

Nucleophilic Addition of Amines to Ruthenium Carbenes: *ortho*-(Alkynyloxy)benzylamine Cyclizations towards 1,3-Benzoxazines

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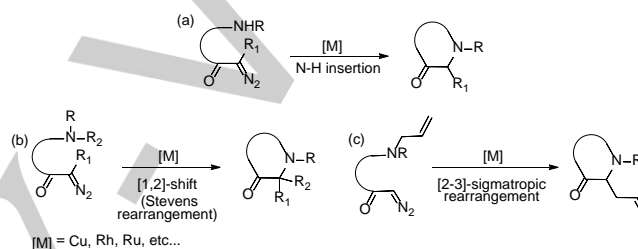
Dedication ((optional))

Abstract: A new ruthenium-catalyzed cyclization of *ortho*-(alkynyloxy)benzylamines to dihydro-1,3-benzoxazines is reported. The cyclization is thought to take place via the vinyl ruthenium carbene intermediates that are easily formed from Cp*RuCl(cod) and N₂CHSiMe₃. The mild reaction conditions and the efficiency of the procedure allow the easy preparation of a broad range of new 2-vinyl-2-substituted 1,3-benzoxazine derivatives. Rearrangement of an internal C_{sp} atom in the starting material into a tetrasubstituted C_{sp3} atom in the final 1,3-benzoxazine is highly remarkable.

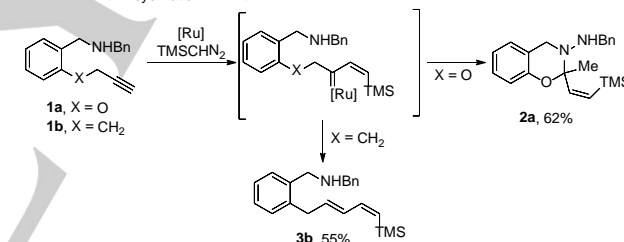
The in situ generation of catalytically active metal carbenes from diazoalkanes (e.g., copper, rhodium and ruthenium) has contributed to the recent development of synthetically useful transformations catalyzed by these intermediates.^[1] Cyclopropanation reactions, which involve interaction of the generated metal carbenes with unsaturated units (alkenes, alkynes, enynes, etc.), and X–H bond insertions (X = C, O, S, N, Si, etc.) are characteristic transformations associated with these metal carbenes.^[2] Recently, efficient syntheses of azaheterocycles by direct Rh-, Cu- and Ru-catalyzed intramolecular addition of amines to metal carbenes have been reported (Scheme 1). Metal carbenoid N–H insertion reactions (eq a) and [1,2]-rearrangements (eq b) or [2,3]-sigmatropic rearrangements of cyclic ammonium ylides (eq c) afforded a broad range of azaheterocycles.^[3] Nevertheless, the major drawback with these methods concerns the often troublesome installation of an activated diazoalkane (e.g., conjugated with a carbonyl group) within the starting material. A simple and mild generation of catalytic vinylcarbene ruthenium intermediates was recently introduced by Dixneuf on using a combination of a ruthenium precatalyst, a commercial diazo compound and an alkyne.^[4] We recently reported carbocyclizations involving the insertion of vinyl ruthenium carbenes into C_{sp3}–H bonds^[5] and we have now envisioned a new entry to azaheterocycles by intramolecular nucleophilic addition of amines to these electrophilic ruthenium carbenes.^[6] To test our hypothesis, we began the study with the cyclization of alkynyloxyamine **1a** in the presence of the precatalyst Cp*RuCl(cod) and TMSCHN₂. To our surprise, six-membered 2,2-disubstituted 1,3-benzoxazine

2a was isolated in fairly good yield (Scheme 1).^[7] The crucial role of the oxygenated tether in this unprecedented rearrangement^[8] became evident when alkynylamine **1b** smoothly evolved to the conjugated diene **3**. To our knowledge, this is the first example of a nucleophilic addition of an amine to in situ-generated vinyl ruthenium carbenes.

Previous works: catalytic cyclizations on activated acyl metal carbenes



This work: catalytic cyclization on vinyl ruthenium carbenes



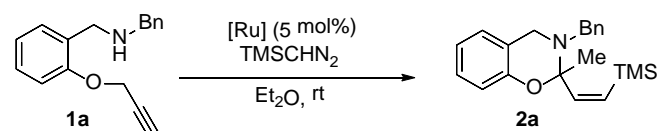
Scheme 1. Azacyclizations catalyzed by metal carbenes.

