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Ruthenium-Catalyzed Stereoselective Intramolecular Carbenoid C–H Insertion for β- and γ-Lactam Formations by Decomposition of α-Diazoacetamides

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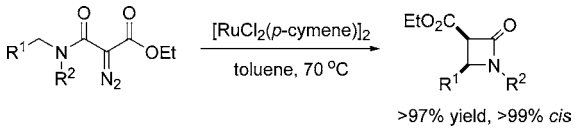
ABSTRACT



An operationally simple catalytic system based on [$RuCl_2$(*p*-cymene)$_2$] was developed for stereoselective cyclization of α-diazoacetamides by intramolecular carbenoid C–H insertion, and β-lactams were produced in excellent yields and >99% *cis*-stereoselectivity. The Ru-catalyzed reactions can be performed without the need for slow addition of diazo compounds and inert atmosphere. With α-diazoanilides as substrate, the carbenoid insertion was directed selectively to aromatic C–H bond leading to γ-lactam formation (>95% yield).

Transition metal-catalyzed intramolecular carbenoid C−H insertion by decomposition of α-diazocarbonyl compounds constitutes a powerful strategy for construction of carbocyclic and heterocyclic compounds.[1] A notable example is the dirhodium(II,II) carboxylate-catalyzed decomposition of α-diazoacetamides for stereoselective preparation of β- and γ-lactams,[1b−e] which are prevalent structures in natural products and many pharmaceuticals.[2] However, apart from rhodium, few transition metal complexes are known to exhibit comparable reactivities for catalytic carbenoid C−H insertion reaction.[3]

The use of ruthenium complexes as catalysts for stereoselective C−C bond formation is receiving current attention.[4] We previously showed that ruthenium porphyrins[5] are effective catalysts for cyclization of tosylhydrazones via intramolecular carbenoid C−H insertion to afford *cis*-disubstituted dihydrobenzofurans and β-lactams in excellent yields and *cis*-stereoselectivity.[6] With an objective to develop

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(3) A recent report on Cu-catalyzed carbenoid C−H insertion, see: Diaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Perez, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 896.

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(5) For selected examples of ruthenium porphyrin catalyzed carbenoid reactions, see: (a) Simonneaux, G.; Galardon, E.; Paul-Roth, C.; Gulea, M.; Masson, S. *J. Organomet. Chem.* **2001**, *617*, 360. (b) Che, C.-M.; Huang, J.-S.; Lee, F.-W.; Li, Y.; Lai, T.-S.; Kwong, H.-L.; Teng, P.-F.; Lee, W.-S.; Lo, W.-C.; Peng, S.-M.; Zhou, Z.-Y. *J. Am. Chem. Soc.* **2001**, *123*, 4119. (c) Zhou, C.-Y.; Yu, W.-Y.; Che, C.-M. *Org. Lett.* **2002**, *4*, 3235. (d) Zhou, C.-Y.; Chan, P. W. H.; Yu, W.-Y.; Che, C.-M. *Synthesis* **2003**, *9*, 1402. (e) Li, G.-Y.; Chen, J.; Yu, W.-Y.; Hong, W.; Che, C.-M. *Org. Lett.* **2003**, *5*, 2153. (f) Li, Y.; Chan, P. W. H.; Zhu, N.-Y.; Che, C.-M.; Kwong, H.-L. *Organometallics* **2004**, *23*, 54.

(6) (a) Cheung, W.-H.; Zheng, S.-L.; Yu, W.-Y.; Zhou, G.-C.; Che, C.-M. *Org. Lett.* **2003**, *5*, 2535. (b) Zheng, S.-L.; Yu, W.-Y.; Xu, M.-X.; Che, C.-M. *Tetrahedron Lett.* **2003**, *44*, 1445.

