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

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Abstract: A new ruthenium-catalyzed cyclization of ortho-(alkynyloxy)benzylamines to dihydro-1,3-benz-oxazines is reported. The cyclization is thought to take place via the vinyl ruthenium carbene intermediates which are easily formed from [Cp*RuCl(cod)] and N_2 CHSiMe₃. 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) in the starting material into a tetrasubstituted $C(sp^3)$ 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] Cyclopropa(e)nation 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 aza-heterocycles by direct rhodium-, copper-, and ruthenium-catalyzed

intramolecular addition of amines to metal carbenes have been reported (Scheme 1). Metal carbenoid N–H insertion reactions (Scheme 1 a) and [1,2] rearrangements (Scheme 1 b) or [2,3] sigmatropic rearrangements of cyclic ammonium ylides (Scheme 1 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

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Previous works: catalytic cyclizations on activated acyl metal carbenes





Scheme 1. Azacyclizations catalyzed by metal carbenes. TMS = trimethylsilyl.

was recently introduced by Dixneuf and co-workers and employs 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 into 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 the alkynyloxyamine 1a in the presence of the precatalyst [Cp*RuCl(cod)] and TMSCHN₂. To our surprise, the six-membered 2,2-disubstituted 1,3-benzoxazine 2a was isolated in fairly good yield (Scheme 1 d).^[7] The crucial role of the oxygenated tether in this unprecedented rearrangement^[8] became evident when the alkynylamine **1b** smoothly evolved into the conjugated diene 3b. To our knowledge, this is the first example of a nucleophilic addition of an amine to in situ generated vinyl ruthenium 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 exhibiting 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] even though procedures based on transition-

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metal-catalyzed cyclizations remain scarce. Rhodium-catalyzed allylic rearrangement of 2-(allyloxy)benzylamines,^[13] copper-catalyzed C–H bond oxidative activation^[14] and photooxidation of aminoalcohols with photoredox catalysts of iridium^[15] and ruthenium^[16] are the most remarkable contributions. Herein we report a new and efficient ruthenium-catalyzed cyclization of *ortho*-(alkynyloxy)benzyl-amines towards 1,3-benzoxazines under very mild reaction conditions (Scheme 1 d).

The reaction was optimized using *N*-benzyl-1-[2-(prop-2yn-1-yloxy)phenyl]methanamine (**1a**) as the test substrate (Table 1). The reaction of **1a** with TMSCHN₂ in the presence

 Table 1: Optimization of the ruthenium-catalyzed cyclization of

 N-benzyl-1-[2-(prop-2-yn-1-yloxy)phenyl]methanamine 1 a.^[a]

| | N ^{Bn} [Ru] (5 mo TMSCHN 1a | $ \begin{array}{c} \%\rangle \\ _2 \\ T \\ 2a \end{array} $ | n ^e TMS _/ |
|-------|--|---|-----------------------------|
| Entry | [Ru] catalyst | TMSCHN ₂ (equiv) | Yield [%] ^[b] |
| 1 | [Cp*Ru(cod)Cl] | 2.1 | 62 |
| 2 | [CpRu(cod)Cl] | 2.1 | - |
| 3 | [Cp*Ru(CH ₃ CN) ₃]PF ₆ | 2.1 | _[c] |
| 4 | [Cp*Ru(CH₃CN)₃]PF ₆ / NEt₄Cl | 2.1 | 10 |
| 5 | [Cp*Ru(cod)Cl] | 2.1 | 46 ^[d] |
| 6 | [Cp*Ru(cod)Cl] | 3.0 | 50 |
| 7 | [Cp*Ru(cod)Cl] | _[e] | _[f] |

[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] Cp*Ru(cod)Cl, (10 mol%). [e] N₂CHCOOEt (2.1 equiv) was used. [f] Ethyl 2-(benzyl(2-(prop-2-yn-1-yloxy)benzyl)amino)acetate **1a**'' was obtained in 51% yield. cod = 1,5-cyclooctadiene, Cp*=C₅Me₅.

of [Cp*RuCl(cod)] (5% mol) in Et₂O at room temperature gave 2a in 62% yield (entry 1). The reaction was extremely sensitive to the electronic and steric nature of the ruthenium catalyst since the starting material was totally recovered upon using [CpRuCl(cod)] (entry 2). Besides, cationic [Cp*Ru-(CH₃CN)₃PF₆] or in situ formation of a neutral ruthenium catalyst, by treatment with Et₄NCl,^[17] dramatically affected either the course of the reaction or the catalytic activity, thus giving very low yields of the methylated starting material 1a' $(9\%)^{[3,18]}$ or **2a** (10%), respectively (entries 3 and 4). Curiously, an increase in the catalyst loading or the amount of TMSCHN₂ was not beneficial for the cyclization reaction, with 2a isolated in slightly lower yields (entries 5 and 6). The nature of the solvent was crucial as other cyclic ethers such as 1,4-dioxane or THF were tolerated but gave lower yields, but bulkier ethers and more polar protic or halogenated solvents were detrimental to the cyclization.^[18] Electronic variation on the diazoalcane dramatically affected the course of the reaction since the α -aminoester 1a'', derived from the carbenoid N-H insertion reaction,[3] was obtained when N₂CHCOOEt was used (entry 7).^[18]

Once the optimized reaction conditions were established, the scope and limitations of the cyclization reaction were explored by starting with electronically distinct benzylamine **Table 2:** Ruthenium-catalyzed cyclization of the *ortho*-(alkynyloxy)-benzylamines 1 c-l to the 1,3-benzoxazines 2 c-l.



