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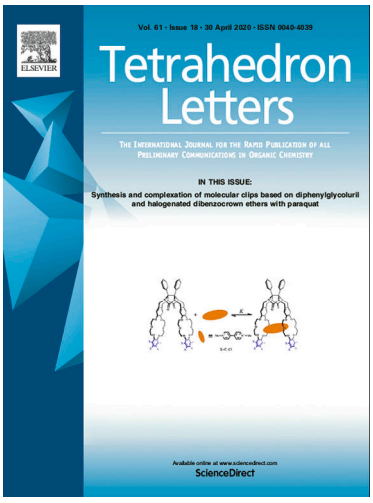


# Synthesis of γ-lactams *via* Ru(II)–Pheox-catalyzed regioselective intramolecular $Csp^3$ –H insertion of diazoacetamides

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PII: S0040-4039(20)30743-7
DOI: https://doi.org/10.1016/j.tetlet.2020.152276
Reference: TETL 152276

To appear in: *Tetrahedron Letters*

Received Date: 24 May 2020
Revised Date: 17 July 2020
Accepted Date: 20 July 2020

Please cite this article as: Fujii, T., Thu, H.D.T., Iwasa, S., Synthesis of γ-lactams *via* Ru(II)–Pheox-catalyzed regioselective intramolecular $Csp^3$ –H insertion of diazoacetamides, *Tetrahedron Letters* (2020), doi: https://doi.org/10.1016/j.tetlet.2020.152276

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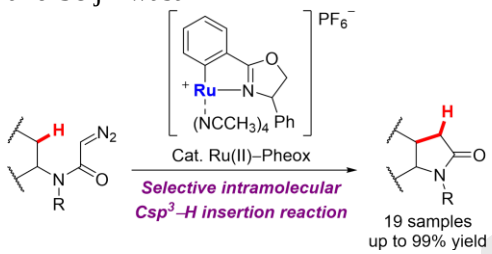

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# Synthesis of γ-lactams *via* Ru(II)–Pheox-catalyzed regioselective intramolecular $Csp^3$–H insertion of diazoacetamides

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ARTICLE INFO

*Article history:*
Received
Received in revised form
Accepted
Available online

*Keywords:*
C–H Insertion
γ-Lactam
Ruthenium
Carbene
Diazoacetamide

ABSTRACT

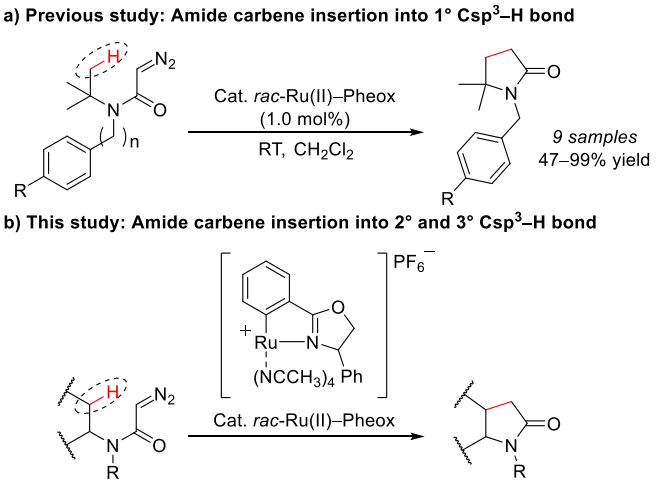
Herein, γ-lactam derivatives are obtained in high yield *via* highly regioselective intramolecular $Csp^3$–H insertion reactions of α-diazoacetamides catalyzed by a *rac*-Ru(II)–Pheox complex. The catalytic system is applicable to a wide range of diazoacetamides under mild conditions to produce the corresponding γ-lactams.



γ-Lactam ring is frequently an important building block of numerous biologically active compounds, including natural products and pharmaceuticals [1]. Although its synthetic approaches, such as the cyclization of amino acids [2], intramolecular *N*-alkylation [3], and formal [3+2] annulations [4], have been commonly used for more than a hundred years, transition-metal-catalyzed reactions have recently offered opportunities to access this important heterocyclic motif [5].