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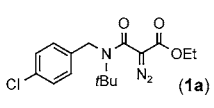
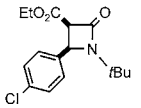
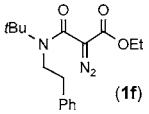
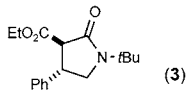
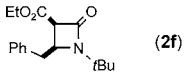
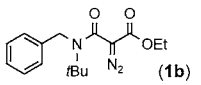
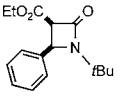
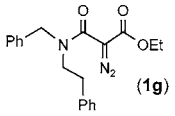
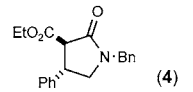
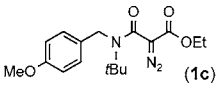
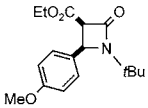
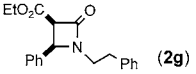
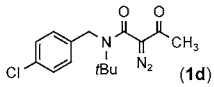
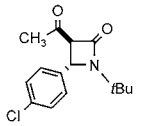
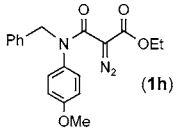
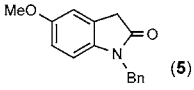
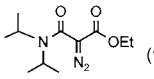
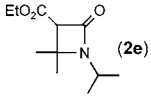
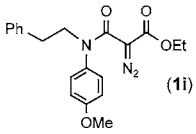
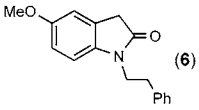
Table 1. Ruthenium-Catalyzed Intramolecular Carbenoid C−H Insertion of α-Diazoacetamides

entry	substrate	product	% yield [b]	entry	substrate	product	% yield [b]
1	 (**1a**)	 (**2a**)	99 [c]	6 [d]	 (**1f**)	 (**3**)	51
						 (**2f**)	12
2	 (**1b**)	 (**2b**)	99 [c]	7 [d]	 (**1g**)	 (**4**)	53
3	 (**1c**)	 (**2c**)	99 [c]			 (**2g**)	28
4	 (**1d**)	 (**2d**)	99 [c]	8 [e]	 (**1h**)	 (**5**)	97
5	 (**1e**)	 (**2e**)	89	9 [e]	 (**1i**)	 (**6**)	92

[a] Reaction conditions: A mixture of diazo compound (0.1 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (0.5 mol %) was stirred in toluene at 70 °C in an open atmosphere unless otherwise noted. [b] Isolated yield. [c] Yields determined by ^1H NMR analysis of the crude reaction mixture. [d] Reaction performed under N_2 atmosphere. [e] $[RuCl_2(p\text{-cymene})]_2$ loading = 2.5 mol %.

enantioselective carbenoid reactions, the rather laborious procedure required for structural modification of the porphyrin ligands prompted us to search for some non-porphyrin-based ruthenium systems that would be more amenable to structural variation. In developing operationally simple and practical protocols for catalytic carbenoid transformations, we now report that $[RuCl_2(p\text{-cymene})]_2$ can mediate catalytic intramolecular carbenoid C−H insertion reactions by decomposition of α-diazoacetamides. The *β*-lactam products were obtained in >90% yield with remarkable stereoselectivity (>99% *cis*). There are extensive reports describing $[RuCl_2(p\text{-cymene})]_2$ as a catalyst for a variety of reactions such as transfer hydrogenation,[7a,b] alkene metathesis,[7c,d] aerobic oxidation,[7e] and alkene cyclopropanation.[7f−h] As yet, however, examples for $[RuCl_2(p\text{-cymene})]_2$-catalyzed carbenoid C−H insertion are unprecedented in the literature.

Treatment of *N*-*p*-chlorobenzyl-*N*-*tert*-butyl-α-ethoxycarbonyl-α-diazoacetamide (**1a**, 0.1 mmol) with $[RuCl_2(p\text{-cymene})]_2$ (0.5 mol %) in toluene (10 mL) at 70 °C under an argon atmosphere afforded *N*-*tert*-butyl-*cis*-1-ethoxycarbonyl-2-*p*-chlorophenyl-*β*-lactam (**2a**) in quantitative yield after 0.5 h (Table 1, entry 1). No *trans*-*β*-lactam product was detected by ^1H NMR analysis of the crude mixture. The stereochemistry of the *cis*-*β*-lactam was established by ^1H NMR spectroscopy.

