaction with the target C−H bond will require a closer approach of the metallocarbenoid to the C−H bond. This leads to a later transition state that is more compact.[7b] The involvement of a more compact transition state means that TS-**B** and **B′** have inherently higher energies (severe ring strain and nonbonded interactions) than TS-**A** and **A′**. Therefore, the reaction proceeds preferentially via the relatively more stable TS-**A** and **A′**[18] to give only the γ-lactam products (**16** and **23**). Further, in the case of **6g**, the diastereoselectivity of the C−H insertion reaction was found to be higher with Rh_2(acam)$_4$ (*cis*-**23**/*trans*-**23**; 1:3) than with Rh_2(OAc)$_4$ (*cis*-**23**/*trans*-**23**; 1:1) as catalysts. A reasonable explanation for the higher diastereoselectivity in the Rh_2(acam)$_4$-catalyzed reaction is that the corresponding Rh(II)−carbenoid is much less electrophilic than the Rh_2(OAc)$_4$−carbenoid, which means that TS-**A** and **A′** are even more compact in the Rh_2(acam)$_4$-catalyzed reaction. In TS-**A′** (E = H, R = Me, R′ = C_5H_{11}, R″ = H), a severe 1,3-diaxial interaction between the C_5H_{11} (R′) unit and the hydrogen moiety in the carbenoid carbon destabilizes this transition state over TS-**A**, wherein the C_5H_{11} unit occupies the pseudoequatorial position. Preferential reaction via the lower energy TS-**A**[18] results in a higher ratio of *trans*-**23**.

The reaction of the α-acetyl- and α-carbomethoxydiazoacetamides **4f**−**h** and **5g** produced β- and γ-lactam products. The Rh(II)−carbenoid derived from these compounds are more electrophilic (vide supra), which means that early, more open transition states are involved. The results suggest that C−H insertion proceeds through all four transition states, TS-**A**, **A′**, **B** and **B′** (E = MeC(O), CO_2Me, R = Me, R′ = C_5H_{11}, R″ = H), resulting in the formation of the observed β- and γ-lactam products.

For compound **4f**, both γ-lactam (**14f**, major) and β-lactam (**17f**, minor) products were obtained. This outcome indicates that Rh(II)-carbenoid insertion into the methine C−H (via TS-**A**, **A′**) and the amide N-activated tertiary C−H (via TS-**B**, **B′**) bonds are competitive wherein the former process is moderately favored. Also, TS-**B** and **B′** are now energetically easier to attain due to their more open structures. A similar line of reasoning can be applied to **4g** (**4h**, **5g**) except that the electrophilic Rh(II)-carbenoid intermediate now shows a marked preference for the more nucleophilic amide N-activated tertiary C−H (TS-**B**, **B′**) over the secondary methylene C−H[16] (TS-**A**, **A′**) bonds, resulting in the formation of the β-lactam (**24**) as the major product. It was also found that the *trans*-β-lactam was favored over the *cis*-diastereomer in the reaction of **4g** (**5g**), and this outcome can be rationalized by consideration of TS-**B** and **B′** (E = MeC(O), R = Me, R′ = C_5H_{11}, R″ = H). In TS-**B**, a *syn*-methyl/acetyl interaction is present, but this steric interaction is not as severe as the *syn*-$CH_2C_5H_{11}$/acetyl interaction present in TS-**B′**. Consequently, TS-**B′** is relatively more destabilized and C−H insertion prefers to occur via TS-**B** to give the trans-β-lactam.

Conclusions

In conclusion, the effectiveness of the *N*-bis(trimethylsilyl)methyl group for conformational control about the amide N−C(O) bond in tertiary diazoamides was demonstrated. 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. A transition state model is proposed to rationalize the regioselectivity of the C−H insertion reaction of the *N*-BTMSM diazoamides. Further studies are directed at expanding the use of *N*-BTMSM diazoamides in the synthesis of N-heterocycles, such as trisubstituted γ-lactams and tetrahydro-β-carbolines.

