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Ruthenium-Catalyzed One-Pot Carbenoid N–H Insertion Reactions and Diastereoselective Synthesis of Prolines

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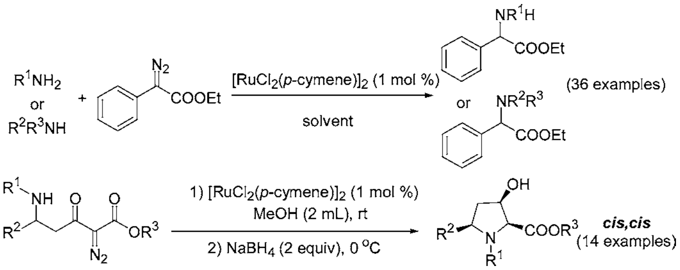
ABSTRACT



Aryl- and aliphatic-substituted 3-hydroxyprolines and various other amino esters are conveniently prepared by $[RuCl_2(p\text{-cymene})]_2$-catalyzed one-pot intramolecular and intermolecular carbenoid N–H insertion reactions, respectively, and the prolines are formed with high diastereoselectivities. The catalytic reactions are tolerant toward air/moisture, and the product yields are insensitive to the organic solvents used.

Metal-catalyzed carbenoid N−H insertion reactions are of great utility for the generation of building blocks to be used in the construction of natural products and other pharmaceuticals.[1] Several decades ago, it was demonstrated that transition-metal complexes such as those of Cu, Rh, and Fe were effective catalysts for carbenoid N−H insertion reactions. The first notable application of a metal-catalyzed carbenoid N−H insertion[2] was the synthesis of a bicyclic β-lactam in 1978.[3] Of the previously reported catalytic reactions, relatively few have involved the use of ruthenium complexes. Simonneaux and co-workers[4] suggested that the carbenoid species generated by the reaction between diazoesters and ruthenium porphyrins may undergo N−H and S−H insertion as well as alkene cyclopropanation. Zotto and co-workers[5] revealed that $[RuCl(\eta^5\text{-}C_5H_5)(PPh_3)_3]$-catalyzed

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(1) (a) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161. (b) Aller, E.; Buck, R. T.; Drysdale, M. J.; Ferris, L.; Haigh, D.; Moody, C. J.; Pearson, N. D.; Sanghera, J. B. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2879. (c) Deng, G.; Jiang, N.; Ma, Z.; Wang, J. *Synlett* **2002**, 1913. (d) Dong, C.; Deng, G.; Wang, J. *J. Org. Chem.* **2006**, *71*, 5560.

(2) For reviews involving catalyzed diazo compound N-H insertion reactions, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998; Chapter 8.2. (b) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. For recent examples, see: (c) Hrytsak, M.; Durst, T. *Heterocycles* **1987**, *26*, 2393. (d) Morilla, M. E.; Diaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Perez, P. J. *Chem. Commun.* **2002**, *24*, 2998. (e) Aviv, I.; Gross, Z. *Synlett* **2006**, *6*, 951. For example of highly enantioselective metal-catalyzed intermoelcular carbenoid N-H insertion reactions, see: (f) Liu, B.; Zhu, S.-F.; Zhang, W.; Chen, C.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 5834.

(3) Cama, L. D.; Christensen, B. G. *Tetrahedron Lett.* **1978**, *19*, 4233.

(4) (a) Galardon, E.; Maux, P. L.; Simonneaux, G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2455. (b) Galardon, E.; Maux, P. L.; Simonneaux, G. *Tetrahedron* **2000**, *56*, 615.

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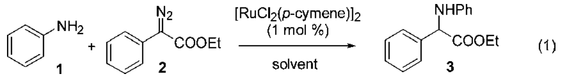
N−H and S−H insertion reactions with diazoketones. Herein, we show that the commerically available $[RuCl_2(p\text{-cymene})]_2$[6] is an efficient catalyst for inter- and intramolecular carbenoid N−H insertion reactions with diazocarbonyl compounds, and that prolines can be obtained from $[RuCl_2(p\text{-cymene})]_2$ catalyzed intramolecular carbenoid N−H insertion reactions with high diastereoselectivities.

