ORGANIC LETTERS

2001
Vol. 3, No. 22
3539−3542

Regio- and Stereocontrol Elements in Rh(II)-Catalyzed Intramolecular C–H Insertion of α-Diazo-α-(phenylsulfonyl)-acetamides

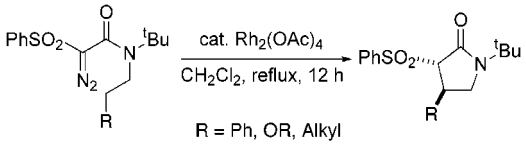
Cheol Hwan Yoon, Michael J. Zaworotko, Brian Moulton, and Kyung Woon Jung*

Department of Chemistry, University of South Florida, 4202 E. Fowler Avenue, Tampa, Florida 33620-5250

kjung@chuma.cas.usf.edu

Received August 24, 2001

ABSTRACT



Intramolecular C–H insertion reaction of α-diazo-α-(phenylsulfonyl)acetamides proceeded with high regio- and stereoselectivities to afford highly functionalized γ-lactams predominantly or exclusively. The high regioselectivity was attributed to the use of the phenylsulfonyl moiety, which altered electron density at the carbenoid center and exerted a steric effect during the insertion reaction. Also described herein are three control elements to determine regioselectivity, which are amide conformational, stereoelectronic, and substituent effects.

The pyrrolidinone functionality is a prevalent scaffold in various syntheses and serves as a crucial synthetic intermediate for numerous natural products. A vast number of synthetic methods have been developed for the construction of γ-lactam rings,[1] and intramolecular C−H insertion reaction of α-diazoamides appeared to be an attractive procedure.[2] However, insertion reactions of various α-diazoamides resulted in the formation of regioisomers including β- and γ-lactams as well as stereoisomers. The ratio of each product depended on the nature of the substrates examined and rhodium catalyst ligands utilized.[3]

Padwa and Wee demonstrated that the α-substituent of carbenoid carbon could affect the chemoselectivity and regioselectivity during the course of the C−H insertion reaction.[2d,e] In our related studies to vary α-substituents, we discovered the phenylsulfonyl moiety[4] altered electron density of the metallocarbenoid and exerted a steric effect

(1) (a) Meyers, A. I.; Burgess, L. E. *J. Org. Chem.* **1992**, *57*, 1656. (b) Knaus, E. E.; Wei, Z.-Y. *Tetrahedron Lett.* **1993**, *34*, 4439. (c) Gennari, C.; Pain, G.; Moresca, D. *J. Org. Chem.* **1995**, *60*, 6248. (d) DiCosimo, R.; Gavagan, J. E.; Fager, S. K.; Fallon, R. D.; Folsom, P. W.; Herkes, F. E.; Eisenberg, A.; Hann, E. C. *J. Org. Chem.* **1998**, *63*, 4792. (e) Komatsu, M.; Ryu, I.; Matsu, K.; Minakata, S. *J. Am. Chem. Soc.* **1998**, *120*, 5838. (f) Poli, G.; Giambastiani, G.; Pacini, B.; Porcelloni, M. *J. Org. Chem.* **1998**, *63*, 804. (g) Buono, G.; Fotiadu, F.; Pardigon, O. *Tetrahedron Lett.* **1999**, *40*, 867. (h) Woerpel, K. A.; Roberson, C. W. *J. Org. Chem.* **1999**, *64*, 1434. (i) Dieter, R. K.; Lu, K. *Tetrahedron Lett.* **1999**, *40*, 4011 and references therein.

(2) For the synthesis of the γ-lactams by the intramolecular C−H insertion reaction, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. In *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998. See also references therein. (b) Doyle, M. P.; Taunton, J.; Pho, H. Q. *Tetrahedron Lett.* **1989**, *30*, 5397. (c) Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q. *J. Org. Chem.* **1991**, *56*, 820. (d) Wee, A. G. H.; Liu, B.; Zhang, L. *J. Org. Chem.* **1992**, *57*, 4404. (e) Padwa, A. P.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669. (f) Wee, A. G. H.; Slobodian, J. *J. Org. Chem.* **1996**, *61*, 2897. (g) Doyle, M. P.; Kalinin, A. V. *Tetrahedron Lett.* **1996**, *37*, 1371. (h) Hashimoto, S.-I.; Anada, M. *Tetrahedron Lett.* **1998**, *39*, 79. (i) Wee, A. G. H.; Liu, B.; McLeod, D. D. *J. Org. Chem.* **1998**, *63*, 4218. (j) Moody, C. J.; Miah, S.; Slawin, A. M. Z.; Mansfield, D. J.; Richards, I. C. *Tetrahedron* **1998**, *54*, 9689.

