Ruthenium-Catalyzed Tandem Carbene/Alkyne Metathesis/N-H insertion. Synthesis of Benzofused Six-Membered Azaheterocycles

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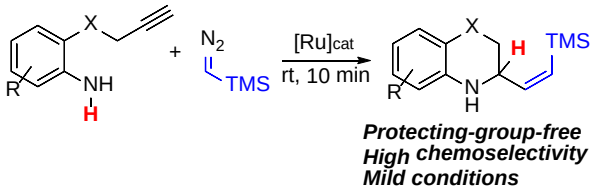
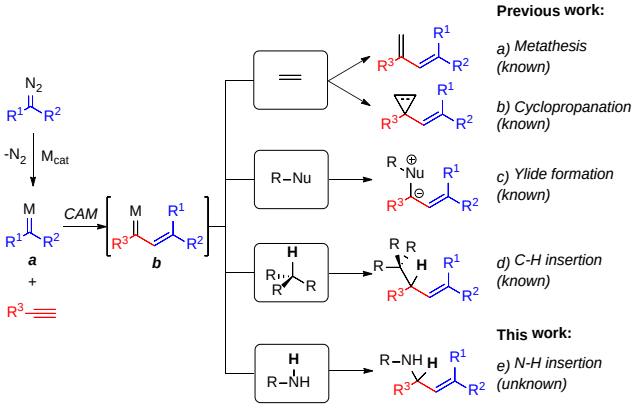
Supporting Information Placeholder



ABSTRACT: Cp*RuCl-based catalyst enables the expedient access to a variety of benzofused six-membered azaheterocycles from unprotected *o*-alkynylanilines and trimethylsilyldiazomethane through an unprecedent tandem carbene/alkyne metathesis/N-H insertion reaction. The transformation takes place under mild reaction conditions (room temperature, < 15 min) and with excellent functional group tolerance. The synthetic utility of the final products and a mechanistic rationale are also discussed.

Tandem processes involving catalytic metal carbenes have proved to be useful strategies for the rapid generation of molecular complexity.[1] In particular, in situ generation of metal vinyl carbenes through carbene/alkyne metathesis (CAM) represents a versatile route for alkyne bifunctionalization.[2] These intermediates are known to react with olefins to give dienes[3] (Scheme 1a) or vinyl cyclopropa(e)nes[4] (Scheme 1b), with nucleophiles to afford ylide intermediates[5] (Scheme 1c) or with C-H bonds to give new C-C bonds[6] (Scheme 1d). However, as far as we know, a tandem CAM process ending up in a N-H insertion reaction has never been reported (Scheme 1e).

Scheme 1. Reactivity pattern of metal vinyl carbenes formed through CAM.



The development of such a tandem process is challenging. The coexistence of two metal carbenes (***a*** and ***b*** in Scheme 1) in the reaction media may lead to competitive processes such as dimerizations or unselective N-H insertions. Besides, current methodologies for intramolecular N-H insertions typically require the amine to be protected as amide, carbamate or sulfonamide,[7,8] thus leading to less atom-economic processes.

We now report our efforts in the development of the first tandem carbene/alkyne metathesis coupled with an intramolecular N-H insertion leading to unprotected benzofused six-membered azaheterocycles,[9] which are privileged scaffolds present in a myriad of bioactive compounds and natural products (Figure 1).[10,11]

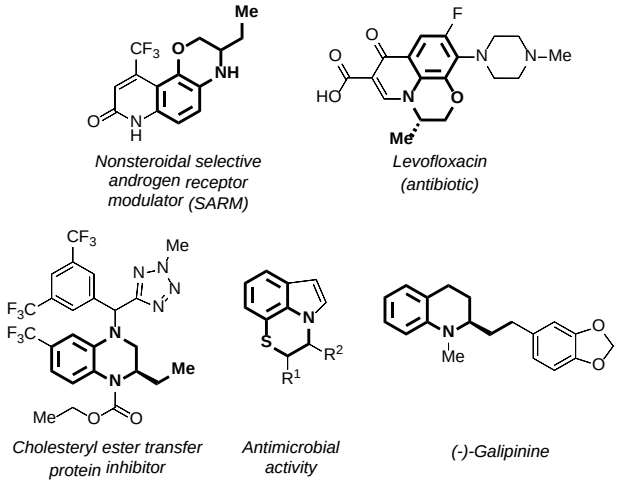
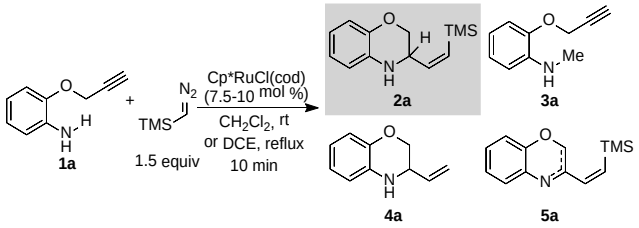


