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Ruthenium Porphyrin Catalyzed Intramolecular Carbenoid C–H Insertion. Stereoselective Synthesis of Cis-Disubstituted Oxygen and Nitrogen Heterocycles

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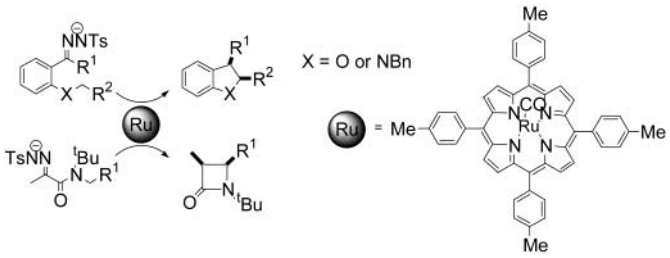
ABSTRACT



A ruthenium porphyrin-catalyzed stereoselective intramolecular carbenoid C–H insertion is described. Using [Ru^{II}(TTP)(CO)] as catalyst, aryl tosylhydrazones are converted to 2,3-dihydrobenzofurans, 2,3-dihydroindoles, and *β*-lactams in good yields and remarkable *cis* selectivity (up to 99%). Enantioselective synthesis of 2,3-dihydrobenzofurans is also achieved with [Ru^{II}(D$_4$-Por*)(CO)] as catalyst, and up to 96% ee is attained.

Transition-metal-catalyzed carbenoid insertion into a saturated C−H bond is an appealing methodology for construction of carbon−carbon bonds and natural product synthesis.[1] The carbenoid C−H insertions have proven to be a unique and effective strategy for stereo- and enantioselective synthesis of five- and four-membered heterocycles.[1] Significant advances in this area have been made with the Rh-/Cu-catalyzed decomposition of α-diazo esters, and highly reactive metal−carbenes are postulated.[2,3]

Metalloporphyrins for catalytic carbenoid transformations are receiving growing attention;[4,5] in particular, ruthenium porphyrins[4a−d,f−h,5a,c] represent a new class of highly robust catalysts with superior stability (Figure 1). Importantly,

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(1) For reviews, see: (a) Taber, D. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 3, p 1045. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley & Sons: New York, 1998. (c) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. (d) Pfaltz, A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springler-Verlag: New York, 1999; Vol. 2, p 513. (e) Lydon, K. M., McKervey, M. A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springler-Verlag: New York, 1999; Vol. 2, p 539.

(2) For isolation of a stable rhodium carbenoid complex, see: Snyder, J. P.; Padwa, A.; Stengel, T.; Arduengo, A. J., III; Jockisch, A.; Kim, H.-J. *J. Am. Chem. Soc.* **2001**, *123*, 11318.

(3) For a theoretical study on rhodium-carbenoid, see: Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 7181.

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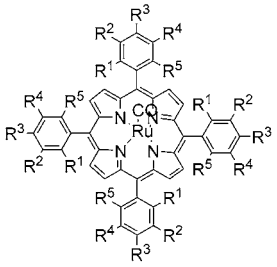


[Ru^{II}(TTP)(CO)] (R^1=R^2=R^4=R^5=H; R^3=Me)

[Ru^{II}(*p*-F-TPP)(CO)] (R^1=R^2=R^4=R^5=H; R^3=F)

[Ru^{II}(TMP)(CO)] (R^2=R^4=H; R^1=R^3=R^5=Me)

[Ru^{II}(TDCPP)(CO)] (R^2=R^3=R^4=H; R^1=R^5=Cl)

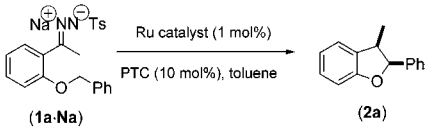
[Ru^{II}(3,4,5-MeO-TPP)(CO)] (R^1=R^5=H; R^2=R^3=R^4=OMe)