[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*Ru(cod)Cl], (10 mol%). [d] [Cp*Ru(cod)Cl], (10 mol%), 1,4-dioxane as solvent, 65 °C.

derivatives (Table 2). Electron-withdrawing and electrondonating aryl substituents are tolerated since the 1,3-benzoxazines 2c-f were obtained in reasonably good yields. Thus, para-methoxy-, para-methyl-, para-trifluoromethyl-, and even para-bromobenzylamine smoothly gave the substituted 1,3benzoxazines 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 2 f-i in fairly good yields. Further manipulation of the above aryl bromides and chlorides using palladium-catalyzed cross-coupling reactions provide an easy entry to polysubstituted benzoxazines.^[19] Notably, cyclization of the naphthylamine derivative 1j smoothly gave the naphthoxazine 2j in very good yield. Gratifyingly, the nonterminal benzylamine derivative 1k also cyclized to give 2k in very good yield,^[20] albeit with a longer reaction time compared to that of 2f (60 h versus 6 h) and the need for a higher catalyst loading (10 mol%). Even a benzylamine with a long-chain-substituted alkyne, that is, 11, was able to cyclize to the corresponding 1,3-benzoxazine 21, albeit in low yield. In all cases the benzoxazines 2 were isolated with complete Z stereoselectivity for the silvlated double bond.

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 atom of the benzylamines **1**, for example, 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 the N-allyl-substituted benzylamine **1q**, from which **2q**, with an intact allyl group, was isolated in moderate yield. Interestingly, this result indicates

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Table 3:Ruthenium-catalyzed cyclization of N-substituted ortho-(alky-nyloxy)benzylamines (1 m-n, 1 q-v) to 1,3-benzoxazines (2 m-n, 2 q-v).v)..[a,b]



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

that polar nucleophile/electrophile interactions dominate the reactivity of the putative carbene intermediate. Finally, the diastereoselectivity of the cyclization was explored with the chiral benzylamine 1r, which gave 2r (5.1 d.r. 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 rutheniumcatalyzed cyclization of the corresponding benzylamines 1s**u** bearing a methyl substituent in the propargylic position $(R^3 = Me, R^4 = H)$. Furthermore, the isopropyl-substituted 1,3-benzoxazine 2v was isolated from the reaction of the dimethylated substrate 1v (R³, R⁴ = Me). These results clearly indicate that the propargylic carbon atom 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 ruthenium-catalyzed cyclization of deuterated benzylamine [D]-1f ($R^2=D$) was carried out under the optimized reaction conditions, deuterium scrambling was not observed and the deuterium atom was located at the vinylic position of the corresponding benzoxazine [D]-2f.^[18]

The results obtained, including those of the labeling study and the cyclization of the propargylic-substituted benzylamines 2s-v, strongly support the initial mechanistic hypoth-



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

esis 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 TMSCHN_2 and 1 to give the ruthenium carbene species A. Oxidative coupling to the ruthenacyclobutene followed by ring opening would lead to the ruthenium vinyl carbene species \mathbf{B} , in which the coordination of the pendant amine could disfavor the coordination of a second diazoalkane unit.^[24] The electrophilic ruthenium carbene could induce nucleophilic attack by the amine group to afford the zwitterionic intermediate C.^[25] This intermediate is probably not formed when the nucleophilic character of the amine is diminished as in the tosylamide 10. Ring strain of the cyclic intermediate C, which has a good leaving group (phenoxide), would facilitate ring opening to afford the enamine intermediate D, with recovery of A. The reaction vields obtained for 1,3-benzoxazines (e.g., 2 f versus 2c) seem to be consistent with the leaving capacity of the phenoxides 1. In the absence of a phenoxide as a leaving group, the cyclization did not take place and **B** would evolve by β elimination to afford the observed diene 3. Finally, iminium formation from **D** is trapped with the phenoxide to give the final 1,3-benzoxazine 2 with concomitant release of the ruthenium complex which re-enters the catalytic cycle.^[26]

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.

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- [21] With a poorly coordinating and less nucleophilic nitrogen atom in tosylamide 10 the reaction resulted in a complex mixture. On the other hand, tertiary pyrrolidine derivative 1p was recovered unaltered after 24 h.



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

> N Bn H 4, X = S 5, X = NTs

[23] Alternatively, direct attack of the amine to the triple bond followed by ring opening without formation of the initial ruthenium 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 the diene **3b** was observed and suggests the formation of a vinyl ruthenium carbene intermediate.

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- [26] For a Brønsted acid catalyzed cyclization through benzoylimine intermediates, see Ref. [12h].



Communications

Synthetic Methods

C. González-Rodríguez,* J. R. Suárez, J. A. Varela, C. Saá* _____ **■■■**

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



A new addition: A new ruthenium-catalyzed cyclization of *ortho*-(alkynyloxy)benzylamines to 1,3-benzoxazines is reported. Vinyl ruthenium carbenes are proposed as the key intermediates, and the mechanistic hypothesis supposes the first example of a nucleophilic addition of amines to vinyl ruthenium carbenes. Rearrangement of an internal C(sp) into a tetrasubstituted C(sp³) is highly remarkable. TMS = trimethylsilyl.

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