Figure 1. Selected bioactive compounds and natural products

o-Alkynylaniline **1a**, an unprotected primary aromatic amine, was synthesized and subjected to our previously reported conditions for

aliphatic secondary amines (Table 1, entry 1).[5f] Gratifyingly, 3-vinyldihydrobenzoxazine **2a** was selectively formed in 77% yield as a single *Z* stereoisomer[12] in less than 10 min of reaction at room temperature. A direct comparison between the Cp*RuCl(cod) precatalyst and traditional Rh(II) catalysis ($Rh_2(OAc)_4$, entry 2 and $Rh_2(esp)_2$, entry 3) highlights the virtues of the half-sandwich ruthenium complex in promoting CAM rather than direct N-H insertion. In fact, the reaction proved to be very sensitive to the electronic nature of the ruthenium precatalyst and the diazo compound as the use of the cationic analog $[Cp^*Ru(CH_3CN)_3]PF_6$ (entry 4) or ethyl diazoacetate (entry 5) gave rise to a mixture of the desilylated product **4a** together with minor amounts of the direct N-H insertion product **3a** and a complex mixture, respectively. The use of the tetranuclear complex $[Cp^*RuCl]_4$ afforded a similar result as Cp*RuCl(cod), but an incomplete consumption of **1a** was observed (entry 6), probably due to a faster deactivation of the catalyst. The nature of the solvent also proved to be crucial as the employment of more polar (protic and aprotic) solvents led to low conversions (entry 7) and the formation of side products of type **5a**. Pleasingly, we discovered that it is possible to scale up the reaction up to 2 mmol and diminish the catalyst loading from 10 mol % to 7.5 mol % by using 1,2-dichloroethane as solvent at reflux (entry 8).

Table 1. Optimization of the reaction conditions.[a]

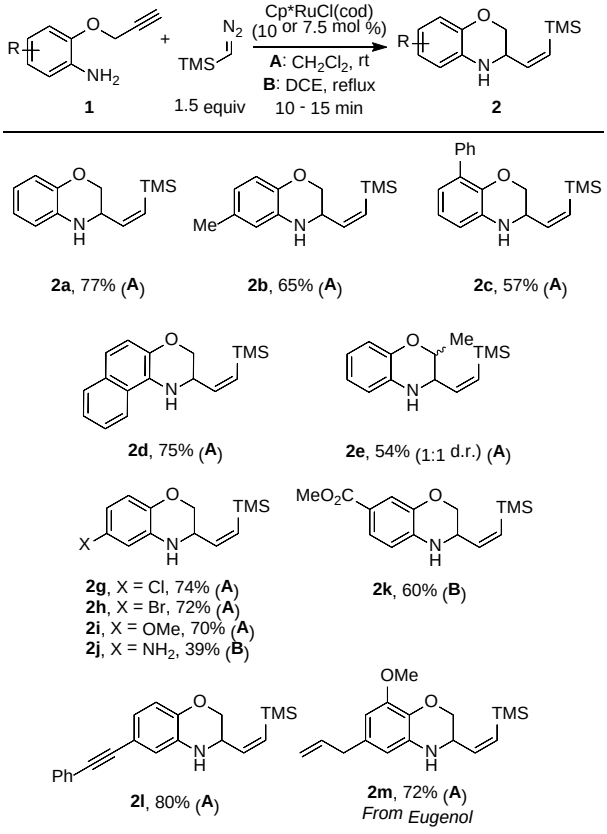


entry	deviation from standard conditions	product/yield (%)[b]
1	none	**2a**/77
2	5 mol % $Rh_2(OAc)_4$ instead of Cp*RuCl(cod)	**3a**/15[c,d]
3	5 mol % $Rh_2(esp)_2$ instead of Cp*RuCl(cod)	**3a**/8[c,d]
4	$[Cp^*Ru(CH_3CN)_3]PF_6$ instead of Cp*RuCl(cod)	**3a**+**4a**/n.d.[c]
5	EtO_2CCHN_2 instead of $TMSCHN_2$	complex mixture
6	$[Cp^*RuCl]_4$ instead of Cp*RuCl(cod)	**2a**/60[c]
7	THF/MeOH/iPrOH/CH_3CN instead of DCM	**2a**+**5a**/10-31[c]
8	7.5 mol % of Cp*RuCl(cod)/DCE reflux/2 mmol scale	**2a**/73