Experimental Section

General Procedure for Rhodium(II)-Catalyzed Reactions. The appropriate catalyst (2 mol %) in dry CH_2Cl_2 (3 mL) was refluxed at 45 °C under argon. A solution of the appropriate diazo compound in dry CH_2Cl_2 (2 mL) was added via cannula to the refluxing solution. The progress of the reaction was monitored by TLC. After the reaction was complete, the reaction mixture was cooled to rt and concentrated in vacuo and the residue purified by flash chromatography.

1-[Bis(trimethylsilyl)methyl]-3-acetyl-4-phenyl-2-pyrrolidinone (7a). IR ν_{max} (neat): 3030, 1717, 1667 cm^{-1}. ^{1}H NMR (200 MHz) δ: 0.10 (s, 18H), 2.42 (s, 1H), 3.01−3.17 (bs, 1H), 3.38 (dd, 1H, *J* = 7.2, 11.2 Hz), 3.74 (d, 1H, *J* = 7.2 Hz), 3.69−3.91 (m, 1H), 4.80 (dd, 1H, *J* = 7.2, 15.2 Hz), 7.05−7.45 (m, 5H). ^{13}C NMR (50.3 MHz) δ: 0.04, 30.7, 37.1, 38.3, 55.6, 62.6, 127.2, 127.3, 128.4, 141.3, 167.6, 203.4.

1-[Bis(trimethylsilyl)methyl]-3-methoxycarbonyl-4-phenyl-2-pyrrolidinone (8a). IR ν_{max}: 3030, 1742, 1633 cm^{-1}. ^1H NMR (200 MHz) δ: 0.10 (s, 18H), 2.90−3.12 (bs, 1H), 3.45 (dd, 1H, J = 8.4, 10.1 Hz), 3.65 (d, 1H, J = 9.1 Hz), 3.68−3.86 (m, 1H), 3.80 (s, 3H), 4.0 (dd, 1H, J = 8.4, 16.9), 7.45−7.10 (m, 5H). ^{13}C NMR (50.3 MHz) δ: 0.05, 37.5, 41.5, 52.5, 55.1, 55.5, 126.0, 127.5, 128.3, 140.0, 167.3, 170.16. HRMS: calcd for $C_{18}H_{28}NO_3Si_2$ (M − 15) 362.1607, found 362.1598.

1-[Bis(trimethylsilyl)methyl]-4-phenyl-2-pyrrolidinone (9a). Mp: 66.8−68.4 °C. IR ν_{max} ($CDCl_3$): 3038, 1661, 1604 cm^{-1}. ^1H NMR (200 MHz) δ: 0.10 (d, 18H), 2.66 (dd, 1H, J = 8.8, 16.4 Hz), 2.78 (dd, 1H, J = 8.8, 16.4 Hz), 3.10−3.24 (bs, 1H), 3.32−3.60 (m, 1H), 3.44 (dd, 1H, J = 7.8, 15.9 Hz), 3.70 (dd, 1H, J = 7.8, 15.9 Hz), 7.05−7.45 (m, 5H). ^{13}C NMR (50.3 MHz) δ: 0.0, 35.3, 37.6, 37.9, 55.9, 125.5, 125.9, 128.89, 142.0, 172.1. HRMS: calcd for $C_{17}H_{29}NOSi_2$ (M^+) 319.1778, found 319.1783.

1-[Bis(trimethylsilyl)methyl]-3-acetyl-4-benzyl-2-pyrrolidinone (7b). IR ν_{max}: 3023, 1713, 1658 cm^{-1}. ^1H NMR (200 MHz) δ: 0.10 (s, 18H), 2.69−2.79 (m, 2H), 2.99−3.25 (m, 3H), 3.33 (d, 1H, J = 4.4 Hz), 3.41−3.58 (m, 1H), 7.00−7.40 (m, 5H). ^{13}C NMR (50.3 MHz) δ: 0.03, 30.2, 34.5, 37.1, 38.99, 53.5, 61.0, 126.7, 128.7, 128.8, 138.5, 166.8, 204.2. HRMS: calcd for $C_{20}H_{33}NO_2Si_2$ (M^+) 375.2050, found 375.2053.

