Regio- and diastereocontrolled C–H insertion of chiral γ- and δ-lactam diazoacetates. Application to the asymmetric synthesis of (8*S*,8a*S*)-8-hydroxyindolizidine†

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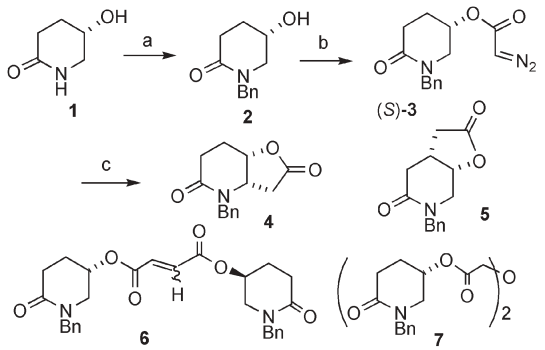
Received (in Bloomington, IN, USA) 5th May 2006, Accepted 27th June 2006
First published as an Advance Article on the web 2nd August 2006
DOI: 10.1039/b606436a

γ- and δ-Lactam diazoacetates undergo efficient intramolecular C–H insertion catalyzed by Rh_2(MPPIM)$_4$ with excellent regioselectivity and *cis*-diastereoselectivity to provide synthetically useful bicyclic lactam lactones.

The Rh(II)-catalyzed intramolecular carbon–hydrogen insertion reaction continues to attract considerable attention due to the high levels of regio-, chemo- and diastereoselectivity that can be achieved.[1] A decade ago, Doyle reported the intramolecular C–H insertion reactions of chiral non-racemic alkyl substituted cyclohexyl diazoacetates catalyzed by dirhodium(II) carboxamidates.[2a] The catalysts showed a matched/mismatched relationship to the diazo substrates; Rh_2(MEPY)$_4$ and Rh_2(MEOX)$_4$ emerged as effective catalysts, which promoted highly regioselective C–H insertion into equatorial secondary and tertiary C–H bonds to give lactone products. The regioselectivity in Rh_2(MPPIM)$_4$-catalyzed reactions, however, was found to be substrate dependent.[2] The regio- and diastereoselectivity of C–H insertion in equivalent heterocyclic diazoacetates have not been extensively examined. Previously, we showed the Rh(II)-carboxamidate-catalyzed C–H insertion of 3-(*N*-Cbz-pyrrolidinyl)diazoacetate did not exhibit a matched/mismatched relationship, and also demonstrated the use of the method in the synthesis of (−)-turneforcidine.[3] In keeping with our ongoing interest in the synthesis of piperidine- and pyrrolidine-containing alkaloids, we needed access to functionalized piperidine and pyrrolidine building blocks that would permit the facile assembly of a wide variety of substituents and stereochemical diversity around the pyrrolidine and piperidine framework. We investigated the rhodium(II)-catalyzed diazo decomposition of γ- and δ-lactam diazoacetates and, herein, report the results of our study.

δ-Lactam diazoacetate (*S*)-**3** was readily obtained (Scheme 1) from the known[4] (*S*)-5-hydroxy-2-piperidinone (**1**) *via* hydroxyl group protection (TBDMSCl) and *N*-benzylation. *O*-Desilylation (HCl, MeOH) then afforded the alcohol **2**[5] {$[\alpha]_D^{22}$ −16.7° (*c* 3.30, $CHCl_3$), 89% over three steps}. Treatment of **2** with *p*-TSHACl[6] gave an excellent yield (98%) of (*S*)-**3** {$[\alpha]_D^{25}$ +25.0° (*c* 5.90, $CHCl_3$)}.

The diazoacetate (*S*)-**3** was evaluated against achiral and chiral Rh(II) carboxylate and carboxamidate catalysts to delineate optimal reaction conditions for C–H insertion reaction and to determine product distribution.



Scheme 1 *Reagents and conditions*: a. (i) TBDMSCl, imidazole, DMAP, DMF, 40 °C; (ii) BnBr, NaH, DMF; (iii) HCl, MeOH; 89%; b. *p*-TSHACl, $PhNMe_2$, iPr_2NEt, CH_2Cl_2, 0 °C, 98%; c. Rh(II) cat. (2 mol%), CH_2Cl_2, reflux (see Table 1 for details).