1,3-Benzoxazine derivatives often display a wide range of biological activities,^[9] undergo useful synthetic transformations^[10] and also polymerize by cationic ring-opening polymerization to form polybenzoxazines, which are thermosetting polymers that exhibit versatility in a wide range of applications.^[11] The remarkable and useful properties of these compounds means that their preparation is always of great interest,^[12] although procedures based on transition metal-catalyzed cyclizations remain scarce. Rh-catalyzed allylic rearrangement of 2-(allyloxy)benzylamines,^[13] Cu-catalyzed C–H bond oxidative activation^[14] and photooxidation of aminoalcohols with photoredox catalysts of Ir^[15] and Ru^[16] are the most remarkable contributions. Herein we report a new and efficient ruthenium-catalyzed cyclization of *ortho*-(alkynyloxy)benzylamines towards 1,3-benzoxazines under very mild conditions (Scheme 1). The reaction was optimized using *N*-benzyl-1-[2-(prop-2-yn-1-yloxy)phenyl]methanamine (**1a**) as the test substrate (Table 1). The reaction of **1a** with TMSCHN₂ in the presence of Cp*RuCl(cod) (5% mol) in Et₂O at rt gave the 1,3-benzoxazine **2a** in 62% yield (entry 1). The reaction was extremely sensitive to the electronic and steric nature of the ruthenium catalyst since starting material was totally recovered on using CpRuCl(cod)

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(entry 2). Besides, cationic $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ or in situ formation of a neutral ruthenium catalyst by treatment with Et_4NCl ^[17] dramatically affected either the course of the reaction or the catalytic activity giving very low yields of methylated starting material **1a'** (9%)^[3, 18] or benzoxazine **2a** (10%), respectively (entries 3 and 4). Curiously, an increase in the catalyst loading or the amount of TMSCHN_2 was not beneficial for the cyclization reaction, with the 1,3-benzoxazine **2a** isolated in slightly lower yields (entries 5 and 6). The nature of the solvent was crucial as other cyclic ethers such as dioxane or THF were tolerated but gave lower yields, whereas bulkier ethers and more polar protic or halogenated solvents were detrimental to the cyclization.^[18] Electronic variation on the diazoalkane dramatically affected the course of the reaction since α -aminoester **1a''**, derived from metal carbenoid N–H insertion reaction,^[3] was obtained when $\text{N}_2\text{CHCOOEt}$ was used (entry 7).^[18]

Table 1. Optimization of Ru-catalyzed cyclization of *N*-benzyl-1-[2-(prop-2-yn-1-yloxy)phenyl]methanamine **1a**.^[a]



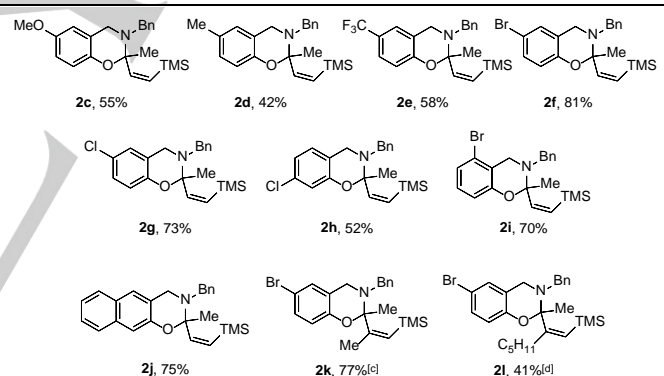
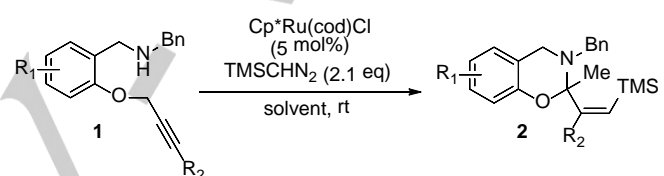
Entry	[Ru] catalyst	TMSCHN_2 (equiv)	Yield (%) ^[b]
1	$\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$	2.1	62
2	$\text{CpRu}(\text{cod})\text{Cl}$	2.1	—
3	$\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$	2.1	[c]
4	$\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6/\text{NEt}_4\text{Cl}$	2.1	10
5	$\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$	2.1	46 ^[d]
6	$\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$	3.0	50
7	$\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$... ^[f]	[g]

[a] Typical reaction conditions: [Ru] (5 mol%), **1a** (0.3 mmol), [**1a**] = 0.25 M, rt. [b] Yields of isolated products. [c] *N*-benzyl-*N*-methyl-1-[2-(prop-2-yn-1-yloxy)phenyl]methanamine (**1a'**) was obtained (9%). [d] $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$, (10 mol %). [e] Starting material recovered. [f] $\text{N}_2\text{CHCOOEt}$ (2.1 eq) was used. [g] Ethyl 2-(benzyl(2-(prop-2-yn-1-yloxy)benzyl)amino)acetate **1a''** was obtained in 51% yield.