1-[Bis(trimethylsilyl)methyl]-3-methoxycarbonyl-4-benzyl-2-pyrrolidinone (8b). IR ν_{max}: 3027, 1742, 1683 cm^{-1}. ^1H NMR (200 MHz) δ: 0.10 (s, 18H), 2.78 (d, 2H, J = 7.3 Hz), 2.94−3.17 (m, 3H), 3.21 (d, 1H, J = 6.9 Hz), 3.49 (dd, 1H, J = 7.3, 9.1 Hz), 3.63 (s, 3H), 7.05−7.40 (m, 5H). ^{13}C NMR (50.3 MHz) δ: 0.20, 37.9, 39.9, 52.7, 54.1, 89.8, 126.9, 128.8, 129.0, 138.3, 167.8, 171.0. HRMS: calcd for $C_{20}H_{33}NO_3Si_2$ (M − 15) 376.1764, found 376.1765.

1-[Bis(trimethylsilyl)methyl]-4-benzyl-2-pyrrolidinone (9b). Mp: 69.3−71.8 °C. IR ν_{max}: 3065, 1657 cm^{-1}. ^1H NMR (200 MHz) δ: 0.10 (s, 18H), 2.19 (dd, 1H, J = 5.8, 16.1 Hz), 2.40−2.80 (m, 4H), 3.08 (bs, 1H), 3.15 (dd, 1H, J = 5.1, 9.9 Hz), 3.42 (dd, 1H, J = 6.9, 9.8 Hz), 7.05−7.40 (m, 5H). ^{13}C NMR (50.3 MHz) δ: 0.04, 33.2, 36.5, 40.8, 54.7, 90.0, 126.5, 128.6, 128.7, 139.1, 172.4. HRMS: calcd for $C_{17}H_{28}NOSi_2$ (M − 15) 318.1709, found 318.1710.

2-[Bis(trimethylsilyl)methyl]-2,3,4,9a-tetrahydro-1*H*-cyclohepta[*c*]pyridin-1-one (10). IR ν_{max}: 3026, 1633, 1622 cm^{-1}. ^1H NMR (200 MHz) δ: 0.10 (s, 18H), 2.40−2.72 (m, 3H), 3.20−3.62 (m, 2H), 4.30−4.10 (bs, 1H), 5.39 (dd, 1H, J = 5.1, 9.0 Hz), 5.99−6.04 (bs, 1H), 6.08−6.27 (m, 1H), 6.42−6.63 (m, 2H). ^{13}C NMR (50.3 MHz) δ: 0.12, 30.9, 39.1, 45.5, 47.8, 118.4, 120.3, 122.4, 125.7, 129.8, 130.1, 132.8, 168.4. HRMS: calcd for $C_{17}H_{29}NOSi_2$ (M^+) 319.1788, found 319.1783.

1-[Bis(trimethylsilyl)methyl]-3-acetyl-4-(methoxycarbonylmethyl)-2-azetidinone (11). IR ν_{max}: 1741, 1713, 1641 cm^{-1}. ^1H NMR (200 MHz) δ: 0.10 (s, 18H), 2.05 (s, 1H), 2.27 (s, 3H), 2.48 (dd, J = 7.9, 16.7 Hz), 2.74 (dd, 1H, J = 6.5, 16.7 Hz), 3.93 (s, 3H), 3.93 (d, 1H, J = 2.0 Hz), 4.30−4.14 (m, 1H). ^{13}C NMR (50.3 MHz) δ: −0.1, −0.2, 30.1, 35.5, 38.6, 51.6, 52.1, 67.1, 161.7, 170.4, 200.1. HRMS: calcd for $C_{14}H_{26}NO_4Si_2$ (M − 15) 328.1400, found 328.1413.

1-[Bis(trimethylsilyl)methyl]-3-methoxycarbonyl-4-(methoxycarbonylmethyl)-2-azetidinone (12). IR ν_{max}: 1738, 1689, 1625 cm^{-1}. ^1H NMR (200 MHz) δ (*cis* diastereomer in brackets): 0.10 (s, 18H), 2.10 (s, 1H), 2.50 (dd, J = 8.2, 16.1 Hz), 2.90−2.65 (m, 1H), 3.65 (d, J = 2.0 Hz) and [3.69 (d, J = 5.1 Hz)] (1H), 3.70 (s, 3H), 3.75 (s, 3H), 3.95−4.15 (m, 1H). ^{13}C NMR (50.3 MHz) δ (*cis* diastereomer in brackets): −0.3, −2.0, 33.3, 35.6, 36.4, (52.5), 52.6, 53.7, 6.32, 59.0, 167.8, 170.2, 170.9. HRMS: calcd for $C_{15}H_{29}NO_5Si_2$ (M^+) 359.1583, found 359.1587.