Figure 1. Ruthenium porphyrins.

ruthenium porphyrins react with diazo compounds to afford ruthenium−carbene complexes,[6] some of which have been structurally characterized.[5b−d] Here, we report an extensive study on ruthenium porphyrin catalyzed cyclization of aryl tosylhydrazones to form *cis*-2,3-disubstituted 2,3-dihydrobenzofurans via carbenoid C−H insertion. In the course of this study, Zheng *et al*.[7] communicated the use of ruthenium porphyrin for the synthesis of (±)-*epi*-conocarpan. Dihydrobenzofurans (e.g., lignans and neolignans) are widespread in nature, and they exhibit a broad range of biological activities including anticancer effects.[8] In this report, we also describe stereoselective synthesis of *cis*-disubstituted *β*-lactams[9] by employing the ruthenium-catalyzed protocol.

In this work, we employed aryl tosylhydrazones as precursors for *in situ* generation of diazo compounds, where handling or accumulation of unstable intermediates can be avoided.[10] Treating the sodium salt of **1a** (1 mmol) with [Ru^{II}(TTP)(CO)] (1 mol %) and *n*-Bu_4NBr (10 mol %) as phase-transfer catalyst in toluene at 60−70 °C for 48 h afforded dihydrobenzofuran **2a** in 76% isolated yield (Table 1, entry 1). ^{1}H NMR analysis revealed that *cis*-disubstituted product was predominantly formed (*cis*/*trans* = 98:2) by comparing the integral ratios of the methyl protons of the *cis* (0.78 ppm) and *trans* isomers (1.38 ppm).[11] Using benzyl α,α-d_2-alcohol (98% D), we prepared a deuterium-labeled **1a′**. Under the Ru-catalyzed conditions, facile cyclization of **1a′** to *cis*-dihydrobenzofuran **2a′** (ca. 83% yield) was achieved exclusively (Table 1, entry 2). On the basis of ^{1}H NMR and mass spectroscopic analyses, the deuterium content was conserved after the cyclization reaction. The NMR spectrum of **2a′** unequivocally reveals that the deuterium atom at the C3 position originates from the benzylic C−D bond. This result suggests that the Ru-catalyzed cyclization of aryl tosylhydrazones involves cleavage of the benzylic C−H bond as the principal step.

Table 1. Ru-Catalyzed Intramolecular Carbenoid C−H Insertion



(**1a**·**Na**) (**2a**)

entry	Ru catalyst	PTC	*T* (°C)	time (h)	yield (%)	*cis*/*trans*[b]
1	[Ru^{II}(TTP)(CO)]	*n*-Bu_4NBr	60−70	48	76	98:2
2	[Ru^{II}(TTP)(CO)]	*n*-Bu_4NBr	110	12	83	>99%[c]
3	[Ru^{II}(TTP)(CO)]	$BnEt_3NCl$	60−70	48	77	98:2
4	[Ru^{II}(TTP)(CO)]	*n*-Bu_4NBr	110	2	86	98:2
5	[Ru^{II}(OEP)(CO)]	*n*-Bu_4NBr	60−70	48	79	98:2
6	[Ru^{II}(p-F-TPP)(CO)]	*n*-Bu_4NBr	60−70	48	79	98:2
7	[Ru^{II}(3,4,5-MeO-TPP)(CO)]	*n*-Bu_4NBr	60−70	48	79	98:2
8	[Ru^{II}(TDCPP)(CO)]	*n*-Bu_4NBr	60−70	48	12	94:6
9	[Ru^{II}(TMP)(CO)]	*n*-Bu_4NBr	60−70	48	10	45:55

[a] Isolated yield. [b] Determined by ^{1}H-NMR. [c] α,α-d_2-**1a**-Na as substrate, *cis*-d_2-**2a** was determined by NMR analysis.