In general, it was found that chiral Rh(II) catalysts were better than achiral ones at promoting C–H insertion reaction (Table 1). Carbon–hydrogen insertion was inefficient with Rh_2(OAc)$_4$ and the less electrophilic Rh_2(cap)$_4$ as catalysts. The use of Rh_2(*S*-PTTL)$_4$ led to a noticeable improvement on the yield (28%) of **4**, however, the yield of **4** was synthetically unacceptable. We then turned our attention to three enantiomeric pairs of Rh(II) carboxamidates and evaluated their efficiency in catalyzing the C–H insertion reaction of (*S*)-**3**.

With Rh_2(5*S*-MEPY)$_4$, a modest yield (45%) of **4** was obtained and the outcome was encouraging. However, the enantiomeric Rh_2(5*R*-MEPY)$_4$ gave a significantly lower yield of **4** (14%). In all the cases (entries 1–5) studied thus far, the regioisomer **5** was not

Table 1 Rh(II)-catalyzed reaction of (*S*)-**3**[a]

Entry	Rh_2L_4	**4** (%)	**5** (%)	**6** (%) (*E* : *Z*)[b]	**7** (%)
1	Rh_2(OAc)$_4$	6	0	14 (1 : 1)	21
2	Rh_2(cap)$_4$	11	0	64 (1 : 3)	23
3	Rh_2(*S*-PTTL)$_4$	28	0	11 (1 : 3)	0
4	Rh_2(5*S*-MEPY)$_4$	45	0	28 (1 : 3)	13
5	Rh_2(5*R*-MEPY)$_4$	14	0	12 (1 : 3)	3
6	Rh_2(4*S*-MEOX)$_4$	44	0	28 (1 : 3)	9
7	Rh_2(4*R*-MEOX)$_4$	16	23	0	12
8	Rh_2(4*S*-MPPIM)$_4$	87	0	0	3
9	Rh_2(4*R*-MPPIM)$_4$	14	72	0	10

[a] Product yields are isolated yields. [b] Ratio of *E* : *Z* isomers was based on the integration of the singlets due to the olefinic hydrogens centered at δ 6.12 (*Z*) and δ 6.64 (*E*).

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† Electronic supplementary information (ESI) available: Experimental section. See DOI: 10.1039/b606436a

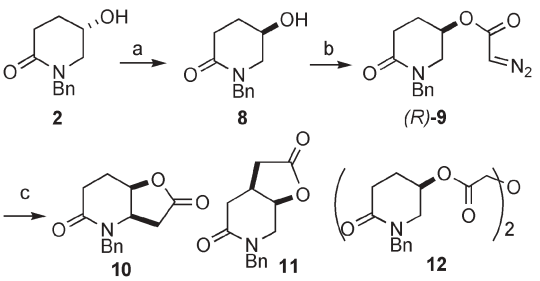
detected. The results from the reactions catalyzed by the Rh_2(4*S*/*R*-MEOX)$_4$ and Rh_2(4*S*/*R*-MPPIM)$_4$ were especially interesting and displayed important differences from those obtained from Rh_2(*S*-PTTL)$_4$ and Rh_2(5*R*/*S*-MEPY)$_4$. Although the result obtained for Rh_2(4*S*-MEOX)$_4$ mirrored that for Rh_2(5*S*-MEPY)$_4$ (see entries 4 and 6), the reaction catalyzed by Rh_2(4*R*-MEOX)$_4$ gave a 1 : 1.4 ratio of **4** : **5** in a combined yield of 39% (entry 7). The use of the hindered Rh_2(4*S*-MPPIM)$_4$ resulted in the highest yield (87%) of **4**, whereas with Rh_2(4*R*-MPPIM)$_4$, the regiosomer **5** was formed as the major product (72%). The C–H insertion reaction proceeded with excellent regioselectivity and *cis*-diastereoselectivity, which was confirmed by NOESY1D. Neither the *trans*-fused γ- nor spirocyclic β-lactones were detected, in contrast to the results from Rh_2(MPPIM)$_4$-catalyzed intramolecular C–H insertion reaction of cyclohexyl diazoacetates.[2a]