1-Bis(trimethylsilyl)methyl-3-acetyl-4,4-dimethyl-2-pyrrolidinone (14d). Mp: 54.8−56.7 °C. IR ν_{max}: 1715, 1677 cm^{-1}. ^1H NMR (200 MHz) δ: 0.01 (s, 18H), 1.10 (s, 3H), 1.24 (s, 3H), 1.88 (s, 1H), 2.28 (s, 3H), 3.0 (d, 1H, J = 8.9 Hz), 3.20 (s, 1H), 3.40 (d, 1H, J = 8.9 Hz). ^{13}C NMR (50.3 MHz) δ: 0.2, 22.6, 28.4, 29.6, 32.8, 36.8, 62.0, 65.7, 169.3, 205.7. HRMS: calcd for $C_{14}H_{28}NO_2Si_2$ (M − 15) 298.1658, found 298.1660.

1-Bis(trimethylsilyl)methyl-3-acetyl-4,4,5-trimethyl-2-pyrrolidinone (14f) and 1-[Bis(trimethylsilyl)methyl]-3-acetyl-4-isopropyl-4-methyl-2-azetidinone (17f). IR ν_{max}: 1741, 1710, 1676 cm^{-1}. ^1H NMR (300 MHz) δ (mixture of γ- and β-lactam diastereomers): 0.08, 0.10, 0.13, 0.14, 0.15 (s, 18H), 0.98 (d, J = 6.5 Hz), 1.01 (d, J = 6.7 Hz), 1.04 (d, J = 6.5 Hz), 1.05 (s), 1.09 (s), 1.16 (d, J = 6.7 Hz),1.21 (s) and 1.22 (s) (9H), 1.76 (s), 1.94 (s) and 1.98 (s) (1H), 1.80−2.00 (m, 1H), 2.19 (s) and 2.28 (s) (3H), 3.14 (s) and 3.15 (s) (1H), 3.17 (q, J = 6.7 Hz) and 3.52 (q, J = 6.7 Hz) (1H), 3.55 (s, 1H). HRMS: calcd for $C_{15}H_{30}NO_2Si_2$ (M − 15) 312.1815, found 312.1782.

1-[Bis(trimethylsilyl)methyl]-3-methoxycarbonyl-4,4-dimethyl-2-pyrrolidinone (15d). IR ν_{max}: 1736, 1677 cm^{-1}. ^1H NMR (200 MHz) δ: 0.13 (s, 18H), 1.08 (s, 3H), 1.21 (s, 3H), 1.90 (s, 1H), 3.03 (s, 1H), 3.04 (d, 1H, J = 9.6 Hz), 3.41 (d, 1H, J = 9.6 Hz), 3.70 (s, 3H). ^{13}C NMR (50.3 MHz) δ: 0.3, 23.1, 29.7, 36.4, 51.8, 60.0, 62.0, 168.5, 170.0. HRMS: calcd for $C_{14}H_{28}NO_3Si_2$ (M − 15) 314.1607, found 314.1608.

1-[Bis(trimethylsilyl)methyl]-4,4-dimethyl-2-pyrrolidinone (16d). Mp: 54.7−55.3 °C. IR ν_{max}: 1654 cm^{-1}. ^1H NMR (200 MHz) δ: 0.08 (s, 18H), 1.13 (s, 6H), 2.06 (s, 1H), 2.20 (s, 2H), 3.12 (s, 2H). ^{13}C NMR (50.3 MHz) δ: 0.1, 28.3, 32.3, 35.1, 45.5, 62.8, 172.7. HRMS: calcd for $C_{13}H_{29}NOSi_2$ (M^+) 271.1788, found 271.1781.