Other phase-transfer catalysts such as $BnEt_3NCl$ are equally effective for the Ru-catalyzed cyclization of **1a** (entry 3). Toluene was found to be the solvent of choice; using other solvents such as CH_2Cl_2 and THF resulted in sluggish reaction and low product yield (<6%) with >90% of the starting hydrazone being recovered. It is well-known that [$Rh_2(CH_3CO_2)_4$] is a highly effective catalyst for the analogous C−H insertions. However, in this work, when the

(4) Works by others; see, for example: (a) Smith, D. A.; Reynolds, D. N.; Woo, L. K. *J. Am. Chem. Soc.* **1993**, *115*, 2511. (b) Galardon, E.; Maux, P. L.; Simonneaux, G. *Chem. Commun*. **1997**, 927. (c) Frauenkron, M.; Berkessel, A. *Tetrahedron Lett*. **1997**, *38*, 7175. (d) Galardon, E.; Maux, P. L.; Simonneaux, G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2455. (e) Galardon, E.; Roué, S.; Maux, P. L.; Simonneaux, G. *Tetrahedron Lett*. **1998**, *39*, 2333. (f) Gross, Z.; Galili, N.; Simkhovich, L. *Tetrahedron Lett*. **1999**, *40*, 1571. (g) Galardon, E.; Maux, P. L.; Simonneaux, G.; *Tetrahedron* **2000**, *56*, 615. (h) Hamaker, C. H.; Djukic, J.-P.; Smith, D. A.; Woo, L. K. *Organometallics* **2001**, *20*, 5189. (i) Mirafzal, G. A.; Cheng, G.; Woo, L. K. *J. Am. Chem. Soc*. **2002**, *124*, 176.

(5) Work done by us: (a) Lo, W.-C.; Che, C.-M.; Cheng, K.-F.; Mak, T. C.-W. *J. Chem. Soc., Chem. Commun*. **1997,** 1205. (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) Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M. *J. Am. Chem. Soc*. **2001**, *123*, 4843. (d) Zheng, S.-L.; Yu, W.-Y.; Che, C.-M. *Org. Lett*. **2002**, *4*, 889. (e) Zhang, J.-L.; Che C.-M. *Org. Lett*. **2002**, *4*, 1911. (f) Zhou, C.-Y.; Yu, W.-Y.; Che, C.-M. *Org. Lett*. **2002**, *4*, 3235.

(6) (a) Collman, J. P.; Brothers, P. J.; McElwee-White, L.; Rose, E.; Wright, L. J.; *J. Am. Chem. Soc*. **1985**, *107*, 4570. (b) Collman, J. P.; Rose, E.; Venburg, G. D. *J. Chem. Soc., Chem. Commun*. **1993**, 934. (c) Park, S.-B.; Sakata, N.; Nishiyama, H. *Chem. Eur. J*. **1996**, *2*, 203. (d) Galardon, E.; Maux, P. L.; Toupet, L.; Simonneaux, G. *Organometallics* **1998**, *17*, 565. (e) Klose, A.; Solari, E.; Floriani, C.; Geremia, S.; Randaccio, L. *Angew. Chem*. **1998**, *110*, 155; Klose, A.; Solari, E.; Floriani, C.; Geremia, S.; Randaccio, L. *Angew. Chem., Int. Ed*. **1998**, *37*, 148.

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(8) (a) MacRae, W. D.; Towers, G. H. N. *Phytochemistry* **1984**, *23*, 1207. (b) Ward, R. S. *Nat. Prod. Rep*. **1995**, 183. (c) Ayers, A. C.; Loike, J. K. *Lignans: Chemical, Biological and Clinical Properties*; Cambridge University Press: Cambridge, 1990.

(9) For an alternative approach for highly *cis*-selective *β*-lactam synthesis using [2 + 2] cycloaddition, see: Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc*. **2002**, *124*, 6626 and references therein.

(10) Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. *Org. Lett*. **2001**, *3*, 2785.