Once the optimized conditions had been established, the scope and limitations of the cyclization reaction were explored starting with electronically distinct benzylamine derivatives (Table 2). Electron-withdrawing and electron-donating aryl substituents are tolerated since 1,3-benzoxazines **2c–f** were obtained in reasonably good yields. Thus, *para*-methoxy-, *para*-methyl-, *para*-trifluoromethyl- and even *para*-bromobenzylamine smoothly gave substituted 1,3-benzoxazines **2c–f**, with slightly better yields obtained for substrates bearing electron-poor substituents in the position *para* to the propargylic ether.

Interestingly, the functionalized 4-, 5- and 6-halo-substituted benzylamines could be efficiently converted into their corresponding halo-substituted 1,3-benzoxazines **2f–i** in fairly good yields. Further manipulation of the above aryl bromides and chlorides using Pd-catalyzed cross coupling reactions provide an easy entry to polysubstituted benzoxazines.^[19] Notably, cyclization of naphthylamine derivative **1j** smoothly gave naphthoxazine **2j** in very good yield. Gratifyingly, non-terminal benzylamine derivative **1k** also cyclized to give benzoxazine **2k** in very good yield,^[20] albeit with a longer reaction time compared to the terminal **2f** (60 h vs 6 h) and the need for a higher catalyst loading (10 mol%). Even a benzylamine with a long-chain substituted alkyne, i.e., **1l**, was able to cyclize to the corresponding 1,3-benzoxazine **2l**, albeit in low yield. In all cases the benzoxazines **2** were isolated with complete *Z* stereoselectivity for the silylated double bond.

Table 2. Ru-catalyzed cyclization of ortho-(alkynyloxy)benzylamines **1c–l** to 1,3-benzoxazines **2c–l**.^{[a], [b]}



[a] Typical reaction conditions: [Ru] (5 mol %), **1** (1 equiv), TMSCHN_2 (2.1 equiv), [**1**] = 0.25 M, rt. [b] Yields of the isolated products. [c] $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$, (10 mol %). [d] $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$, (10 mol %), dioxane as solvent, 65 °C.

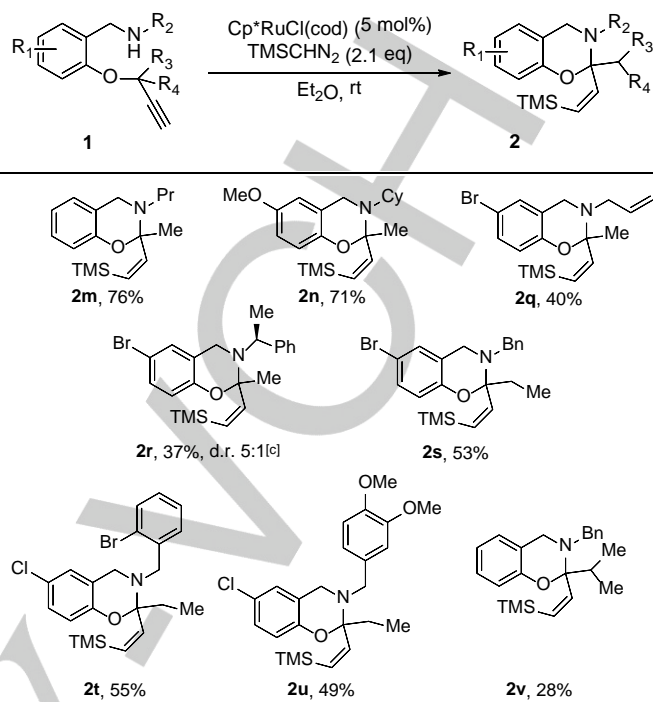
We proceeded to investigate the effect of the *N*- and propargylic substitutions on the course of the reaction (Table 3). Gratifyingly, the presence of primary and secondary alkyl substituents on the nitrogen of benzylamines **1**, e.g., cyclohexyl or propyl, allowed the corresponding 1,3-benzoxazines **2m** and **2n** to be obtained in very good yields.^[21] The chemoselectivity of the reaction was analyzed in the cyclization of *N*-allyl substituted benzylamine **1q**, from which 1,3-benzoxazine **2q** with an intact allyl group was isolated in moderate yield. Interestingly, this result indicates that polar nucleophile/electrophile interactions dominate the reactivity of the putative carbene intermediate. Finally, the diastereoselectivity of the cyclization was explored

with chiral benzylamine **1r**, which gave benzoxazine **2r** (5.1 dr ratio) in low yield.