We evaluated a number of Ru complexes for their ability to catalyze carbenoid N−H insertion reaction between aniline **1** (0.2 mmol) and ethyl phenyldiazoacetate **2** (0.2 mmol). The insertion reaction was effectively catalyzed by $[RuCl_2(p\text{-cymene})]_2$ (1 mol %) to afford ethyl 2-(phenylamino)-2-phenylacetate **3** in 98% yield within 10 min and by $RuCl_2(p\text{-cymene})PPh_3$ to give the same product in 97% yield in 5 h. The dimeric coupling product, 2,3-diphenyldiethyl ester, was not detected in any of the cases examined. Under the same conditions, PPh_3 alone and [Ru(Por)CO] (Por = TMP, 2,6-Cl_2TPP) individually showed no catalytic activities, and only the starting material could be recovered (see the Supporting Information). We found that reaction 1 was essentially insensitive to air, moisture and the solvent used, as similar product yields were found when the reaction was conducted in different organic solvents, under an atmosphere of argon (anhydrous conditions) or open to the atmosphere (Table 1). No reaction was observed when water was used as the solvent (Table 1, entry 6); presumably, this is due to the insolubility and instability of the ruthenium catalyst and diazo compound in aqueous medium.[7] The reactions of different diazo compounds with aniline were also investigated (Table 2). The donor/acceptor-substituted carbenoid derived from ethyl phenyldiazoacetate afforded the product in 98% yield in 10 min, the less reactive acceptor-substituted carbenoid derived from ethyl diazoacetate gave the product in 90% yield in 2 h. The reaction of the carbenoid derived from ethyl methyldiazoacetate with aniline gave the product in only 50% yield.[8]

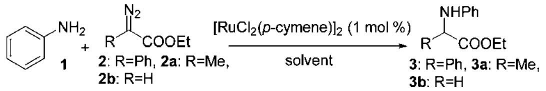
Table 1. Solvent Effects for $[RuCl_2(p\text{-cymene})]_2$-Catalyzed Intermolecular Carbenoid N−H Insertion Reactions



		under argon		open to the atmosphere	
entry[a]	solvent	time (min)	yield[b] (%)	time (min)	yield[b] (%)
1	toluene	30	94	15	93
2	$ClCH_2CH_2Cl$	15	97	15	95
3	MeCN	10	96	15	94
4	THF	15	97	15	96
5	CH_2Cl_2	10	98	10	98
6	H_2O	24 h	*e*		

[a] Reaction conditions: **1** (0.2 mmol) and **2** (0.2 mmol) were stirred with 1 mol % $[RuCl_2(p\text{-cymene})]_2$ in CH_2Cl_2 (4 mL) at room temperature. [b] Isolated yield. [e] No detectable reaction.

Table 2. $[RuCl_2(p\text{-cymene})]_2$-Catalyzed Carbenoid N−H Insertion Reaction of Aniline with Different Diazo Compounds



entry[a]	R	solvent	time	yield[b] (%)
1[c]	Ph	CH_2Cl_2	10 min	98
2	Me	CH_2Cl_2	6 h	50
3	H	CH_2Cl_2	2 h	90

[a] Reaction conditions: **1** (0.2 mmol) and **2**/**2a**/**2b** (0.2 mmol) were stirred with 1 mol % catalyst in the solvent (4 mL) under reflux an atmosphere of argon. [b] Isolated yield. [c] At room temperature.

$[RuCl_2(p\text{-cymene})]_2$ was found to be the most effective catalyst. Consequently, we investigated its ability to catalyze the reactions between ethyl phenyldiazoacetate and a selection of anilines and amines (Table 3, reaction 2, entries 1−33; Table S2 in the Supporting Information, entries 2−20) and amides (Table 3, entries 34−36). The corresponding products were obtained in up to 99% yield. In general, the reactions with alkyl amines required a longer reaction time and higher temperature than analogous reactions with aryl amines and amides. This apparently correlates to the pKa (DMSO) values, which are in the order: alkyl amines (pK_a ~44)>arylamines (pK_a 30−20)>/~amides (pK_a ~23).[9] A screening of the solvents has been performed; we found that the less reactive alkyl amines gave the highest product yields in MeCN while no reaction for those alkyl amines were found in CH_2Cl_2. The time for the completion of reaction 2 varied from 15 min in the case of *p*-OMe aniline to <1 min in the case of *p*-NO_2 aniline at a high catalyst loading of 5.0 mol % of $[RuCl_2(p\text{-cymene})]_2$ and from 30 min in the case of *p*-OMe aniline to 2 min in the case of *p*-NO_2 aniline at a catalytic loading of 1.0 mol %. At a low catalyst loading of 0.2 mol % of $[RuCl_2(p\text{-cymene})]_2$, the time for the completion of reaction 2 varied from 6.5 h in the case of *p*-OMe aniline to 5 min in the case of *p*-NO_2 aniline (Table S3 in the Supporting Information), consistent with the observation that the pK_a value of N−H moiety is an important factor affecting the reaction.