Among the reported metal-catalyzed methods, intramolecular carbene C–H insertion reactions of diazoacetamides have attracted significant research attention for the preparation of lactam derivatives [6]. However, this methodology has not been extensively investigated for cyclization, because of the difficulty in controlling the chemo- and regioselectivities. Moreover, mono-substituted diazoacetamides are less commonly used than di-substituted diazoacetamides, diazoesters, and diazoketones. The extent of side reactions is determined by the catalyst and the nitrogen-protecting group. Although several nitrogen-protecting groups such as *N*-*tert*-butyl [7], *N*-benzyl [8], *N*-bis(trimethylsilyl)-methyl [9], and *N*-(2,3,4,5,6-pentafluorobenzyloxy) [10] have been proposed, effective catalysts for regioselective intramolecular carbene C–H insertion reactions have not been widely investigated [11]. Therefore, for highly selective intramolecular C–H insertion reactions of diazoacetamides, new metal catalysts that present reactivity profiles complimentary to those of existing catalyst families are required.

In our previous studies, we have demonstrated that Ru(II)–Pheox complexes are highly efficient catalysts for carbene transfer reactions, such as asymmetric cyclopropanation, and N–H and Si–H insertion reactions [12]. Recently, we successfully reported a highly regio- and enantioselective intramolecular carbene insertion reaction into a primary $Csp^3$–H bond of a *tert*-butyl group (Scheme 1a) and an inactive aromatic ring of a benzyl group (Büchner ring expansion) to produce the corresponding γ-lactam derivatives with diazoacetamides [12g,h]. Herein, we report that Ru(II)–




**Scheme 1.** Ru(II)–Pheox-catalyzed regioselective $Csp^3$–H insertion reaction.

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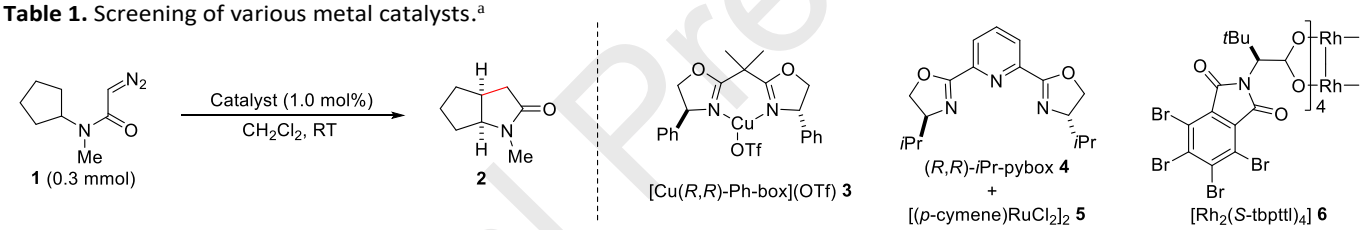
carbon bond, catalyzes the intramolecular carbene insertion reaction into the $Csp^3$–H bonds of diazoacetamides to produce a broad range of γ-lactam derivatives in good to high yield under mild conditions (Scheme 1b).

Initially, we tested the intramolecular insertion reaction of *N*-cyclopentyl-2-diazo-*N*-methylacetamide **1**, as an amide carbene precursor, under our previously described reaction condition for the ruthenium-catalyzed functionalization of primary C–H bonds of diazoacetamides (1.0 mol% of cat. Ru(II)–Pheox, $CH_2Cl_2$, room temperature) [12g]. Unexpectedly, the reaction catalyzed by Ru(II)–Pheox proceeded rapidly to furnish **2** in 94% yield under the mild condition (Table 1, entry 1). To further investigate the activity and selectivity of other metals that are well-known catalysts for carbene transfer reactions, subsequently, we applied copper(I), ruthenium(II), and dirhodium(II) under the reaction conditions (Table 1, entries 2–7). Consequently, the Ru(II)–Pheox catalyst exhibited the optimal chemoselectivity for the selective formation of the five-membered lactam ring among all the considered metal catalysts. Copper catalysts such as CuI and [Cu(*R*,*R*)-Ph-box](OTf) [13] resulted in low yield (Table 1, entries 2 and 5), whereas $Rh_2(OAc)_4$ and [$Rh_2$(*S*-tbpttl)$_4$] [14] generated the desired product in moderate yields of 50 and 42%, respectively (Table 1, entries 4 and 7). In contrast to the copper and rhodium catalysts, other ruthenium complexes [15] as catalysts (Table 1, entries 3 and 6) did not afford lactam **2**. Although asymmetric catalyst **3** and **6** showed 9 and 37% ee of **2** respectively (Table 1, catalyst was conducted in order to find a suitable catalytic system for the general synthesis of *rac*-γ-lactams.