Without $[RuCl_2(p\text{-cymene})]_2$ as catalyst, no *β*-lactam formation was observed and the starting **1a** was quantitatively recovered. It is noteworthy that the *cis*-stereoselectivity observed in this work is comparable to that for the ruthenium porphyrin-catalyzed aryl tosylhydrazone cyclizations. According to the literature, dirhodium-catalyzed decompositions of α-diazoacetamides are known to favor *trans*-*β*-lactam formation.[8]

Presumably, the *β*-lactam formation is mediated by a reactive ruthenium carbene species, which undergoes carbenoid insertion to the benzylic C−H bond. In this work, when $[RuCl_2(p\text{-cymene})]_2$ was reacted with diphenyldiazomethane (4 equiv) in toluene at 70 °C under nitrogen, complete decomposition of the diazo compounds resulted affording tetraphenylethylene in 83% yield. However, attempts to isolate the putative ruthenium carbene complex were futile. Previously, Nishiyama and co-workers reported that $[RuCl_2(p\text{-cymene})]_2$ reacted with vinyl diazoacetate to generate a *π*-allyl ruthenium complex, which was structurally characterized by X-ray crystallography.[9]

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(8) (a) Padwa, A.; 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. (b) Yoon, C. H.; Zaworotko, M. J.; Moulton, B.; Jung, K. W. *Org. Lett*. **2001**, *3*, 3539.

(9) Nishiyama, H.; Konno, M.; Aoki, K.; Davies, H. M. L. *Organometallics* **2002**, *21*, 2536.

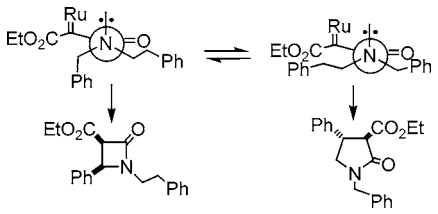
According to earlier reports,[5,7f−h,10] slow addition of α-diazo compounds and inert atmosphere were often necessary for ruthenium-catalyzed carbenoid transformations. The slow addition procedure is to avoid/minimize the diazo coupling reaction. In this work, we found that the $[RuCl_2(p\text{-cymene})]_2$-catalyzed intramolecular carbenoid C−H insertion reaction could be performed without using the slow addition procedure or an inert atmosphere. For example, heating a mixture of **1a** (0.1 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (0.5 mol %) at 70 °C in open atmosphere (i.e., without Ar/N_2 protection) furnished *cis*-*β*-lactam in quantitative yield within 0.5 h (Table 1, entry 1). No diazo coupling products (fumarate/maleate) were detected by ^{1}H NMR analysis.

Employing the reaction conditions: Ru (1 mol %), toluene, 70 °C, other ruthenium complexes such as $[Ru^{II}(TTP)(CO)]$ [H_2TPP = *meso*-tetrakis(*p*-tolyl)porphyrin], $[Ru^{II}(salen)(PPh_3)_2]$ [salen = *N*,*N*′-bis(2,4-dibromosalicyclidene)-1,2-cyclohexanediamine)], $[Ru^{II}(6,6'\text{-}Cl_2\text{-}bpy)_2(H_2O)_2](CF_3SO_3)_2$ (6,6′-Cl_2-bpy = 6,6′-dichloro-2,2′-bipyridine),[11] $[Ru^{II}(PPh_3)_2Cl_2]$, and $[Ru(COD)Cl_2]_n$ (COD = 1,8-cyclooctadiene) failed to effect catalytic cyclization of **1a** with complete recovery of the starting material. Under an inert atmosphere, $[Cp^*RuCl_2]_2$ (Cp* = pentamethylcyclopentadienyl) was found to catalyze cyclization of **1a** to give *cis*-lactam **2a** exclusively in 96% yield (NMR) within 2 h. However, when the identical reaction was conducted in an open atmosphere, the *cis*-lactam product was obtained in only 62% yield at 80% substrate conversion after 5 h of reaction.

In this work, common solvents such as toluene, $CHCl_3$, CH_2Cl_2, acetone, EtOAc, and THF could be utilized without prior treatment for the cyclization of **1a** with >95% yields and complete *cis*-selectivity being attained in most cases (see the Supporting Information). However, when DMF, CH_3CN, and MeOH were used as solvent, no substrate conversion was observed within 3 h.