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(5) Zotto, A. D.; Baratta, W.; Rigo, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3079.

(6) Choi, M.-K.; Yu, W.-Y.; Che, C.-M. *Org. Lett.* **2005**, *7*, 1081.

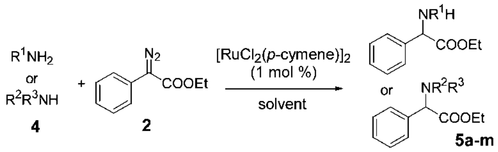
(7) For catalysts that work in water, see: (a) Candeias, N. R.; Gois, P. M. P.; Afonso, C. A. M. *J. Org. Chem.* **2006**, *71*, 5489. (b) Sutoh, T.; Kondo, A.; Musashi, J. *Tetrahedron* **2004**, *60*, 5453. (c) Estevan, F.; Lloret. J.; Sanau, M.; Ubeda, A. *Organometallics* **2006**, *25*, 4977. (d) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2002**, *4*, 4531.

(8) For the literatures on the reactivity of different carbenoids, see: (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (b) Davies, H. M. L.; Nikolai, J. *Org. Biomol. Chem.* **2005**, *3*, 4176.

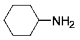
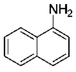
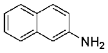
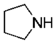
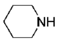
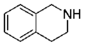
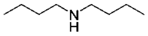
(9) http://www.chem.wisc.edu/areas/reich/pkatable,

(10) For examples of rhodium-catalyzed intramolecular carbenoid N-H insertion, see: (a) Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223. (b) Garcia, C. F.; McKervey, M. A.; Ye, T. *Chem. Commun.* **1996**, *12*, 1465.

Table 3. $[RuCl_2(p\text{-cymene})]_2$-Catalyzed Intermolecular Carbenoid N−H Insertion Reactions with Amines and Amides



(2)

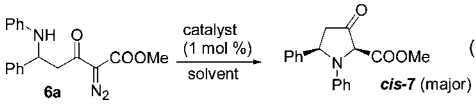
entry[a]	4	time (min)	yield[b] (%)
1 -24	anilines [c]	<5–30	90-99
25[d]	$BnNH_2$	7 h	54
26[d]		7 h	52
27		<10	99
28		<10	91
29[d]	BnNHBn	6 h	88
30[d]		11 h	81
31[d]		7 h	85
32[d]	 **4l**	6 h	70
33[d]	 **4m**	6 h	91
34	$TsNH_2$	<15	92
35	$PhCONH_2$	<15	96
36	$BocNH_2$	<10	99

[a] Reaction conditions: **4** (0.2 mmol) and **2** (0.2 mmol) were stirred with 1 mol % catalyst in CH_2Cl_2 (4 mL) at room temperature. [b] Isolated yield based on 100% conversion. [c] See Table S3 in Supporting Information. [d] Reaction performed in MeCN (1 mL) under reflux.

An elegant application of intramolecular N−H insertion[10] is Davis'[11a, c] rhodium-catalyzed method for the synthesis of highly functionalized pyrrolidines. Even though a number of structural variations have been achieved, one drawback on the rhodium-catalyzed reactions was the moderate diastereocontrol of the process. Therefore, we decided to explore if ruthenium-catalyzed reactions could improve the selectivity. In this work, we studied the catalytic activity of $[RuCl_2(p\text{-cymene})]_2$ toward intramolecular carbenoid N−H insertion. Under similar reaction conditions, we treated diazo compound **6a**[12] with a selection of ruthenium catalysts. We quantified the amount of substituted proline (3-carbonyl-1,5-diphenylpyrrolidine-2-carboxylic acid methyl ester **7**) formed (reaction 3) and examined the cis/trans selectivity (Table 4).