(3) Padwa, A.; Austin, D. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1797.

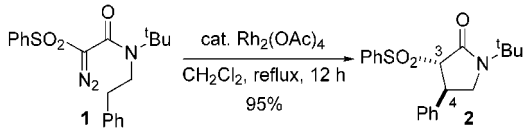
(4) For leading references to other studies with α-diazo-α-phenylsulfonyl compounds, see: (a) References 2d and 2f. (b) Monteiro, H. J. *Tetrahedron Lett.* **1987**, *28*, 3459. (c) Durst, T.; Babu, S. D.; Hrytsak, M. D. *Can. J. Chem.* **1989**, *67*, 1071. (d) Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Roos, G. H. *J. Chem. Soc., Chem. Commun.* **1990**, 361. (e) Moody, C. J.; Davies, M. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 9. (f) Padwa, A.; Straub, C. S. *Org. Lett.* **1999**, *1*, 83.

10.1021/ol016647l CCC: $20.00
Published on Web 10/05/2001

to enhance regio- and stereoselectivities. We herein describe a detailed study of the intramolecular C−H insertion reaction using various α-diazo-α-(phenylsulfonyl)acetamides as precursors.

As representatively shown in Scheme 1, C−H insertion reaction of the diazo substrate **1**[5] was performed using

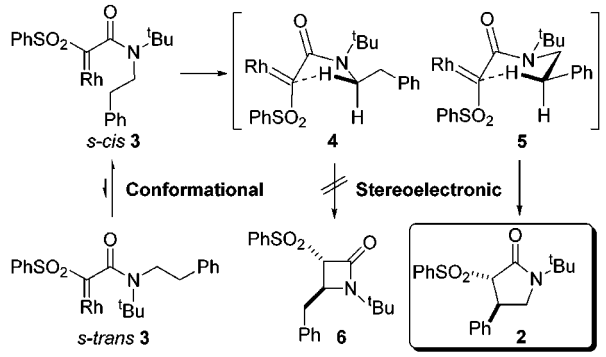
Scheme 1



$Rh_2(OAc)_4$, which surprisingly afforded *trans* γ-lactam **2**[6] exclusively in 95% yield without the formation of β-lactam or aromatic cycloaddition product.

The outstanding regio- and stereoselectivities are rationalized in Scheme 2. During the insertion reaction, the conformationally restricted metallocarbenoid **3** would adopt a *s-cis* conformer as a result of the severe nonbonded interaction between the *tert*-butyl group and the carbonyl substituents present in the *s-trans* conformer (conformational effect). Only the *s-cis* conformer is suitable for cyclization, and the two regioisomers β- and γ-lactam can be obtained through transition states **4** and **5**, respectively.

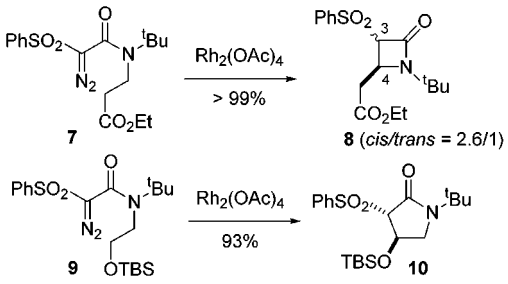
Scheme 2



Padwa and Doyle reported that C−H insertion of the α-diazo-α-acetoacetamide analogue to **1** afforded a mixture of the β- and γ-lactam, which was obtained through both transition states.[7] The selectivity was improved in favor of the γ-lactam when a Rh catalyst with an electron-donating ligand was used. Presumably, the electron-donating ligand would stabilize the electrophilic carbenoid carbon, thereby causing the insertion reaction to proceed through a relatively late transition state with a resulting increase in selectivity.[3,8] Likewise, the excellent result of our phenylsulfonyl carbenoid insertion implied that the insertion reaction of α-diazo-α-(phenylsulfonyl)acetamide would proceed via a later transition state as a result of the extra stabilization by a phenylsulfonyl group. Hence, the cyclization would occur through the stereoelectronically favorable transition state **5** (stereoelectronic effect). The formation of *trans*-stereochemistry at C-3/C-4 was also explained by the adopted chairlike transition state **5**, wherein the C−Rh bond would be aligned with the target C−H bond and the phenyl group would occupy a pseudoequatorial position.[9]

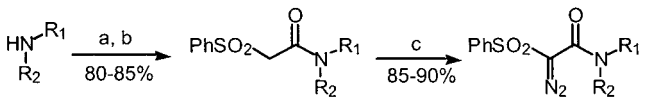
In addition to the aforementioned effects, a substituent effect was also envisioned to be in play, and electron density at the insertion center was varied (Scheme 3). Intramolecular C−H insertion of **7** afforded only β-lactam **8** in nearly quantitative yield,[10] which resulted from the deactivating influence of the carboethoxy group on C−H insertion into the adjacent methylene group.[11] However, insertion reaction of substrate **9**, which possessed an electron-donating TBS ether,[12] yielded *trans* γ-lactam **10** exclusively in high yield.