1-[Bis(trimethylsilyl)methyl]-4-methyl-4-phenyl-2-pyrrolidinone (16e). IR ν_{max}: 3050, 1672, 1588 cm^{-1}. ^1H NMR δ (300 MHz): 0.15 and 0.05 (s, 18H), 1.50 (s, 3H), 2.55 (d, 1H, J = 15.9 Hz), 2.86 (d, 1H, J = 15.9 Hz), 3.15 (bs, 1H), 3.51 (d, 1H, J = 9.6 Hz), 3.70 (d, 1H, J = 9.6 Hz), 7.10−7.20 (m, 5H). ^{13}C NMR (75.5 MHz) δ: 0.2, 0.3, 30.2, 36.7, 40.2, 44.5, 62.5, 125.4, 126.6, 128.7, 147.1, 172.2. HRMS: calcd for $C_{17}H_{28}NOSi_2$ 318.1709 (M^+ − 15), found 318.1708.

1-[Bis(trimethylsilyl)methyl]-4,4-dimethyl-5-methyl-2-pyrrolidinone (16f). IR ν_{max}: 1677 cm^{-1}. ^1H NMR (200 MHz) δ: 0.10 (s, 18H), 0.81 (s, 3H), 1.05 (d, 3H, J = 6.2 Hz), 1.13 (s, 3H), 1.98 (s, 1H), 2.03 (d, 1H, J = 16.0 Hz), 2.16 (d, 1H, J = 16.0 Hz), 3.17 (q, 1H, J = 6.2 Hz). ^{13}C NMR (50.3 MHz) δ: 0.5, 1.0, 14.1, 23.2, 28.5, 38.8, 44.9, 66.2, 172.5. HRMS: calcd for $C_{14}H_{31}NOSi_2$ (M^+) 285.1944, found 285.1938.

2-[Bis(trimethylsilyl)methyl]-4-methyl-3,4-dihydro-2*H*-cyclohepta[*c*]pyridin-1(9aH)-one (20). IR ν_{max}: 3023, 1637 cm^{-1}. ^1H NMR δ (300 MHz) δ: 0.10 (s, 18H), 1.12 (d, 3H, J = 6.9 Hz), 2.76−2.88 (m, 1H), 3.16 (dd, 1H, J = 12.4, 7.4 Hz), 3.28−3.55 (m, 2H), 2.50 and 4.18 (bs, 1H), 5.20−5.30 (m, 1H), 5.99−6.03 (m, 1H), 6.18−6.25 (m, 1H), 6.55−6.60 (m, 2H). ^{13}C NMR (75.5 MHz) δ: 0.5, 18.3, 35.2, 45.9, 50.0, 55.0, 59.8, 119.0, 121.3, 126.1, 130.0, 131.2, 139.1 (C=O not observed). HRMS: calcd for $C_{17}H_{28}NOSi_2$ (M^+ − 15) 318.1709, found 318.1718.

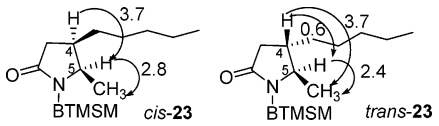
3-Acetyl-1-[bis(trimethylsilyl)]methyl-5-methyl-4-pentyl-2-pyrrolidinone (21). IR ν_{max}: 1717, 1676 cm^{-1}. ^1H NMR (300 MHz, mixture of four diastereomers) δ: 0.09, 0.11 and 0.12 (s, 18H), 1.04 and 1.21 (d, 3H, J = 7.5 Hz), 1.22−1.60 (m, 9H), 1.93−2.20 (br s, 1H), 2.35 and 2.38 (s, 3H), 2.86 (dddd, 0.2H, 7.1, 7.1, 7.1, 7.1, 10.7 Hz), 3.06−3.16 (m, 0.6H) and 3.47 (quint, 0.2H, J = 7.1 Hz) (H-5), 3.20 (d, J = 5.0 Hz) and 3.21 (d, J = 9.9 Hz) (1H, H-3).