[a] Reaction conditions: **1a** (0.2 mmol), $TMSCHN_2$ (1.5 equiv), solvent (0.15 M) and with the indicated catalyst at rt. [b] Isolated yields. [c] Incomplete consumption of **1a** was observed. [d] Slow addition of the diazo compound over 1 h.

Having established the optimal reaction conditions for the tandem CAM/N-H insertion reaction, we decided to explore the scope and limitations of our methodology. First, O-tethered *o*-alkynylanilines were tested (Scheme 2). The cascade reaction tolerates any substitution pattern on the aromatic ring, affording the corresponding 1,4-benzoxazines **2a**-**d** from moderate to good yields. Substitution at the propargylic position was also tolerated, albeit benzoxazine **2e** was obtained as a 1:1 mixture of diastereomers in 54% yield.[13] Remarkably, the reaction proceeded with excellent chemoselectivity in the presence of a wide range of functional groups such as halides (**2g** and **2h**), ethers (**2i**), unprotected anilines (**2j**), esters (**2k**), internal alkynes (**2l**) or terminal olefins (**2m**). Considering the slight excess of $TMSCHN_2$ used for this transformation, one might expect further evolution of the final products **2** through N-H insertion of the resulting secondary aniline, unselective N-H insertion with the primary aniline **2j**, CAM with the internal alkyne **2l** or metathesis/cyclopropanation with the terminal olefin **2m**, however, none of these side reactions were detected in the analysis of the crude mixtures.

Scheme 2. Scope and functional group tolerance for the tandem CAM/N-H insertion of O-tethered *o*-alkynylanilines.[a]

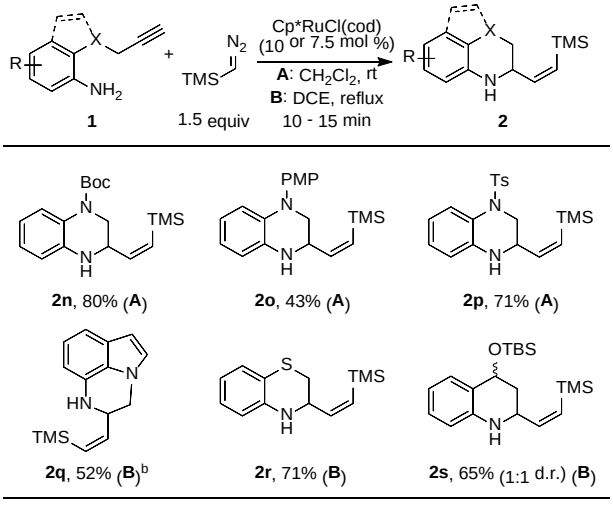


[a] Conditions: Method **A**: **1** (0.2 mmol), $TMSCHN_2$ (1.5 equiv), CH_2Cl_2 (0.15 M) and Cp*RuCl(cod) (10 mol %) at rt for 10 – 15 min. Method **B**: The same conditions as method **A** but using 7.5 mol % of Cp*RuCl(cod) and DCE as solvent at reflux for 15 min.

The extension of the tandem CAM/N-H insertion to the synthesis of other kind of six-membered heterocycles was subsequently analyzed (Scheme 3). To our delight, the cyclization reaction allowed

the access to a variety of functionalized tetrahydroquinoxalines (**2n-2p**) and indoloquinoxalines (**2q**), dihydrobenzothiazines (**2r**) or tetrahydroquinolines (**2s**) from moderate to good yields. These results further exemplify the excellent functional group tolerance towards carbamates, sulfonamides, heteroaromatic systems, thioethers or silylethers. Curiously, these results are in striking contrast to our previous experience with secondary benzylamines in the tandem CAM/ylide rearrangement, where N-, S- or C-tethered *o*-alkynylamines were not tolerated.[5f]