(11) Snider, B. B.; Han, L.; Xie, C. *J. Org. Chem*. **1997**, *62*, 6978.

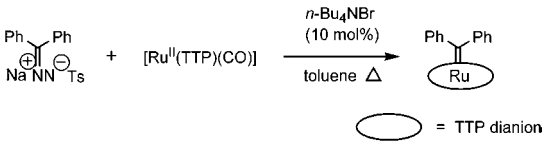
cyclization of **1a** was conducted under the reaction conditions: $[Rh_2(CH_3CO_2)_4]$ (1 mol %), **1a** (1 mmol) and *n*-Bu_4NBr (10 mol %) in toluene at 60−70 °C, a mixture of *cis*- and *trans*-**2a** (*cis*/*trans* = 47:53) was obtained in only 21% yield. Previously, Davies[12a] and Hashimoto[12b] independently reported the chiral Rh-catalyzed enantioselective synthesis of *cis*-2-aryl-3-methoxycarbonyl-2,3-dihydrobenzofurans by intramolecular carbenoid C−H insertion strategy. According to their reports, low temperature (−78 or −50 °C) was employed to give a high degree of *cis* stereoselectivity.

In refluxing toluene (110 °C), the Ru-catalyzed cyclization of **1a** would attain complete substrate consumption within 2 h affording **2a** in 86% yield (entry 4) with excellent *cis* selectivity (*cis*/*trans* = 98:2). In the absence of ruthenium porphyrin catalyst, heating **1a** in refluxing toluene led to decomposition of the hydrazone without any formation of the dihydrobenzofuran product.

Several ruthenium(II) porphyrins, [Ru^{II}(Por)(CO)], [H_2-Por: H_2OEP = octaethylporphyrin; H_2-*p*-F-TPP = *meso*-tetrakis(*p*-fluorophenyl)porphyrin; H_2-3,4,5-MeO-TPP = *meso*-tetrakis-(3,4,5-trimethoxyphenyl)porphyrin] were found to be equally effective catalysts for the intramolecular carbenoid C−H insertion, and **2a** was isolated in 79−88% yields (entries 5−7) and excellent *cis* selectivities (*cis*/*trans* = 98:2). And yet, when the sterically bulky [Ru^{II}(TDCPP)(CO)] [H_2TDCPP = *meso*-tetrakis(2,6-dichlorophenyl)porphyrin] was employed as catalyst, **2a** was formed in only 12% yield (entry 8) with a *cis*/*trans* ratio of 96:4. Likewise, with [Ru^{II}(TMP)(CO)] [H_2TMP = *meso*-tetrakismesitylporphyrin] as catalyst, **2a** was formed in 10% yield and low *cis* selectivity (*cis*/*trans* = 45:55) (entry 9).

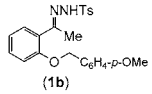
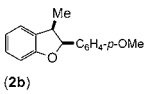
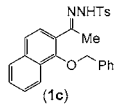
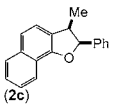
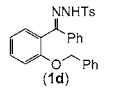
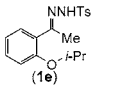
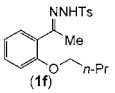
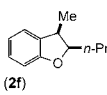
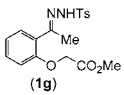
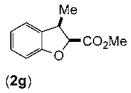
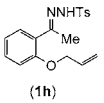
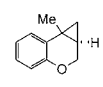
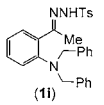
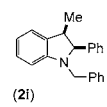
Reacting [Ru^{II}(TTP)(CO)] with sodium salt of benzophenone tosylhydrazone (2 equiv) at ca. 65 °C in toluene for 4 h under an argon atmosphere was found to give [(TTP)Ru=CPh_2],[5b] which was characterized by $^1H/^{13}C$ NMR and FAB-MS (see Supporting Information). An attempt to isolate the carbenoid species derived from **1a** with [Os^{II}(TTP)(CO)] was not successful; only the C−H insertion product was obtained in 81% yield (Scheme 1).

