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Synthesis of chiral γ-lactams via Rh(II) catalyzed intramolecular C–H insertion: α-substituents and conformational effects

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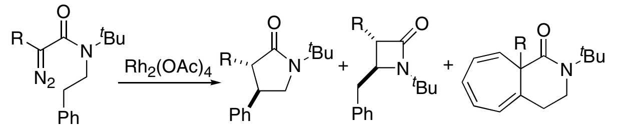
Abstract—Highly functionalized chiral γ-lactams are efficiently synthesized via Rh(II) catalyzed intramolecular C–H insertion from various α-diazoamides. Independent of α-substituents, regio- and stereoselectivities are enhanced through a conformational effect exerted by a bicyclic transition state.

Rhodium catalyzed intramolecular C–H insertion of various diazo compounds has been used for the construction of carbocyclic and heterocyclic compounds.[1] Usually, the cyclization exhibits a preference for the formation of five-membered rings[2] except in the case of cyclization of diazoamides,[3] which afford β-, γ-lactams, and stereoisomers depending on the nature of the substrates examined and rhodium catalyst ligands utilized.[4]

Recently, we reported rhodium catalyzed intramolecular C–H insertion of α-diazo-α-(phenylsulfonyl)-acetamides to afford γ-lactams with high regio- and stereoselectivity.[5] The success of this methodology was governed by the α-phenylsulfonyl moiety, which presumably stabilized the electrophilic carbenoid carbon during the cyclization, resulting in the selective formation of γ-lactam via a relatively late transition state.[5a,6] Scheme 1 shows the efficiency of this methodology in the formation of γ-lactams.

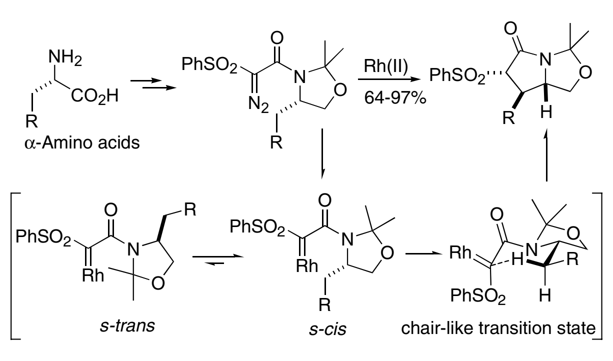


R	yield	products
H^a	85%	32 : 0 : 68
MeCO^b	94%	49 : 51 : 0
PhSO$_2$	95%	100 : 0 : 0

^{a} reference 3(a); ^{b} reference 3(e)

Scheme 1.

Encouraged by these results we adapted this methodology to facilitate the use of α-amino acids.[7] Various chiral γ-lactams were obtained from α-amino acids derived α-diazo-α-(phenylsulfonyl)-acetamides via intramolecular C–H insertion (Scheme 2).[8] The cyclizations were highly regio- and stereoselective affording functionalized chiral γ-lactam motifs in high yields. The *gem*-dimethyl moiety forces the diazo-intermediate to adopt an *s-cis* conformation, which is the only conformation suitable for C–H insertion. In the absence of the *gem*-dimethyl moiety, the unfavorable *s-trans* conformer is predominant and C–H insertion does not occur.[9] Based on these results, conformational factors rather than α-substituents play a key role in the insertion of the rigid cyclic system. This prompts our study of α-substituent effects



Scheme 2.

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on the regio- and stereoselectivities of C–H insertion of α-diazoamides.

The diazoamides **3**–**6** used in this study were prepared from (L)-phenylalanine (**1**) as shown in Scheme 3. Acylation of *N*,*O*-acetal **2** with bromoacetyl bromide and TEA in dichloromethane at 0 °C, followed by treatment with sodium benzenesulfinate in DMF at room temperature afforded the α-(phenylsulfonyl)-acetamide. Subsequent diazo transfer using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) and DBU yielded α-diazo-α-(phenylsulfonyl)-acetamide **3**. Reaction of **2** with ethyl malonyl chloride and TEA in dichloromethane gave ethyl malonyl amide, which was subjected to diazo transfer reaction affording α-(carboethoxy)-α-diazoacetamide **4**. Treatment of **2** with diketene in the presence of a catalytic amount of DMAP followed by *p*-ABSA afforded α-diazo-α-acetoacetamide **5**, which was converted to α-diazoacetamide **6** via deacetylation under aqueous basic conditions.