All the Ru catalysts depicted in Table 4, $[RuCl_2(p\text{-cymene})]_2$, $RuCl_3{\cdot}nH_2O$, $[Ru(CO)_3Cl_2]_2$, $[Ru(2,6\text{-}Cl_2TPP)CO]$, and [Ru(TMP)CO], catalyzed the intramolecular carbenoid N−H insertion to give the proline product (cis major) in a yield of 94%, 93%, 86%, 85%, and 86%, respectively (Table 4, entries 1−6). Analogous to the results obtained for the intermolecular carbenoid N−H insertions, $[RuCl_2(p\text{-cymene})]_2$ gave the highest product yield and also *the highest cis/trans ratio, 134:1, when MeOH was used as the solvent* (Table 4, entry 1). No competitive O−H insertion was observed with MeOH. The diastereoselectivity given by $[RuCl_2(p\text{-cymene})]_2$ is higher than that of 1.5:1 and 6:1 catalyzed by $Rh_2(OAc)_4$ for similar reactions documented in the literature (see data given in reference 11). $RuCl_3{\cdot}nH_2O$ and $[Ru(2,6\text{-}Cl_2TPP)CO]$ catalyzed reaction 3 to give **7** with cis/trans ratios of 7:1 and 2:1, respectively (Table 4, entries 4 and 6). Immediately after completion of the N−H carbenoid insertions (as determined by ^1H NMR analysis), the ketone moieties were reduced by a direct addition of $NaBH_4$ to afford the corresponding substituted prolines **8** (Table 5). Only one isomer of **8** was obtained after this reduction step, which was suggested to adopt a cis−cis configuration by its NOE spectrum. The cis−cis configuration of **8g** was confirmed by X-ray crystallographic analysis (see the Supporting Information).

Table 4. Ru Complex-Catalyzed Intramolecular Carbenoid N−H Insertion Reactions



(3)

entry[a]	catalyst	solvent	time (h)	cis/trans[b]	yield[c] (%)
1[d]	$[RuCl_2(p\text{-cymene})]_2$	MeOH	5	134:1	94
2	$[RuCl_2(p\text{-cymene})]_2$	THF	6	45:1	93
3	$[RuCl_2(p\text{-cymene})]_2$	CH_2Cl_2	6	6:1	92
4	$RuCl_3{\cdot}3H_2O$	THF	6	7:1	93
5[d]	$[Ru(CO)_3Cl_2]_2$	toluene	4	13:1	86
6[d]	$[Ru(2,6\text{-}Cl_2TPP)CO]$	toluene	4	2:1	85
7[d]	[Ru(TMP)CO]	toluene	8	2:1	86

[a] Reaction conditions: **6a** (0.2 mmol) were stirred with 1 mol % catalyst in solvent (2 mL) at room temperature. [b] Determined by ^1H NMR. [c] Isolated yield based on 100% conversion. [d] Reaction was heated at 80 °C.

A number of substrates, including both aryl (10 examples) and aliphatic (3 examples) ones, were tested for intramolecular carbenoid N−H insertions using $[RuCl_2(p\text{-cymene})]_2$ as the catalyst. The results are shown in Tables 5 and 6. Complete substrate conversion was found in all the cases examined and the products were obtained in 85−95% yields and in a cis−cis configuration. For reaction 5 (Table 6), the Boc-protected group could be removed, after the reduction step, by adding trifluoroacetic acid (TFA) to give **10**, the latter is a core structure commonly employed in the synthesis of natural products.[13] The configuration of **10** remains to be cis−cis for R to be aryl or aliphatic group.

The stereochemistry of **7** can be rationalized with reference to the mechanism proposed by Doyle,[2a,14] Taber,[15] and

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(11) (a) Davis, F. A.; Fang, T.; Goswami, R. *Org. Lett.* **2002**, *4*, 1599. (b) Davis, F. A.; Yang, B.; Deng, J. *J. Org. Chem.* **2003**, *68*, 5147. (c) Davis, F. A.; Deng, J. *Tetrahedron* **2004**, *60*, 5111.

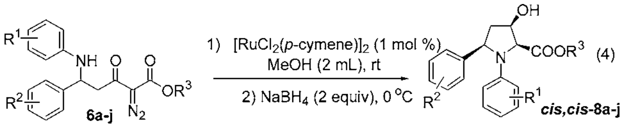
(12) Doyle, M. P.; Kundu, K.; Russell, A. E. *Org. Lett.* **2005**, *7*, 5171.

(13) (a) Agami, C.; Platzer, N.; Puchot, C.; Sevestre, H. *Tetrahedron* **1987**, *43*, 1091. (b) Barrett, A. G. M.; Pilipauskas, D. *J. Org. Chem.* **1990**, *55*, 5194. (c) Mulzer, J.; Meier, A.; Buschmann, J.; Luger, P. *J. Org. Chem.* **1996**, *61*, 566.

(14) Doyle, M. P.; Westrum, L. J.; Wolthuis, N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958.