To confirm the above outcome, the enantiomeric diazoacetate (*R*)-**9** was synthesized (Scheme 2). (*S*)-Alcohol **2** was transformed to its enantiomer **8** {$[\alpha]_D^{22}$ +17.4° (*c* 3.30, $CHCl_3$)}, *via* Mitsunobu inversion[7] ($ClCH_2CO_2H$, DEAD, Ph_3P) and subsequent base hydrolysis. Alcohol **8** was treated with *p*-TSHACl[6] to give the desired diazoacetate (*R*)-**9** {$[\alpha]_D^{25}$ −22.0° (*c* 5.90, $CHCl_3$)}. The Rh_2(4*R*-MPPIM)$_4$-catalyzed reaction of (*R*)-**9** gave a high yield (85%) of bicyclic lactam lactone **10**, but with Rh_2(4*S*-MPPIM)$_4$, the major product obtained was the regioisomer **11** (68%).

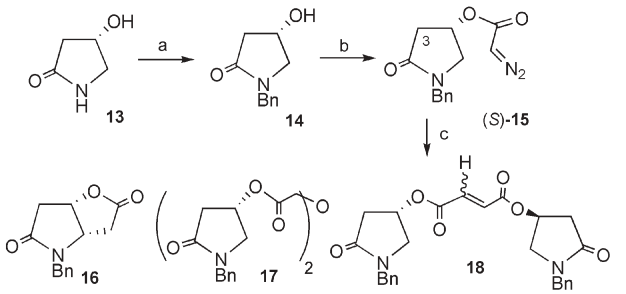
These results show that the optimal catalyst for achieving high regioselectivity in the formation of bicyclic lactam lactone is the use of Rh_2(MPPIM)$_4$ as catalyst; (*S*)-**3**/Rh_2(4*S*-MPPIM)$_4$ and (*R*)-**9**/Rh_2(4*R*-MPPIM)$_4$ represent the matched pairs for highly regioselective C–H insertion reaction.

Next, the efficiency and regioselectivity of the C–H insertion reaction of the γ-lactam diazoacetate **15** were studied. Compound **15** was synthesized (Scheme 3) from commercially available (*S*)-4-hydroxy-2-pyrrolidinone (**13**)[8] in the manner described for compound (*S*)-**3**.

On the basis of the results obtained for (*S*)-**3**, we chose Rh_2(4*S*/4*R*-MEOX)$_4$ and Rh_2(4*S*/4*R*-MPPIM)$_4$ as catalysts. The results in Table 2 clearly show that reaction temperature has a definite influence on the efficiency of the reaction. In refluxing CH_2Cl_2, which was found to be effective for (*S*)-**3**, poor to moderate yields of the C–H insertion product **16** were obtained (entries 1, 3). Gratifyingly, a significantly higher yield (70%) of **16** was realized when the Rh_2(4*S*-MPPIM)$_4$-catalyzed reaction of (*S*)-**15** was



Scheme 2 *Reagents and conditions*: a. (i) $ClCH_2CO_2H$, Ph_3P, DEAD, CH_2Cl_2; (ii) K_2CO_3, MeOH; 70%; b. *p*-TSHACl, $PhNMe_2$, *i*Pr_2NEt, CH_2Cl_2, 0 °C, 98%; c. Rh_2(4*R*-MPPIM)$_4$ (2 mol%), CH_2Cl_2, reflux, **10** (85%), **11** (0%), **12** (4%); Rh_2(4*S*-MPPIM)$_4$ (2 mol%), CH_2Cl_2, reflux, **10** (17%), **11** (67%), **12** (14%).



Scheme 3 *Reagents and conditions*: a. (i) TBDMSCl, imidazole, DMAP, DMF, 40 °C; (ii) BnBr, BuLi, DMF, THF, −15 °C; (iii) HCl, MeOH; 82%; b. *p*-TSHACl, $PhNMe_2$, *i*Pr_2NEt, DCM, 0 °C, 98%; c. Rh cat. (2 mol%), CH_2Cl_2 or 1,2-dichloroethane, reflux (see Table 2 for details).