Having established the broad scope of the methodology, we investigated propargylic substituted benzylamines **1s–v** (Table 3). Interestingly, the ethyl substituted 1,3-benzoxazines **2s–u** were the exclusive cyclized products in the Ru-catalyzed cyclization of the corresponding benzylamines **1s–u** bearing a methyl substituent in propargylic position ($R_3 = \text{Me}$, $R_4 = \text{H}$). Furthermore, the isopropyl substituted 1,3-benzoxazine **2v** was isolated from the reaction of the dimethylated substrate **1v** ($R_3, R_4 = \text{Me}$). These results clearly indicate that the propargylic carbon of the starting *ortho*-(alkynyloxy)benzylamines **1** becomes the alkyl substituent of the generated 2-vinyl-2-alkyl 1,3-benzoxazines **2**. This new rearrangement takes place starting from benzylamines bearing *ortho*-alkynyloxy substituents; however, when *ortho*-alkynylthio or *ortho*-alkynyltosylamide substituents were present in the starting benzylamine, the reaction did not give any cyclized products.^[22]

In an effort to gain further insights into the mechanism of the reaction, a deuterium labeling experiment was conducted. When the Ru-catalyzed cyclization of deuterated benzylamine **1f-d** ($R_2 = d$) was carried out under the optimized conditions, deuterium scrambling was not observed and the deuterium atom was located at the vinylic position of the corresponding benzoxazine **2f-d**.^[18]

The results obtained, including those of the labeling study and the cyclization of propargylic substituted benzylamines **2s–v**, strongly support the initial mechanistic hypothesis shown in Scheme 2.^[23] The reaction begins with the starting complex Cp*RuCl(cod), which easily loses its cod ligand in the presence of TMSCHN₂ and *ortho*-(alkynyloxy)benzylamine **1** to give the ruthenium carbene species **I**. Oxidative coupling to ruthenacyclobutene followed by ring opening would lead to the Ru vinyl carbene species **II**, in which the coordination of the pendant amine could disfavor the coordination of a second diazoalkane unit.^[24] The electrophilic Ru carbene could induce nucleophilic attack by the amine group to afford the zwitterionic intermediate **III**.²⁵ This intermediate is probably not formed when the nucleophilic character of the amine is diminished as in tosylamide **1o**. Ring strain of the cyclic intermediate **III**, which has a good leaving group (phenoxide), would facilitate ring opening to afford the enamine intermediate **IV**, with recovery of the catalytic Ru(II) species **I**. The reaction yields obtained for 1,3-benzoxazines (e.g., **2f** vs **2c**) seem to be consistent with the leaving capacity of the phenoxides in benzylamines **1**. In the absence of a phenoxide as a leaving group, the cyclization did not take place and intermediate **II** would evolve by β -elimination to afford the observed diene **3**. Finally, iminium formation from intermediate **IV** is trapped with the phenoxide to give the final 1,3-benzoxazine **2** with concomitant release of the Ru complex that reenters into the catalytic cycle.^[26]



[a] Typical reaction conditions: [Ru] (5 mol %), **1** (1 equiv), TMSCHN₂ (2.1 equiv), [1] = 0.25 M, rt. [b] Yields of the isolated products. [c] Cp*RuCl(cod), (10 mol%).