Scheme 1. Formation of [(TTP)Ru=CPh_2] from the Decomposition of Benzophenone Tosylhydrazone



The tosylhydrazone salt can be generated *in situ*[10] by reacting tosylhydrazone with a base, and a one-pot process for the Ru-catalyzed intramolecular carbenoid C−H insertion is developed. Several tosylhydrazone derivatives have been employed to demonstrate the generality of the reaction.[10] As shown in Table 2, the reactions of aryl tosylhydrazones **1a**−**c** gave preferentially *cis*-disubstituted dihydrobenzofurans **2a**−**c** in good yields (entries 1−3). However, for substrate **1d**

Table 2. One-Pot Protocol for the Ru-Catalyzed Intramolecular Carbenoid C−H Insertion[a]

entry	substrate	product	yield (%)[b]	*cis*:*trans*[c]
1	 (**1a**)	 (**2a**)	89	95:5
2	 (**1b**)	 (**2b**)	82	89:11
3	 (**1c**)	 (**2c**)	89	>99 *cis*
4	 (**1d**)	 (**2d**)	78	34:66
5	 (**1e**)	 (**2e**)	62	-
6	 (**1f**)	 (**2f**)	73	87:13
7	 (**1g**)	 (**2g**)	66	>99 *cis*[d]
8	 (**1h**)	 (**2h**)	56	-
9	 (**1i**)	 (**2i**)	78	>99 *cis*

[a] Reaction conditions: (1) LiHMDS (1.2 equiv) in THF, −78 °C, 30 min; (2) Ru catalyst, *n*-Bu_4NBr, toluene MS4Å, 110 °C. [b] Isolated yield. [c] *Cis*/*trans* ratio was determined by ^1H NMR. [d] Modified reaction conditions: 70 °C, 60 h.

containing two phenyl substituents, the reaction produced *trans*-diphenyl-2,3-dihydrobenzofuran (**2d**) as the major product (yield = 78%; *cis*/*trans* = 34:66; see entry 4). Tosylhydrazones **1e**,**f** containing aliphatic C−H bonds can be readily converted to their corresponding dihydrobenzofurans (entries 5−6). This features a rare example of Ru-carbenoid insertion into aliphatic C−H bond.

*It is reported that substrates such as **1g** containing electron-withdrawing ester substituents are not reactive for the Rh-catalyzed carbenoid C−H insertion reaction.*[1a] *In this work, with the [Ru^{II}(TTP)(CO)] catalyst, **1g** was found to undergo facile carbenoid C−H insertion, and **2g** was obtained in 66% yield with >99% cis selectivity (entry 7).* However, under the Ru-catalyzed conditions, **1h** containing a C=C bond undergoes preferentially intramolecular cyclopropanation to give cyclopropane **2h** in 56% yield (entry 8). No C−H insertion product was detected by ^1H NMR analysis of the crude reaction mixture.

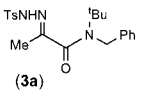
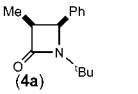
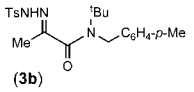
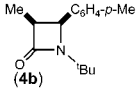
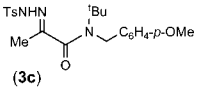
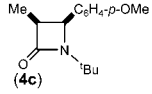
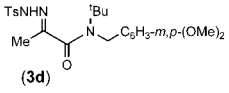
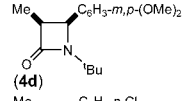
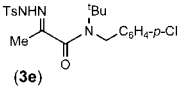
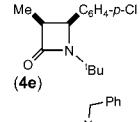
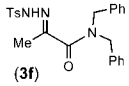
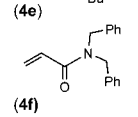
The Ru-catalyzed intramolecular carbenoid C−H insertion reaction is also effective for the formation of *cis*-disubstituted