To further examine the influence of other factors, reaction optimization studies were performed using a range of solvents, temperatures, and Ru(II)–Pheox catalyst loadings (Table 2). The solvent screening indicated that dichloromethane produced a higher yield than acetone, THF, diethyl ether, and toluene (Table 2, entries 1–5). The reaction temperatures were also examined, and the yield decreased leaving the unreacted substrate when the reactions were cooled to below room temperature (Table 2, entries 6 and 7). It was found that heat energy at room temperature is required for this $Csp^3$–H insertion reaction to fully proceed. Lowering the catalyst loading amount from 1.0 to 0.5 mol% caused a significant decrease in the yield, whereas the increased loading (0.5–2.0 mol%) of Ru(II)–Pheox afforded the highest yield **2** at 1.0 mol% of the catalyst (Table 2, entries 8 and 9).

To explore the scope of this reaction, a series of amide *N*-substituents were subsequently investigated under the optimized condition. As demonstrated by the data in Table 3, all *N*-cyclopentyl diazoacetamides could be efficiently converted to the corresponding γ-lactams in good to high yields. Interestingly, even when the *N*-cyclopentyl diazoacetamides possessed alkyl groups, including secondary and tertiary $Csp^3$–H bonds, insertion of the reactive carbene into the C–H bond of the cyclopentyl group proceeded preferentially (Table 3, **8a–c**). When **7b** was used as the

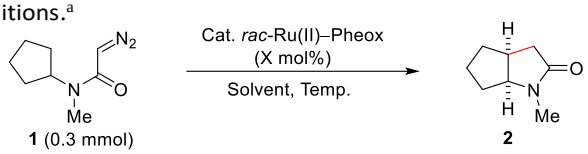
**Table 1.** Screening of various metal catalysts.[a]




| Entry | Catalyst | Time [min] | Yield of **2** [%] |
|---|---|---|---|
| 1 | *rac*-Ru(II)–Pheox | 10 | 94 |
| 2 | CuI | 10 | 25 |
| 3 | [(benzene)$RuCl_2$]$_2$ | 10 | 0 |
| 4 | $Rh_2(OAc)_4$ | 120 | 50 |
| 5 | [Cu(*R*,*R*)-Ph-box)](OTf) **3** | 90 | 19 |
| 6 | (*R*,*R*)-*i*Pr-pybox **4** + [(*p*-cymene)$RuCl_2$]$_2$ **5** | 10 | 0 |
| 7 | [$Rh_2$(*S*-tbpttl)$_4$] **6** | 10 | 42 |

[a] General conditions: A solution of *N*-cyclopentyl-2-diazo-*N*-methylacetamide **1** in $CH_2Cl_2$ was added dropwise to a solution of the catalyst (1.0 mol%) in $CH_2Cl_2$ at RT. [b] Isolated yield.

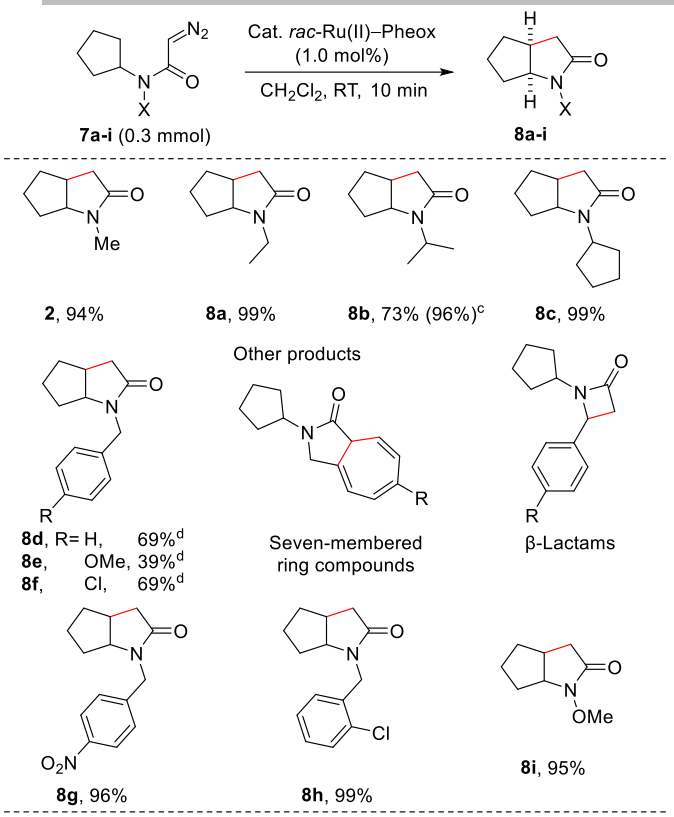
**Table 2.** Optimization of reaction conditions.[a]