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

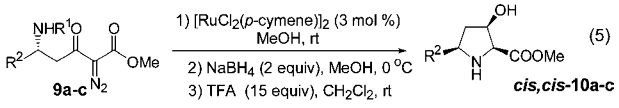
Table 5. [$RuCl_2$(*p*-cymene)$]_2$-Catalyzed Intramolecular Carbenoid N−H Insertion Reactions for the Stereoselective Synthesis of Phenyl-Substituted Prolines



entry^{a}	product	R^{1}	R^{2}	R^{3}	time^{b} (h)	yield^{c} (%)
1	**8a**	H	H	Me	4.5	89
2	**8b**	H	H	Et	2.5	85
3	**8c**	H	*o*-Cl	Et	2	95
4	**8d**	H	*m*-Cl	Et	2	92
5	**8e**	H	*p*-Cl	Et	2	94
6	**8f**	*p*-Cl	H	Et	2	94
7	**8g**	*p*-Br	H	Et	3	86
8	**8h**	H	*p*-Me	Et	4	93
9	**8i**	*p*-OMe	H	Et	5	90
10	**8j**	H	*p*-OMe	Et	6	88
11^{d}	**8a**	H	H	Me	6	87

[a] Reaction conditions: **6** (0.2 mmol) was stirred with 1 mol % catalyst in MeOH (2 mL). $NaBH_4$ was added to the system after the diazo compound was completely consumed. [b] The duration of the first step (i.e., the carbenoid N−H insertion). [c] Isolated yield. [d] Reaction opened to the atmosphere.

Table 6. [$RuCl_2$(*p*-cymene)$]_2$-Catalyzed Intramolecular Carbenoid N−H Insertion Reactions for the Stereoselective Synthesis of Aliphatic and Phenyl-Substituted Prolines



entry^{a}	product	R^{1}	R^{2}	time (h)	yield^{b} (%)
1	**10a**	Boc	Ph	2	87
2	**10b**	Boc	*t*-Bu	2.5	85
3^{c}	**10c**	Boc	cyclohexyl	2.5	84

[a] Reaction conditions: **9** (0.2 mmol) was stirred with 3 mol % catalyst in MeOH. $NaBH_4$ was added to the reaction mixture after the diazo compound was completely consumed. [b] Isolated yield. [c] Reaction performed in CH_2Cl_2.

Davis.[11b] The carbomethoxy group at C-2 is forced into the axial position by the metal (Figure 1). This is followed by either a very fast or concerted proton transfer, leading to the formation of product in a cis configuration. As depicted in Table 4, lower cis/trans ratios were found when [Ru(CO)$_3Cl_2]_2$ or [Ru(2,6-Cl_2TPP)CO] was used as the catalyst, and the reactions catalyzed by these two ruthenium complexes were observed only at temperature ≥80 °C.

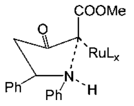


Figure 1. Proposed structure of the reactive intermediate in the Ru-catalyzed intramolecular carbenoid N−H insertion reaction.

The pure cis isomer of 1-(4-bromophenyl)-5-phenylpyrrolidin-3-one ethyl ester that was obtained by recrystallization interconverted gradually into the trans isomer in solution under reflux. This change in stereochemistry is attributed to an enolization, leading to the interconversion of the cis to trans isomer in the reaction medium, which is consistent with the results previously reported by Davis and co-workers.[11] In accordance with this finding, for the [Ru(CO)$_3Cl_2]_2$-catalyzed intramolecular N−H insertion reaction 3 at 80 °C, the cis/trans ratio of product **7** decreased from 24:1 to 13:1 and further to 2:1 by increasing the reaction time from 2 to 4 h and then 30 h (Table S4 in the Supporting Information).

The catalytic processes described in the present work can be scaled up to gram scale with little effect on the overall product yield or stereochemistry. α-(Phenylamino)benzeneacetic acid ethyl ester was obtained in 98% yield by reacting aniline (1.5 g, 8.0 mmol) with ethyl phenyldiazoacetate in the presence of [$RuCl_2$(*p*-cymene)$]_2$ (0.1 mol %) in CH_2Cl_2 for 4.5 h. The phenyl-substituted 3-hydroxy-1,5-diphenylpyrrolidine-2-carboxylic acid methyl ester **8a** was obtained in 91% yield by treating the diazocarbonyl compound **6a** (1.0 g, 3.1 mmol) with [$RuCl_2$(*p*-cymene)$]_2$ (1.0 mol %) in MeOH for 5.5 h.

In conclusion, we have established a convenient and efficient protocol for carbenoid N−H insertion reactions using the commerically available ruthenium catalyst [$RuCl_2$(*p*-cymene)$]_2$. The catalysis is tolerant toward oxygen and moisture in the atmosphere. This new protocol offers direct access to prolines with high stereoselectivities by one pot intramolecular carbenoid N−H insertion reactions.

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

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