Scheme 3



With different alkyl groups introduced, only methine C−H bonds were reacted, giving rise to the formation of β- and

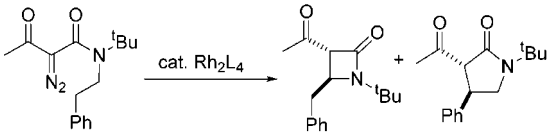
(5) α-Diazo-α-(phenylsulfonyl)acetamides **iii** were easily prepared from secondary amines **i** via the corresponding α-(phenylsulfonyl)acetamides **ii**. Acylation of secondary amines **i** with α-bromoacetyl bromide in TEA and dichloromethane at 0 °C followed by treatment with sodium benzenesulfinate in DMF at room temperature afforded α-(phenylsulfonyl)acetamides **ii**. Subsequent diazo transfer of **ii** with *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) and DBU yielded the corresponding α-diazo-α-(phenylsulfonyl)-acetamides **iii**.



(a) $BrCH_2COBr$, TEA, CH_2Cl_2 (b) $PhSO_2Na$, DMF, r.t. (c) *p*-ABSA, DBU, CH_3CN

(6) The stereochemistry of 4-substituted-3-phenylsulfonyl-2-pyrrolidinone derivatives was assigned by the coupling constant between C3 and C4 protons, which of the *trans* γ-lactam fell in the range of 1.0−3.0 Hz.

(7) Reference 2e. A typical example is shown below.

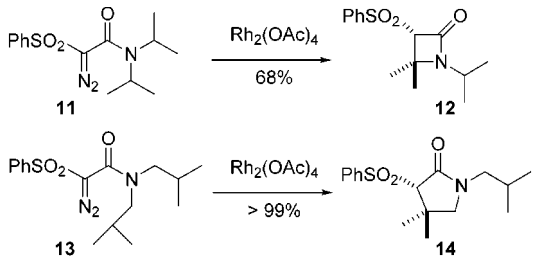


	Yield (%)		
$Rh_2(pfb)_4$	85	56	44
$Rh_2(OAc)_4$	94	49	51
$Rh_2(acam)_4$	90	30	70

(8) Davies, H. M. L.; Panaro, S. A. *Tetrahedron* **2000**, *56*, 4871.

(9) Taber, D. F.; You, K. K.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547.

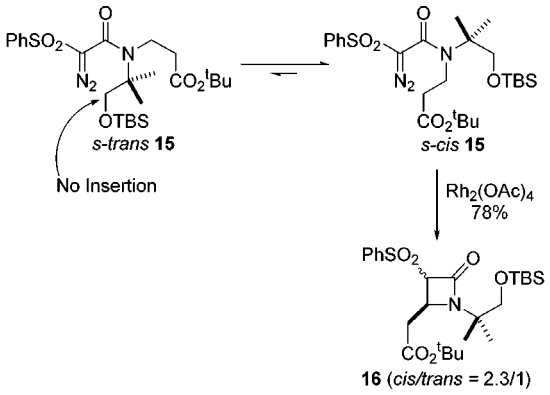
Scheme 4



γ-lactams (**12** and **14**), respectively (Scheme 4).[13] Apparently, biased reactivities depending on substituents of the insertion center influenced the reaction pathways, and electron-enriched groups activated the C−H bond for insertion.

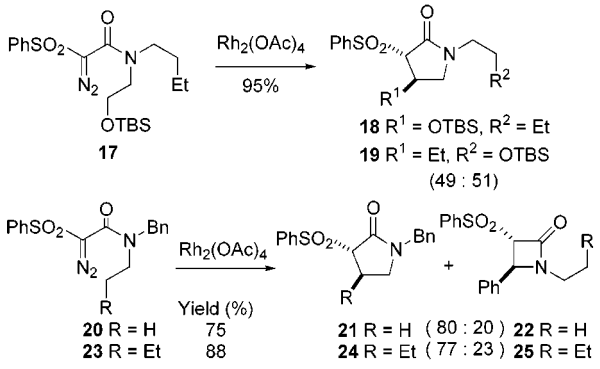
Although the stereoelectronic effect offers γ-lactams, the other two factors often play contradictory roles to give β-lactams or regioisomeric mixtures. For instance, the conformational preference in **15** favored the *s-cis* rotamer, and the substituent effect of the ester group forced the cyclization to provide the β-lactam **16** solely (Scheme 5).[10]