1-[Bis(trimethylsilyl)methyl]-3-carbomethoxy-5-methyl-4-pentyl-2-pyrrolidinone (22). IR ν_{max}: 1743, 1683 cm^{-1}. ^1H NMR (300 MHz, mixture of four diastereomers) δ: 0.09, 0.11 and 0.14 (s, 18H), 1.02 and 1.24 (d, 3H, J = 6.3 Hz), 1.12−1.60 (m, 9H), 1.93−1.98 (br s, 1H), 2.18 (dddd, J = 6.3, 6.3, 6.3, 8.4 Hz), 2.76 (dddd, J = 8.4, 8.4, 8.4, 11.4 Hz), 3.08 (quint, J = 7.3 Hz) and 3.41 (quint, J = 7.3 Hz) (1H), 3.02 (d, J = 6 Hz) and 3.06 (d, J = 12 Hz), 3.68, 3.74 and 3.75 (s, 3H). HRMS: calcd for $C_{18}H_{36}NO_2Si_2$ (M − 15) 370.2234, found 370.2237.

1-Bis(trimethylsilyl)methyl-5-methyl-4-pentyl-2-pyrrolidinone (23). IR ν_{max}: 1735, 1678 cm^{-1}. ^1H NMR δ (200 MHz, *cis*-diastereomer in square brackets): 0.88 (t, 3H, J = 6.1 Hz), 0.10 (m, 18H), [1.10 (d, J = 6.7 Hz)] and 1.15 (d, 3H,

J = 6.5 Hz) (3H), 1.20−1.51 (m, 8H), 1.68−2.36 (m, 3H), 2.49 (dd, 1H, J = 8.8, 16.7 Hz), 3.05−3.24 and [3.31−3.51] (m, 1H). ^{13}C NMR (50.3 MHz) δ: 0.6, 0.8, [13.0] 13.1, 19.3, [21.9] 22.5, 25.6, [27.2] 27.6, (29.6), 29.9, [31.7] 31.7, [35.0] 35.5, [36.2] 36.5, 37.6, 40.3, 6.79, 172.7. HRMS: calcd for $C_{16}H_{34}NOSi_2$ (M − 15) 312.2179, found 312.2163. ^{1}H NMR δ (500 MHz, *cis*-diastereomer in square brackets): 0.01 (m, 18H), 0.88 (t, 3H, J = 6.6 Hz), [1.01 (d, J = 6.7 Hz)] and 1.16 (d, J = 6.4 Hz) (3H), 1.22−1.36 (m, 8H), 1.91−2.08 (m, 2H), 2.25−2.40 (m, 1H), 2.52 (dd, 1H, J = 8.7, 16.8 Hz), 3.14−3.21 and [3.39−3.46] (m, 1H).

NOE Data (500 MHz) for *cis*-23 and *trans*-23. *cis*-23. Irradiation of H-5 (quintet, δ 3.42) resulted in a 3.7% enhancement of the H-4 multiplet (δ 2.00−2.08). When C5-Me (d, δ 1.95) was irradiated, there was no NOE effect observed for H-4. ***trans*-23.** Irradiation of the H-5 quintet (δ 3.18) gave a small NOE at H-4 (m, δ 1.84−1.75) of 0.6%; however irradiation of C5-Me doublet (δ 1.99) produced a 3.7% NOE of the H-4 sigmal.



1-[Bis(trimethylsilyl)methyl]-3-acetyl-4-(1-methylheptyl)-2-azetidinone (24). IR ν_{max}: 1742, 1711 cm^{-1}. ^{1}H NMR (200 MHz) δ (mixture of *cis*/*trans* diastereomers): 0.15 (s, 18H), 0.88 (t, 3H, J = 6.1 Hz), 1.25 and 1.38 (s, 3H), 1.08−1.50 (m, 10H), 1.98 (s, 1H), 2.30 (s, 3H), 3.57 and 3.65 (s, 1H). ^{1}H NMR δ (500 MHz, mixture of *cis*/*trans* diastereomers): 0.17, 0.18, 0.19, 0.20 (s, 18H), 0.89 (t, 3H, J = 7.3 Hz), 1.25 and 1.36 (s, 3H), 1.26−1.42 (m, 10H), 1.98 (s, 1H), 2.29 (s, 3H), 3.57 and 3.65 (s, 1H). ^{13}C NMR (50.3 MHz) δ: 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 $C_{18}H_{36}NO_2Si_2$ (M − 15) 354.2285, found 354.2265.