| Entry | Loading [X mol%] | Solvent | Temp. [°C] | Time [min] | Yield of **2** [%] |
|---|---|---|---|---|---|
| 1 | 1.0 | $CH_2Cl_2$ | RT | 10 | 94 |
| 2 | 1.0 | Acetone | RT | 10 | 24 |
| 3 | 1.0 | THF | RT | 10 | 49 |
| 4 | 1.0 | $Et_2O$ | RT | 120 | 65 |
| 5 | 1.0 | Toluene | RT | 90 | 12 |
| 6 | 1.0 | $CH_2Cl_2$ | 0 | 10 | 85 |
| 7 | 1.0 | $CH_2Cl_2$ | –10 | 2 days | 17 |
| 8 | 0.5 | $CH_2Cl_2$ | RT | 10 | 60 |
| 9 | 2.0 | $CH_2Cl_2$ | RT | 1 | 96 |

[a] General conditions: A solution of *N*-cyclopentyl-2-diazo-*N*-methylacetamide **1** in each of the solvents was added dropwise to a solution of the Ru(II)–Pheox in each of the solvents. [b] Isolated yield.

**Tab**

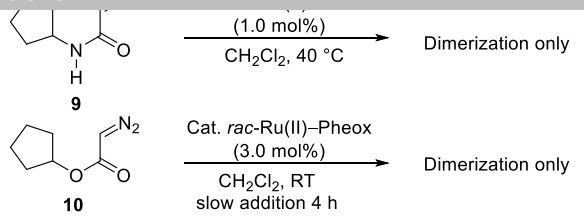



[a] General conditions: Each solution of the diazoacetamides in $CH_2Cl_2$ was added dropwise to a solution of Ru(II)–Pheox in $CH_2Cl_2$.[b] Isolated yield.
[c] Ru(II)–Pheox (3.0 mol%) was used.
[d] The ratios of the products from the crude NMR spectra. (γ-lactams:seven-membered ring compounds:β-lactams), **8d**; (71:16:13), **8e**; (40:60:0), **8f**; (72:21:7).

substrate, increasing the catalyst loading from 1.0 to 3.0 mol% resulted in complete conversion and produced **8b** in 96% yield. When **7d**, **7e**, and **7f** possessing a benzyl group were used as substrates, intramolecular Büchner ring expansions [12h,16] and insertion reactions into the benzylic ring of C–H bonds [17] also occurred. The ratios of the compounds were determined by the integration of the characteristic $^1$H-nuclear magnetic resonance (NMR) absorptions from the spectra of the crude reaction mixtures. Compared to **7f** and **7d**, **7e**, having an more electron-rich benzyl group, promoted the production of the seven-membered ring as the sole side reaction, and the γ-lactam **8e** was obtained in 39% yield. The regioselectivity of the carbene transfer reaction for **7g**, which has a nitro group as the strong electron-withdrawing group, dramatically increased, producing only the desired γ-lactam **8g** in 96% yield. In addition, the *ortho*-chloro-substituted benzyl group was found to realize the highest regioselectivity of the reaction, and **8h** was obtained in 99% yield. In addition to the alkyl and benzyl groups, *N*-alkoxy diazoacetamide **7i** was selectively converted to the corresponding γ-lactam **8i** in 95% yield.

Furthermore, the effects of a secondary amide and an ester were tested, as depicted in Scheme 2. However, *N*-cyclopentyl diazoacetamide **9** and cyclopentyl diazoacetate **10** [18] generated only dimers of the carbene. These results suggested that the *N*-substituents of the amides are necessary to hold the active site of the carbenoids close to the intramolecular C–H bonds.

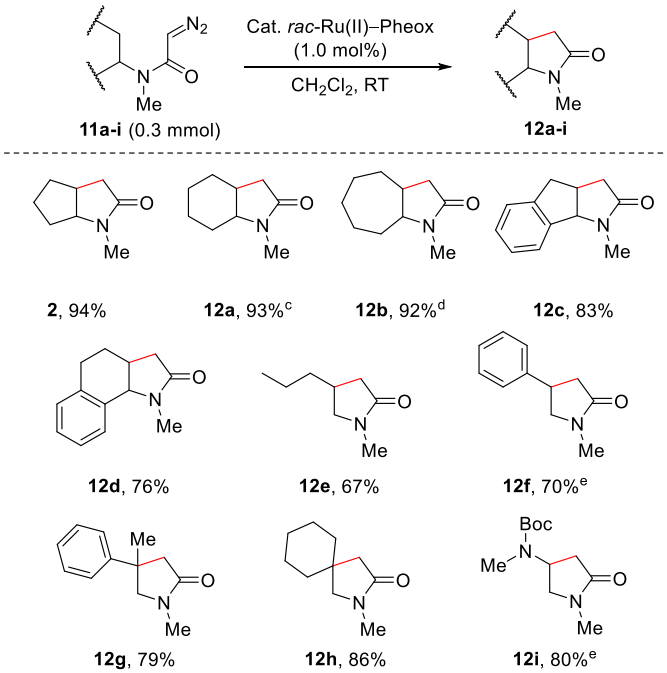
Subsequently, the scope of various *N*-methyl diazoacetamides was also investigated (Table 4.) The