Table 2 Rh(II)-catalyzed reaction of (*S*)-**15**

Entry	Rh_2L_4	Solvent	**16** (%)	**17** (%)	**18** (%) (*E* : *Z*)[b]
1	Rh_2(4*S*-MEOX)$_4$	CH_2Cl_2	17	21	20 (1 : 11)
2	Rh_2(4*R*-MEOX)$_4$	CH_2Cl_2	0	13	11 (1 : 33)
3	Rh_2(4*S*-MPPIM)$_4$	CH_2Cl_2	51	28	20 (2.4 : 1)
4	Rh_2(4*R*-MPPIM)$_4$	CH_2Cl_2	0	37	30 (1.5 : 1)
5	Rh_2(4*S*-MPPIM)$_4$	DCE[a]	70	11	7 (only *E*)
6	Rh_2(4*R*-MPPIM)$_4$	DCE	0	19	0

[a] DCE = 1,2-dichloroethane. [b] Ratio of *E* : *Z* isomers was based on the integration of the singlets due to the olefinic hydrogens centered at δ 6.23 (*Z*) and δ 6.77 (*E*).

conducted in refluxing 1,2-dichloroethane, whereas the corresponding *R*-catalysts failed to give any C–H insertion products. Further, unlike (*S*)-**3**, the *R*-catalysts did not lead to C_3–H insertion to form the corresponding regioisomer of **16**. Neither *trans*-**16** nor the spirocyclic β-lactone was detected.

Using the Rh_2(4*S*- or 4*R*-MPPIM)$_4$-catalyzed reaction of (*S*)-**3** as an example, we envisioned the formation of **4** and **5** to proceed *via* the rapidly interconverting reactive conformers[9,10] **A**, **A**′, **B** and **B**′ depicted in Fig. 1. In conformers **A** and **A**′, the Rh(II)-carbenoid moiety is oriented in the pseudoaxial and pseudoequatorial positions, respectively. Lactone **4** is formed

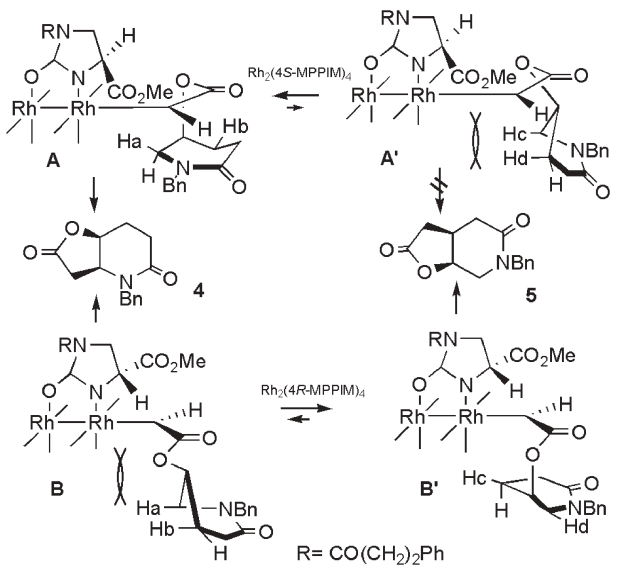
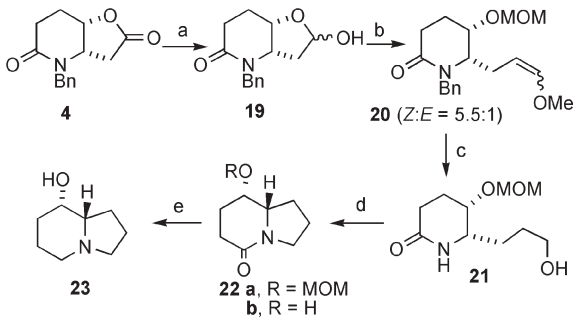


Fig. 1 Reactive conformer models for reaction of (*S*)-**3**.



Scheme 4 *Reagents and conditions*: a. Red-Al, THF–PhMe, −78 °C, 94%; b. (i) Ph_3P=CHOMe, THF, −40 °C, 74%, (ii) MOMCl, cat. Bu_4NI, *i*-Pr_2NEt. 89%; c. (i) Na, liq. NH_3; NH_4Cl. quant., (ii) 1 M aq. HCl then $NaBH_4$, 76%; d. (i) TsCl, Et_3N, cat. DMAP, 91%, (ii) NaH, 95%; e. (i) 1 M aq. HCl, MeOH. 95%, (ii) $BH_3{\cdot}SMe_2$, THF; then EtOH, reflux, 88%.