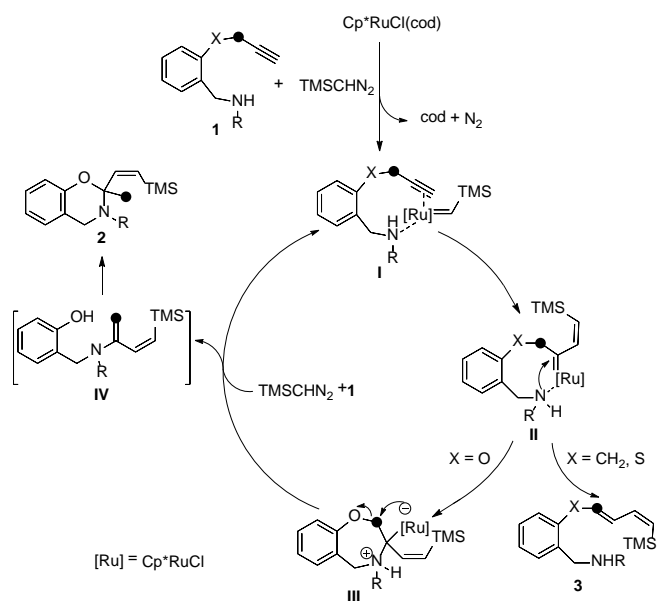
In conclusion, we report a novel entry to 1,3-benzoxazines by ruthenium-catalyzed cyclization of *ortho*-(alkynyloxy)benzylamines. Our method relies on key features such as the use of readily available *ortho*-(alkynyloxy)benzylamines, commercially available TMSCHN₂ and Cp*RuCl(cod), the ability to introduce functionality at the different positions of the benzoxazine ring and the mild reaction conditions employed. This methodology is also the first example of the addition of an amine nucleophile to in situ-generated vinyl ruthenium carbene intermediates for the direct formation of heterocyclic compounds. Rearrangement of an internal C_{sp} of the starting material into a tetrasubstituted C_{sp3} in the final 1,3-benzoxazine is highly remarkable.

Acknowledgements

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Keywords: Ruthenium • carbenes • benzylamines • cyclization • benzoxazines

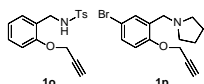
Table 3. Ru-catalyzed cyclization of *N*-substituted *ortho*-(alkynyloxy)benzylamines **1m–n**, **1q–v** to 1,3-benzoxazines **2m–n**, **2q–v**.^{[a], [b]}



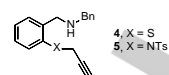
Scheme 2. Mechanistic proposal for the Ru-catalyzed cyclization of *ortho*-(alkynyloxy)benzylamines.

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- [21] With a poorly coordinating and less nucleophilic nitrogen atom in tosylamide **1o** the reaction resulted in a complex mixture. On the other hand, tertiary pyrrolidine derivative **1p** was recovered unaltered after 24 h.



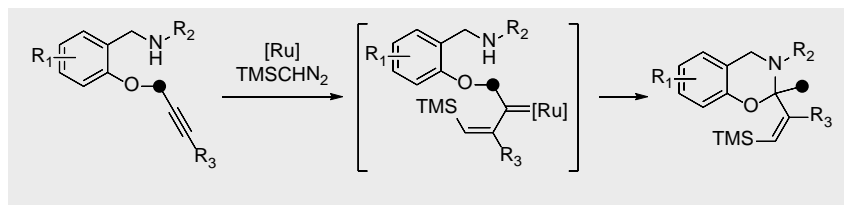
- [22] The reaction of thioether **4** under optimized conditions afforded the corresponding dienyI sulfide **3** in 56% yield and the reaction of tosylamide **5** gave a complex reaction mixture. See Supporting Information for details.



- [23] Alternatively, direct attack of the amine to the triple bond followed by ring opening without formation of the initial Ru carbene cannot be ruled out (O,N-“extended” Rautenstrauch rearrangement).^{4b} However, when **1b** (X = CH₂) was subjected to the reaction conditions, smooth formation of diene **3b** was observed which suggests the formation of a vinyl Ru carbene intermediate.
- [24] J. Le Paih, C. Vovard-Le Bray, S. Dérien, P. H. Dixneuf, *J. Am. Chem. Soc.* **2010**, 132, 7391-7397.
- [25] The mechanistic alternative based on 1,2-propargylic shift to give an enoether intermediate followed by the amine nucleophilic attack was discarded since the parent (prop-2-yn-1-yloxy)benzene gave the expected disyllated Z,Z-diene (84%, via vinyl Ru carbene, ref 24) instead the rearranged enoether derivative (Rautenstrauch product). See Supporting Information for details.
- [26] For a Brønsted acid-catalyzed cyclization through benzoylimine intermediates, see ref. 12h.

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COMMUNICATION



A new approach to 1,3-benzoxazines from Ru-catalyzed cyclization of *ortho*-(alkynyloxy)benzylamines is reported. Vinyl ruthenium carbenes are proposed as the key intermediates of the cyclization processes. The mechanistic hypothesis presented supposes the first example of nucleophilic addition of amines to vinyl ruthenium carbenes. Rearrangement of an internal C_{sp} atom in the starting material into a tetrasubstituted C_{sp3} atom in the final 1,3-benzoxazine is highly remarkable.

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Nucleophilic Addition of Amines to Ruthenium Carbenes: *ortho*-(Alkynyloxy)benzylamine Cyclizations towards 1,3-Benzoxazines