1-[Bis(trimethylsilyl)methyl]-3-methoxycarbonyl-4-(1-methylheptyl)-2-azetidinone (25). IR ν_{max}: 1753, 1731 cm^{-1}. ^{1}H NMR (200 MHz) δ (mixture of *cis*/*trans*-diastereomers): 0.20 (s, 18H), 0.87 (t, 3H, J = 6.7 Hz), 1.24 and 1.37 (s, 3H), 1.12−1.87 (m, 10H), 1.94 (s, 1H), 3.55 and 3.57 (s, 1H), 3.70 and 3.73 (s, 3H). ^{13}C NMR (50.3 MHz) δ: 0.4, 0.5, 14.0, 18.0, [22.5] 22.5, 23.6, [24.9] 25.4, [29.5] 29.7, 31.6, 34.4, 35.3, 40.1, 52.0, [61.1] 61.9, 161.4, 168.3. HRMS: calcd for $C_{19}H_{39}NO_3Si_2$ (M^+) 385.2468, found 385.2476.

3-Acetyl-1-[bis(trimethylsilyl)methyl]hexahydro-1*H*-indol-2(3*H*)-one (27a). IR ν_{max}: 1684, 1708 cm^{-1}. ^{1}H NMR (300 MHz) δ (mixture of *cis*/*trans* diastereomers): 0.05, 0.07, 0.08, 0.10, 0.13 (s, 18H), 1.16−1.96 (m, 9H), 2.00−2.13 (m) and 2.88−2.95 (m) (1H), 2.34 and 2.38 (s, 3H), 2.82 (ddd, J = 10.2, 10.2, 3.4 Hz) and 3.40 (ddd, J = 8.5, 6.8, 5.1 Hz) (1H), 3.04 (d, J = 11.9 Hz) and 3.28 (d, J = 8.5 Hz) (1H). HRMS: calcd for $C_{17}H_{33}NO_2Si_2$ 339.2049, found 339.2046. HRMS: calcd for $C_{16}H_{30}NO_2Si_2$ (M − 15) 324.1815, found 324.1815.

1-[Bis(trimethylsilyl)methyl]hexahydro-1*H*-indol-2(3*H*)-one (27b). IR ν_{max}: 1684 cm^{-1}. ^{1}H NMR (300 MHz) δ (mixture of *cis*/*trans* diastereomers): 0.08, 0.09, 0.12, 0.14 (s, 18H), 1.10−2.08 (m, 9H), 2.19 (dd, 1H, J = 15.5, 6.9 Hz), 2.27 (dd, 1H, J = 15.5 Hz, 6.9 Hz), 2.30−2.45 (m) and 2.89−2.97 (m) (1H), 2.85 (ddd, J = 9.8, 8.3, 2.4 Hz) and 3.33 (ddd, J = 6.3, 4.9, 4.9 Hz) (1H). HRMS: calcd for $C_{15}H_{31}NOSi_2$ 297.1944, found 297.1941. HRMS: calcd for $C_{14}H_{28}NOSi_2$ (M − 15) 282.1709, found 282.1707.

1-[Bis(trimethylsilyl)methyl]-3-acetyl-1-azaspiro[3,5]-nonan-2-one (28a). IR ν_{max}: 1737, 1708 cm^{-1}. ^{1}H NMR (200 MHz) δ: 0.14 (s, 18H), 0.95−2.15 (m, 11H), 2.31 (s, 3H), 3.65 (s, 1H, H-3). ^{13}C NMR (50.3 MHz) δ: 0.4, 0.6, 23.7, 24.4, 24.6, 30.2, 32.2, 43.6, 35.9, 67.7, 203.1. HRMS: calcd for $C_{16}H_{30}NO_2Si_2$ (M − 15) 324.1815, found 324.1805.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council, Canada, and the University of Regina for financial support.

Supporting Information Available: Analytical and spectral characterization of compound **4a**−**h**, **5a**−**d**,**g** and **6a**,**b**,**d**−**h**; ^{1}H NMR spectra for compounds **4a**−**h**, **5a**−**d**,**g**, **6a**,**b**,**d**−**h**, **7**−**9a**,**b**, **10**−**12**, **14d**, **14f**(**17f**), **15d**, **16d**−**f**, **20**−**25**, **27a**,**b**, and **28b**; and ^{13}C NMR spectra for **5g**, **10**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051042E