The scope of the $[RuCl_2(p\text{-cymene})]_2$-catalyzed intramolecular carbenoid C−H insertion has been explored and the results are depicted in Table 1. Analogous to **1a**, other *N*-*para*-Y-substituted benzyl-*N*-*tert*-butyl α-diazoacetamides [Y = H (**1b**), OMe (**1c**)] were converted to the corresponding *cis*-*β*-lactams (99% NMR yields) under the Ru-catalyzed conditions (entries 2 and 3). Even so, the catalytic reaction of α-diazoketone **1d** was found to give *trans*-lactam **2d** exclusively in quantitative yield (entry 4). With *N*,*N*-diisopropyl substituted α-diazoacetamide **1e** as substrate, the Ru-mediated carbenoid insertion was directed to the methine (tertiary) C−H bond furnishing *β*-lactam **2e** in 89% isolated yield (entry 5). No *γ*-lactam due to insertion at the primary C−H bond was detected by ^{1}H NMR analysis. The observed reactivity preference (i.e., tertiary C−H > primary C−H bonds) is similar to the related systems with $[Rh_2(CH_3CO_2)_4]$ as catalyst.[8]

Scheme 1. Proposed Reactive Conformations for Cyclization of α-Diazoacetamide **1g**



Using **1f** as substrate and $[RuCl_2(p\text{-cymene})]_2$ as catalyst (0.5 mol %), a mixture of *trans*-*γ*-lactam **3** (51%) and *cis*-*β*-lactam **2f** (15%) was produced after 16 h of reaction (Table 1, entry 6).[12] Again, no *trans*-*β*-lactam product was detected by ^{1}H NMR analysis of the crude reaction mixture. The *trans*-stereochemistry of *γ*-lactam **3** was established by a 2D-NOESY NMR study (see the Supporting Information).

With $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %) in toluene at 70 °C for 2 h, α-diazoacetamide **1g** containing a benzyl and a phenylethylene group underwent intramolecular carbenoid C−H insertion reaction to afford *trans*-*γ*-lactam **4** and *cis*-*β*-lactam **2g** in 53 and 28% yield, respectively (Table 1, entry 7). Similar results were obtained when $[Rh_2(CH_3CO_2)_4]$ was employed as a catalyst (0.1 mol %) in CH_2Cl_2 at reflux under N_2. Assuming metal-carbenoids are being generated as active intermediates, the formation of *γ*- and *β*-lactams can be explained by the presence of two reactive conformations as depicted in Scheme 1.[13]

We also explored carbenoid insertion into aromatic C−H bonds.[14] When α-diazoanilides **1h** and **1i** were treated with $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %) in toluene at 70 °C for 16 h, effective carbenoid C−H insertion into the *p*-methoxyphenyl group was observed, and *γ*-lactams **5** and **6** were isolated in 97 and 92% yields respectively (Table 1, entries 8 and 9). However, using $[Rh_2(CH_3CO_2)_4]$ as catalyst (CH_2Cl_2 at reflux, 16 h), the analogous reactions yielded *trans*-*β*-lactams (57% for **1h**; 87% for **1i**) and *γ*-lactams (43% for **1h**; 15% for **1i**).

For the Ru-catalyzed reaction of α-diazoanilides, complete substrate consumption was observed within 2 h based on TLC monitoring. However, ^{1}H NMR analysis of the reaction mixtures revealed a complicated spectrum. This finding suggested that decarboxylation of the putative α-ethoxycarbonyl *γ*-lactam may involve several undefined chemical

(10) Selected examples: (a) Lo, W.-C.; Che, C.-M.; Cheng, K.-F.; Mak, T. C. W. *Chem. Commun*. **1997**, 1205, (b) Galardon, E.; Maux, P. L.; Simmoneaux, G. *Chem. Commun*. **1997**, 927. (c) Simal, F.; Jan, D.; Demonceau, A.; Noels, A. F. *Tetrahedron Lett*. **1999**, *40*, 1653. (d) Baratta, W.; Herrmann, W. A.; Kratzer, R. M.; Rigo, P. *Organometallics* **2000**, *19*, 3664. (e) Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron* **2000**, *56*, 3501.

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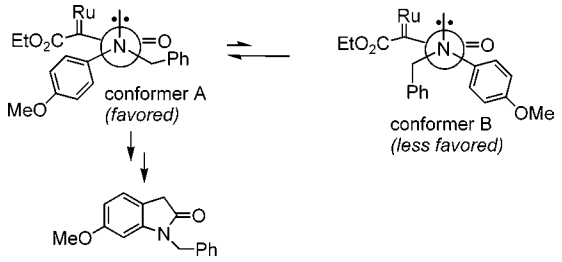
(12) For comparison, we also performed the identical reaction using $[Rh_2(CH_3CO_2)_4]$ as catalyst by employing a reported protocol:[8a] **1f** (0.1 mmol), Rh (0.1 mol %), CH_2Cl_2, N_2, reflux; an equimolar mixture of *β*- and *γ*-lactams was obtained in 96% overall yield.