Exposure of diazo-intermediates **3**, **4**, and **5** to C–H insertion conditions yielded the corresponding chiral γ-lactams **7**,[10] **8**, and **9**[11] with complete regio- and stereoselectivities in high yields.[12] In the case of **6**, however, the electrophilicity of the carbenoid center is higher than those of **3**, **4**, and **5**. As a consequence, the preferred reaction pathway is cyclopropanation of the phenyl ring followed by ring expansion to give the aromatic cycloaddition product **10** albeit with high yield and excellent stereoselectivity.[3a,d] The structure of **10** was confirmed by X-ray crystallographic analysis[13] as shown in Figure 1.

In contrast to previous results (Scheme 1), excellent selectivities were achieved regardless of the α-substituents used, thus highlighting the conformational effect that the rigid cyclic system exerts on this transformation. An increased degree of conformational constraint is experienced as opposed to the flexible acyclic system (Scheme 4).

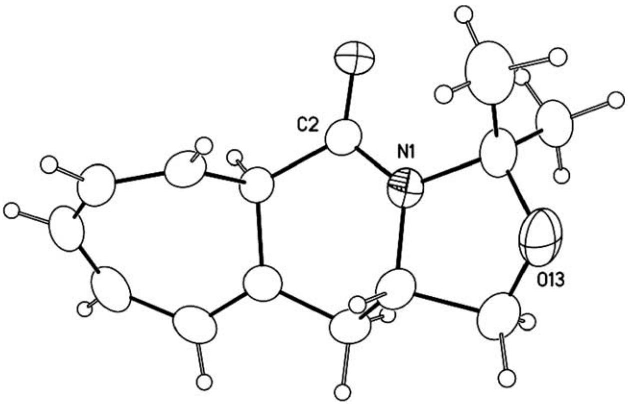
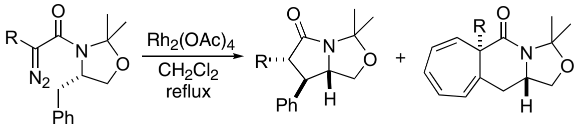


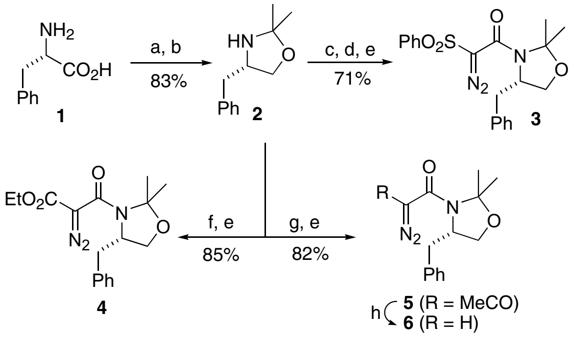
Figure 1. Crystal structure of **10**.



reactant	yield	product	
3 (R = $PhSO_2$)	91%	**7**	-
4 (R = EtO_2C)	95%	**8**	-
5 (R = MeCO)	93%	**9**	-
6 (R = H)	84%	-	**10**

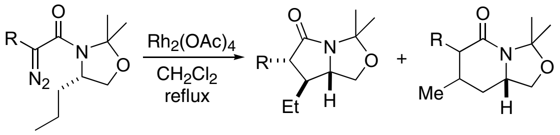
Scheme 4.

We then focused on studying the regioselectivity of the methodology on substrates with varied α-substituents in the presence of multiple C–H activation sites. Our model substrate was changed to the unnatural α-amino acid norvaline, which possesses an *n*-propyl alkyl group. The synthetic route to the diazo-intermediates of norvaline mirrors that of the phenylalanine sequence in Scheme 3. C–H insertion of the diazo-intermediates **11**, **12**, and **13** proceeded smoothly furnishing only γ-lactams **15**, **16**, and **17**,[11] respectively, in high yields (Scheme 5). Although the potential exists to form β- and δ-lactams, no such products were observed. Reaction of **14** formed a 1:2 mixture of γ- and δ-lactam, which can be also explained by the highly reactive carbenoid center resulting in decreased selectivity for the reaction.



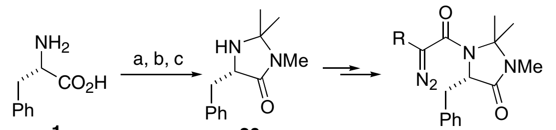
Scheme 3. Reagents: (a) LAH, THF; (b) acetone, Na_2SO_4; (c) $BrCH_2COBr$, TEA, CH_2Cl_2; (d) $PhSO_2Na$, DMF; (e) *p*-ABSA, DBU, CH_3CN; (f) EtO_2CCH_2COCl, TEA, CH_2Cl_2; (g) diketene, cat DMAP, THF; (h) LiOH, aq CH_3CN.