Scheme 5



When the substituent effect was negligible as shown in Scheme 6, the distribution of products was considered to depend on the relative stabilities of the two possible amide

Scheme 6



conformers. For this reason, the diazo precursor **17** led to an equimolar amount of γ-lactams **18** and **19**. The stereochemical assignment for **18** was confirmed by X-ray crystallographic analysis as shown in Figure 1. Similarly, **20** and

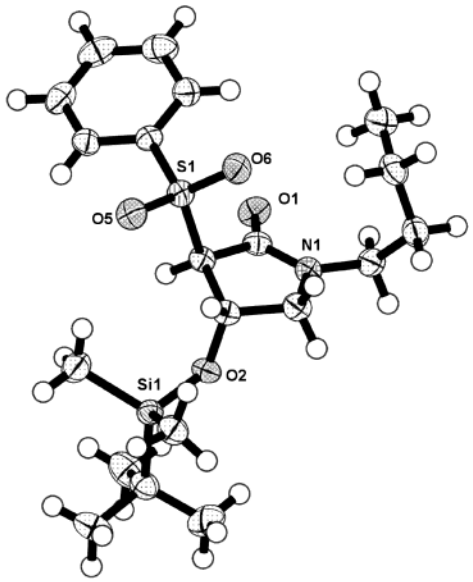
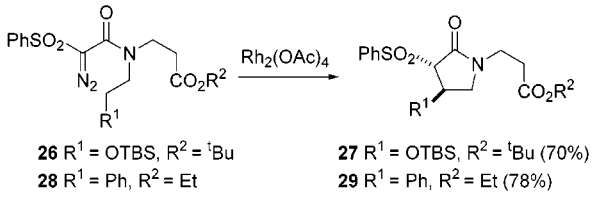


Figure 1. Ortep view of **18**.

23 furnished γ- and β-lactams in a ratio of 4:1. Despite the small difference in the relative stabilities of the two amide conformers, the stereoelectronic effect was significant to form γ-lactams, which was noteworthy in the insertion into the electronically unfavorable methyl C−H bond of the substrate **20**.

With unbiased conformational effect, we sought electronically and sterically different substituents to force the cyclization to occur, resulting in the formation of γ-lactams (Scheme 7). Fortunately, acrylate incorporated α-diazo-α-

Scheme 7



(phenylsulfonyl)acetamides **26** and **28** underwent the intramolecular C−H insertion smoothly to afford only γ-lactams

(10) The ratio of *cis* and *trans* isomers was based on the integration of the α-methylene proton to carboethoxy group by ^{1}H NMR analysis of β-lactam **8**. The *cis* and *trans* isomers were assigned by the comparison of the coupling constant C3−C4. See: (a) Barrow, K. D.; Spotswood, T. M. *Tetrahedron Lett.* **1988**, *29*, 2283. (b) Kagan, H. B.; Basselier, J. J.; Luche, J. L. *Tetrahedron Lett.* **1964**, 941. J_{trans} is in the range of 2.2−2.8 Hz and J_{cis} is 4.9−5.9 Hz.

(11) Stork, G.; Nakatani, K. *Tetrahedron Lett.* **1988**, *29*, 2283.

27 and **29**, respectively, without formation of β-lactams and carbonyl ylide byproducts, which were observed in the case of α-diazo-α-acetoacetamide.[14] In these cases, two substituents were comparable in size, but the difference in substituent effects caused the insertion into the β-propionate substituent to be retarded. To our knowledge, this showcase is the first example to give one regioisomer in the presence of two possible amide conformers.

In conclusion, we have developed a highly regio- and stereoselective C−H insertion reaction with α-diazo-α-(phenylsulfonyl)acetamides for the synthesis of γ-lactams. Common side reactions such as aromatic cycloaddition[2e] and carbonyl ylide formation[2b,c] were not observed at all. Three control elements including conformational, stereoelectronic, and substituent effects were studied, and these were manipulated with great ease to govern regio- and stereoselectivities. Further evidence and pragmatic utility will be reported in due course.

Acknowledgment. We acknowledge generous financial support from the National Institutes of Health (R01 GM 62767).

Supporting Information Available: Representative experimental procedures with spectral data and X-ray crystallography data for compound **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016647L

(12) (a) Spero, D. M.; Adams, J. *Tetrahedron Lett.* **1987**, *28*, 4773. (b) Lee, E.; Choi, I.; Song, S. Y. *J. Chem. Soc., Chem. Commun.* **1995**, 321.

(13) (a) Taber, D.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686. (b) Lee, E.; Jung, K. W.; Kim, Y. S. *Tetrahedron Lett.* **1990**, *31*, 1023.

(14) References 2b and 2e. A typical example is shown below.