(13) (a) Doyle, M. P.; Shanklin, M. S.; Oon, S.-M.; Pho, H. Q.; van der Heide, F. R.; Veal, W. R. *J. Org. Chem*. **1988**, *53*, 3384. (b) Doyle, M. P.; Taunton, J.; Pho, H. Q. *Tetrahedron Lett*. **1989**, *30*, 5397.

(14) (a) Hrytsak, M.; Durst, T. *J. Chem. Soc., Chem. Commun*. **1987**, 1150. (b) Nakatani, K. *Tetrahedron Lett*. **1987**, *28*, 165. (c) Doyle, M. P.; Shanklin, M. S.; Pho, H. Q.; Mahapatro, S. N. *J. Org. Chem*. **1988**, *53*, 1017. (d) Babu, S. D.; Hrytsak, M. D.; Durst, T. *Can. J. Chem*. **1989**, *67*, 1071. (e) Etkin, N.; Babu, S. D.; Fooks, C. J.; Durst, T. *J. Org. Chem*. **1990**, *55*, 1093.

Scheme 2



species. Nevertheless, heating the reaction mixtures for an additional 14 h yielded the γ-lactams exclusively in quantitative yields based on NMR analysis.

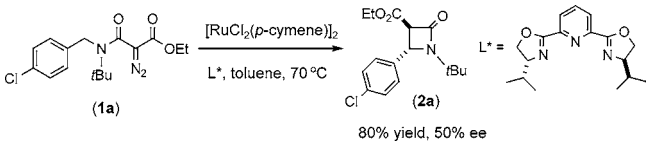
The regioselectivity observed in the Ru-catalyzed aromatic C−H insertion reactions (Scheme 2) can be explained by the putative ruthenium carbenoid preferring to react via conformer A rather than conformer B due to reduced nonbonded interactions between the alkyl chain and the carbonyl group.

The asymmetric synthesis of β-lactams has been a subject of extensive investigation.[1,15] In this work, we have examined enantioselective cyclization of α-diazoacetamides catalyzed by $[RuCl_2(p\text{-cymene})]_2$ in the presence of a chiral pyridine bis(oxazoline) ligand L* (Scheme 3). Earlier work by Nishiyama and co-workers showed that chiral $[RuCl_2(L^*)(C_2H_4)]$ complexes are effective catalysts for enantioselective alkene cyclopropanations.[7f]

Treatment of **1a** with $[RuCl_2(p\text{-cymene})]_2$ (5 mol %) and L* (10 mol %) in toluene at 70 °C for 72 h produced *trans*-

(15) (a) Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Daniel, K. L. *Tetrahedron Lett.* **1992**, *33*, 7819. (b)Watanabe, N.; Anada, M.; Hashimoto, S.; Ikegami, S. *Synlett* **1994**, 1031. (c) Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **1998**, *39*, 79. (d) Anada, M.; Watanabe, N.; Hashimoto, S. *Chem. Commun*. **1998**, 1517. (e) Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **1998**, *39*, 9063. (f) Anada, M.; Watanabe, O. M.; Kitagaki, S.; Hashimoto, S. *Synlett* **1999**, *11*, 1775.

Scheme 3. Regioselective Carbenoid Insertion to Aromatic C−H Bond



β-lactam **2a** exclusively in 80% isolated yield. By means of ^1H NMR analysis with $Eu(hfc)_3$ as shift reagent, the optical purity of *trans*-**2a** was determined to be 50%ee (Scheme 3). Identical results (*trans*-**2a**: 72% yield, 53%ee) were obtained when treating **1a** with $[RuCl_2(L^*)(C_2H_4)]$ as catalyst. Using the "$[RuCl_2(p\text{-cymene})]_2$ + L*" protocol, reactions of other diazoacetamides **1b** and **1c** furnished the corresponding β-lactams in moderate enantioselectivities (41%ee for *trans*-**2b** and 53%ee for *trans*-**2c**; see Table S2, Supporting Information). Yet, the cyclization of **1c** also gave the *cis*-β-lactam as a minor product (8% isolated yield), and the optical purity of the *cis*-**2c** was determined to be 55%ee (Table S2, Supporting Information). The factors governing the stereo- and enantioselectivities for the present Ru-catalyzed carbenoid C−H insertion are under investigation.

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Supporting Information Available: Detail experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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