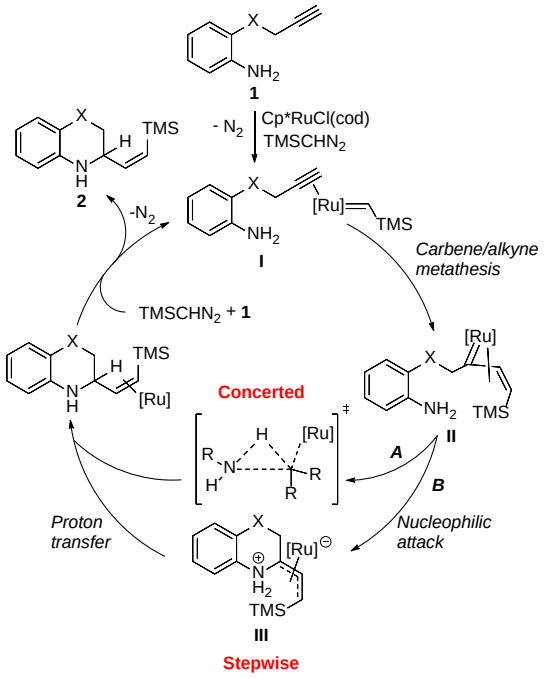
Scheme 3. Scope and functional group tolerance for the tandem CAM/N-H insertion of carbon- and heteroatom-tethered *o*-alkynylanilines.[a]



[a] Conditions: Method **A**: **1** (0.2 mmol), $TMSCHN_2$ (1.5 equiv), CH_2Cl_2 (0.15 M) and Cp*RuCl(cod) (10 mol %) at rt for 10 – 15 min. Method **B**: The same conditions as method **A** but using 7.5 mol % of Cp*RuCl(cod) and DCE as solvent at reflux for 15 min. [b] No full conversion of *o*-alkynylaniline **1q** was observed.

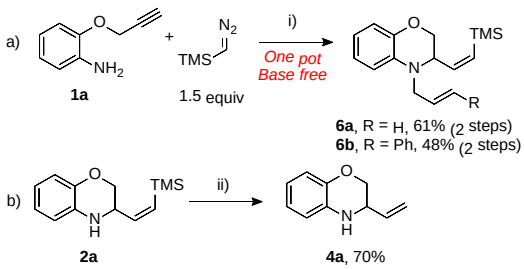
According to precedent literature and the experimental observations, a tentative mechanism was proposed (Scheme 4). The Cp*RuCl(cod) precatalyst would react with the diazo compound to generate a ruthenium carbene that readily coordinates to the *o*-alkynylaniline **1** (**I**). A chemo- and stereoselective CAM process would generate vinyl carbene **II** that then react with the aniline through two alternative routes. In route A, a concerted N-H insertion process would directly give rise to the observed product **2**. In route B, the mild electrophilic ruthenium vinyl carbene would induce a nucleophilic attack by the aniline to give an ylide intermediate **III**, which after a regioselective proton transfer would release **2**. At this stage of our investigations, we were not able to unequivocally determine whether the N-H insertion step occurs in a concerted or stepwise manner.[14,15]

Scheme 4. Mechanistic hypothesis.



The presence of a versatile unprotected allylaniline functionality in the cyclized products **2** led us to explore some manipulations to prove their synthetic utility as potential building blocks for organic synthesis (Scheme 5). First, the mild conditions required for the cyclization enabled the one-pot/base free allylation of the secondary aniline **2a** to afford the corresponding bis-allylaniline **6a** and **6b** in good overall yields. On the other hand, desilylation of **2a** could be performed to render the terminal olefin **4a** in 70% yield.

Scheme 5. Derivatization of benzoxazine 2a.[a]



[a] Conditions: i) **1a** (0.2 mmol), $TMSCHN_2$ (1.5 equiv), Cp*RuCl(cod) (10 mol %) in CH_2Cl_2 (0.15 M) at rt for 10 min, then, the corresponding allyl bromide (RCH=CH-CH_2Br) was added (1.5 equiv) and stirred for 6 – 12 h. ii) **2a** (1 mmol), TBAF (1.5 equiv) in THF (0.5 M) at reflux for 15 h.

To conclude, we have developed the first tandem CAM/N-H insertion reaction to afford unprotected and functionalized benzofused six-membered azaheterocycles. The reaction proceeded under very mild conditions and high chemoselectivity thanks to a fast CAM process catalyzed by a half-sandwich ruthenium complex.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.". Experimental procedures including characterization data.

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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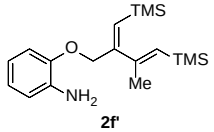

2f'

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