dihydroindoles. Treatment of *N*,*N*-dibenzyl-2-aminoacetophenone tosylhydrazone **1i** according to the one-pot protocol furnished the product dihydroindole **2i** in 78% isolated yield. Again, >99% *cis*-selectivity was observed based on ^{1}H NMR analysis of the product (vicinal coupling constant = 8.9 Hz).[13] The high *cis* stereoselectivity is comparable to the dihydrobenzofuran formation by the ruthenium-carbenoid C−H insertion.

A wide variety of methods have been developed for the preparation of β-lactam rings.[14] Among them, the [$Rh_2(CH_3CO_2)_4$]-catalyzed carbenoid C−H insertion via decomposition of α-diazo acetamides is a highly effective strategy for making this important class of compounds.[15] In this work, we have also explored the Ru-catalyzed intramolecular carbenoid C−H insertion protocol for construction of β-lactam rings. Reaction of the *N*-benzyl-*N*-*tert*-butylacetamide tosylhydrazone **3a** under the Ru-catalyzed conditions gave β-lactam **4a** in 80% isolated yield after chromatographic purification. The C−H insertion reaction proceeded with remarkable *cis*-selectivity (>98%) since only *cis*-β-lactam (vicinal coupling constants = 5−6 Hz) was obtained based on ^{1}H NMR analysis. It is noteworthy that the analogous rhodium(II) acetate catalyzed reactions are known to proceed with *trans* selectivity,[15a] and no *cis*-lactams were produced. Identical results were obtained with a series of ring-substituted acetamide tosylhydrazones, and the *cis*-β-lactams were furnished in 70−89% yields (see Table 3). The bulky *tert*-butyl group was found to be essential for the success of this transformation. When *N*,*N*-dibenzylacetamide tosylhydrazone **3f** was utilized as substrate, only *N*,*N*-dibenzylacrylamide (Table 3, entry 6) was isolated in 70% yield and no β-lactam was evident by ^{1}H NMR analysis of the reaction mixture.

Our preliminary study revealed that enantioselective carbenoid C−H insertion can be achieved using chiral ruthenium porphyrin as catalyst. Subjecting **1c** to the Ru-catalyzed conditions: [Ru^{II}(D_4-Por*)(CO)] (D_4-H_2Por* = 5,10,15,20-tetrakis[(*1S*,*4R*,*5R*,*8S*)-1,2,3,4,5,6,7,8-octahydro-1,4:5,8-dimethanoanthracene-9-yl]porphyrin)[5a−b,16] (5 mol %), *n*-Bu_4NBr (10 mol %) in toluene at 60−70 °C for 48 h, enantioenriched **2c** was obtained in 78% yield (>99% *cis*) and 96% ee (see Supporting Information). *The ee value attained in this work is among the best enantioselectivity (94% ee) reported by Hashimoto and co-workers using the chiral rhodium catalyst.*[12] Further exploration of this methodology for enantioselective carbon−carbon bond formation is underway.

Table 3. One-Pot Protocol for the Ru-Catalyzed *Cis*-β-Lactam Formation[a]

entry	substrate	product	yield (%)[b, c]
1	 (**3a**)	 (**4a**)	80
2	 (**3b**)	 (**4b**)	75
3	 (**3c**)	 (**4c**)	89
4	 (**3d**)	 (**4d**)	85
5	 (**3e**)	 (**4e**)	70
6	 (**3f**)	 (**4f**)	70

[a] Reaction conditions: (1) LiHMDS (1.2 equiv) in THF, −78 °C, 30 min; (2) Ru catalyst (1 mol %), *n*-Bu_4NBr, MS4Å, toluene, 110 °C, 4 h. [b] Isolated yield. [c] >99% *cis* isomer was obtained and determined by ^{1}H NMR.

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

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