preferentially through metallocarbenoid insertion into C–Ha (**A**) as the Rh(II)-carbene and C–Ha σ-bond are aligned parallel to each other and the insertion is also facilitated by the greater nucleophilicity of the σ-bond (early TS) due to the activating influence of the amide nitrogen atom.[11] Insertion of the Rh(II)-carbenoid into C–Hb (**A**) is prevented from occurring because the C–Hb σ-bond and the Rh(II)-carbenoid bond cannot adopt the proper alignment. Conformer **A′** is destabilized by steric interaction of the pseudoaxial C–Hc and C–Hd with the ligand wall/N–C(O)$(CH_2)_2$Ph of the Rh(II) catalyst. Thus, regioisomer **5** is not formed.

In the mismatched Rh_2(4*R*-MPPIM)$_4$-catalyzed reaction, conformer **B** is destabilized by the interaction of C–Ha and C–Hb with the ligand wall/N–C(O)$(CH_2)_2$Ph. However, because C–Ha is activated by the amide nitrogen, its interaction with the vacant p-orbital of the Rh(II)-carbenoid carbon can occur at a greater distance (early TS) resulting in the formation of the minor product **4**. With **B′**, the Rh(II)-carbenoid bond and the C–Hc bond are properly aligned and C–H insertion leads to the regioisomer **5** as the major product. Insertion into C–Hd, as with C–Hb in **A**, is unattainable for geometric reasons.

For (*S*)-**15**, the absence of the regioisomer of **16** suggests that the C_3–H bond in **15** is deactivated towards metallocarbenoid insertion by the amide carbonyl group. This outcome taken together with that obtained in the Rh_2(4*R*-MPPIM)$_4$-catalyzed reaction of (*S*)-**3** to form **5** indicated that C–H bonds located α to an amide carbonyl group are deactivated towards Rh(II)-carbenoid insertion; β-C–H bonds are not deactivated.[12]

To demonstrate the utility of the bicyclic lactam lactone products, the enantioselective synthesis of (8*S*,8a*S*)-8-hydroxyoctahydroindolizidine[13] (**23**) starting from **4** was conducted. Several syntheses[13*a–d*] of (±)-**23** have been described; only one asymmetric synthesis of (8*S*,8a*S*)-**23**, which was obtained in 13 steps and 17% overall yield from a chiral non-racemic 4-formyl-β-lactam intermediate,[13*e*] was reported. Our building block **4** already has the correct configurations at the two stereocentres and seven of the eight carbons of the carbon framework in **23**.

The synthesis began with the chemoselective reduction of **4** with Red-Al®, which gave an excellent yield of the bicyclic lactam lactol **19** (Scheme 4). Wittig olefination (Ph_3P=CHOMe) followed by MOM protection of the secondary alcohol gave the ether **20** as a mixture of *Z*/*E* diastereomers. *N*-Debenzylation[14] of **20** was followed by hydrolysis of the enol ether unit and $NaBH_4$ reduction to provide the primary alcohol **21** in an overall yield of 76%. Tosylation of **21** and cyclization of the primary tosylate (NaH) yielded the bicyclic lactam **22a** (95%). MOM ether deprotection of **22a** gave **22b**;[13*e*] subsequent reduction of the lactam carbonyl group ($BH_3{\cdot}SMe_2$) afforded, initially, a very stable, non-polar **23** : borane complex as a white solid.[15] The volatile indolizidine **23** was obtained only after refluxing the **23** : borane complex in 95% ethanol for 24 h. Compound **23** was purified (Dowex 50x2-400, H^+ form) and characterized as its hydrochloride salt.

In summary, we have shown that the Rh_2(MPPIM)$_4$-catalyzed C–H insertion reaction of γ- and δ-lactam diazoacetates proceeded efficiently with excellent regioselectivity and *cis*-diastereoselectivity. Regioselectivity in the δ-lactam diazoacetate is dependent on the chirality of the Rh(II) catalyst. Reactive conformer models are proposed to explain product formation from (*S*)-**3**. The synthetic utility of the bicyclic lactam lactones is demonstrated by the concise asymmetric synthesis of **23** from **4** (9 steps, 34% overall yield). Applications to other alkaloid targets are in progress.

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

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