We also explored an alternate cyclic system to study the versatility of this methodology. We endeavored to install an amide function to replace the hydroxyl resulting from reduction (Scheme 6). The variation was made possible by substitution of the amino acid methyl ester with methylamine producing the *N*-methylaminoamide, which was then subjected to the acetonide formation providing the *N*,*N*-acetonide **20** almost quantitatively.[14]



reactant	yield	product		
11 (R = $PhSO_2$)	91%	**15**		-
12 (R = MeO_2C)	90%	**16**		-
13 (R = MeCO)	93%	**17**		-
14 (R = H)	84%	**18**	(1:2)	**19**

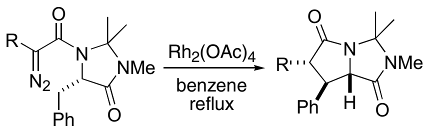
Scheme 5.



1 **20**

21 (R = $PhSO_2$)
22 (R = MeO_2C)
23 (R = MeCO)

Scheme 6. Reagents: (a) $SOCl_2$, MeOH; (b) $MeNH_2$, MeOH; (c) acetone, DMF.



reactant	yield	product
21 (R = $PhSO_2$)	93%	**24**
22 (R = MeO_2C)	97%	**25**
23 (R = MeCO)	99%	**26**

Scheme 7.

This substrate could then be converted to **21**, **22**, and **23** by following the same procedures shown in Scheme 3.

To our satisfaction, intramolecular C–H insertion of **21**, **22**, and **23** occurred readily under refluxing benzene conditions and produced the corresponding γ-lactams **24**, **25**, and **26** with improved yields and excellent stereoselectivity (Scheme 7). We attribute this improvement in yield to the increased rigidity of the *N*,*N*-acetonide. In this case, the diazo-intermediates possess an sp^2 center at the carbonyl as opposed to the sp^3 center present in the *N*,*O*-acetonide system. The conformation of the Rh-carbenoid is likely more restricted resulting in greater efficiency of the C–H insertion.

We have described an efficient and versatile method of synthesizing chiral γ-lactams from α-diazoamides containing various α-substituents via a rigid bicyclic transition state. The 'conformational lock' exerted by the *gem*-dimethyl moiety affords the high regio- and stereoselectivities. This methodology can be applied to chiral natural and unnatural α-amino acids with various α-substituents to yield highly functionalized heterocycles, which can be tailor made for use in any application.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.10.159.

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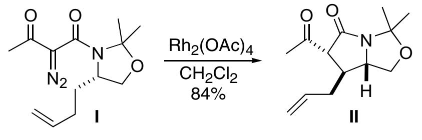
10. The structure of **7** was confirmed by X-ray crystallographic analysis; see Ref. 5a.
11. Hashimoto reported that C–H insertion of α-diazo-α-acetoacetamide **I**, the analog of **5** and **13**, afforded a *trans*-γ-lactam **II** in 84% yield. see Ref. 8c.



12. General procedure for C–H insertion reactions: $Rh_2(OAc)_4$ (11 mg, 2.5 mol%) was added to a solution of an diazoamide compound (1 mmol) in dry CH_2Cl_2 (20 mL,

0.05 M). The mixture was refluxed for 12 h under N_2, cooled to room temperature, and concentrated. The residue was chromatographed to give a lactam compound.

13. Empirical formula: $C_{14}H_{17}NO_2$; formula weight: 231.29; temperature: 200(2) K; wavelength: 0.71073 Å; crystal system: orthorhombic; space group: $P2(1)2(1)2(1)$; unit cell dimensions: $a = 8.3667(19)$ Å, $\alpha = 90°$, $b = 11.572(3)$ Å, $\beta = 90°$, $c = 12.824(3)$ Å, $\gamma = 90°$; volume: 1241.6(5) $Å^3$; Z: 4; density (calculated): 1.237 Mg/m^3; absorption coefficient: 0.083 mm^{-1}; $F(000)$: 496; crystal size: $0.80 \times 0.20 \times 0.10\ mm^3$; theta range for data collection: 2.37°–24.98°; index ranges: $-9 <= h <= 9$, $-13 <= k <= 11$, $-15 <= l <= 13$; Reflections collected: 5844; Independent reflections: 2161 [R(int) = 0.0283]; Completeness to theta = 24.98°, 99.8%; Absorption correction: None; Max. and min. transmission: 1.00 and 0.81; refinement method: full-matrix least-squares on F^2; data/restraints/parameters: 2161/0/156; Goodness-of-fit on F^2: 1.052; final R indices [$I > 2\mathrm{sigma}(I)$]: $R1 = 0.0338$, $wR2 = 0.0778$: R indices (all data): $R1 = 0.0392$, $wR2 = 0.0806$; largest diff. peak and hole: 0.221 and $-0.261\ e\,Å^{-3}$.
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