**Scheme 2.** Reaction of a secondary diazoacetamide and a diazoester.

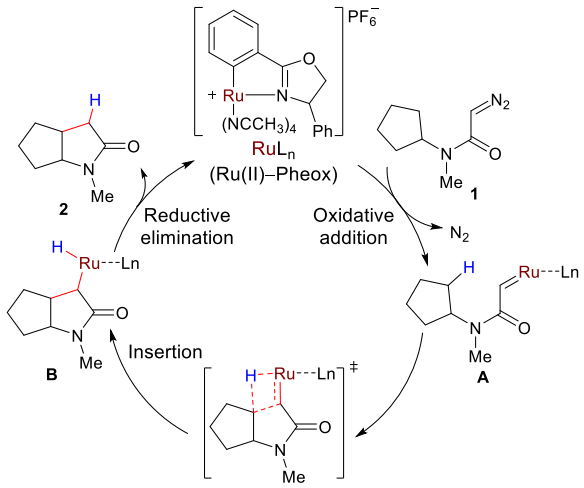
reactions of diazoacetamides, **11a** and **11b**, presented excellent regioselectivities with cyclohexyl and cycloheptyl groups, whereas these *trans*-isomers were also formed with low diastereoselectivities of *trans*:*cis* = 33:67 (**12a**) and 27:73 (**12b**), respectively. When cyclopentyl and cyclohexyl groups containing an aromatic ring were used as the reactive sites, the carbene insertion reactions into the $ArCsp^2$–H bonds and Büchner ring expansion reaction did not occur under the optimized conditions. Therefore, these substrates were converted to *cis*-γ-lactams, **12c** and **12d** in high yield. The substrates with a long carbon chain resulted in good yield for **12e**. Although the reaction of **11f** was ineffective under the optimized conditions, it proceeded rapidly in the presence of 3.0 mol% of the Ru(II)–Pheox catalyst at 40 °C to produce **12f** in a good yield. In contrast, a similar substrate, **11g**, was smoothly converted to **12g** in 79% yield at room temperature. These results suggested that a tertiary C–H bond is more reactive than a secondary one. In addition, spiro-fused γ-lactam **12h** was also obtained in a high yield *via* the selective carbene insertion reaction. The $Csp^3$–H bond adjacent to a Boc-protected nitrogen bond was also transformed into the corresponding C–C bond to produce γ-lactam **12i**.

**Table 4.** Substrate scope.[a,b]




[a] General conditions: Each solution of the diazoacetamides in $CH_2Cl_2$ was added dropwise to a solution of Ru(II)–Pheox in $CH_2Cl_2$. [b] Isolated yield.
[c] *trans*:*cis* = 33:67. [d] *trans*:*cis* = 27:73.
[e] Heated in 40 °C with 3.0 mol% of Ru(II)–Pheox.

process might occur in an asynchronous manner, and a plausible reaction mechanism is proposed in Scheme 3. Initially, the diazoacetamide **1** is reduced by the Ru(II)–Pheox complex to form a ruthenium carbene complex, **A** [20]. Subsequently, a C–H bond reacts with the reactive site of the intermediate, **A**, resulting in the formation of **B**. Finally, the reductive elimination of ruthenium produces **2** with the concurrent regeneration of the Ru(II)–Pheox catalyst.




**Scheme 3.** Proposed reaction mechanism.

In summary, we developed an efficient method for the synthesis of γ-lactams by the intramolecular $Csp^3$–H insertion reaction catalyzed by a Ru(II)–Pheox complex. Various γ-lactams were successfully synthesized in moderate to high yield under mild conditions. The Ru(II)–Pheox catalyst presented higher chemo- and regioselectivities for the synthesis of the γ-lactam derivatives than the conventional metal catalysts. The development of other transformations and asymmetric versions is currently being investigated in our laboratory.

This work was supported by a Grant-in-Aid for Scientific Research (B) (no.26288087) and Ikeda Bussan Co. Ltd..

## Supplementary Material

Supplementary data to this article can be found online at

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