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COMMUNICATION

Ruthenium(II)-Catalyzed Intermolecular Annulation of Alkenyl Sulfonamides with Alkynes: Access to Bicyclic Sultams

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A ruthenium-catalyzed allylic C(sp³)–H activation strategy has been employed to develop an intermolecular coupling of alkenyl sulfonamides with alkynes. This protocol features the diastereoselective construction of [3.3.0] and [4.3.0] bicyclic sultams in one step.

Introduction

Bicyclic sultams are distributed in a variety of active pharmaceutical ingredients such as piroxicam, meloxicam, hydrochlorothiazide and brinzolamide (Figure 1).[1,2] As stable lactam equivalents, these compounds could be used as anti-inflammatory, antihypertensive, carbonic anhydrase inhibitor and so on.[1] Furthermore, bicyclic sultams also serve as chiral auxiliaries in organic synthesis.[3] In this context, considerable efforts have been devoted to their synthesis over the past decades, including cycloaddition,[4] nucleophilic substitution,[5] electrophilic addition,[6] Heck couplings,[7] alkene metathesis,[8] etc.[9] However, only limited methods are able to create core bicyclic framework in one step. For example, intramolecular [3+2],[4b] [4+2],[4c,6c] and [2+2+1][7d] annulations have been demonstrated to construct bicyclic sultams (Scheme 1a-d).

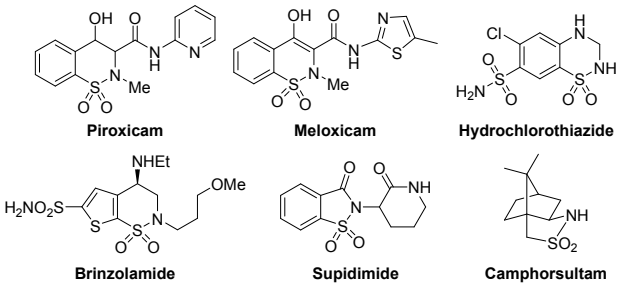
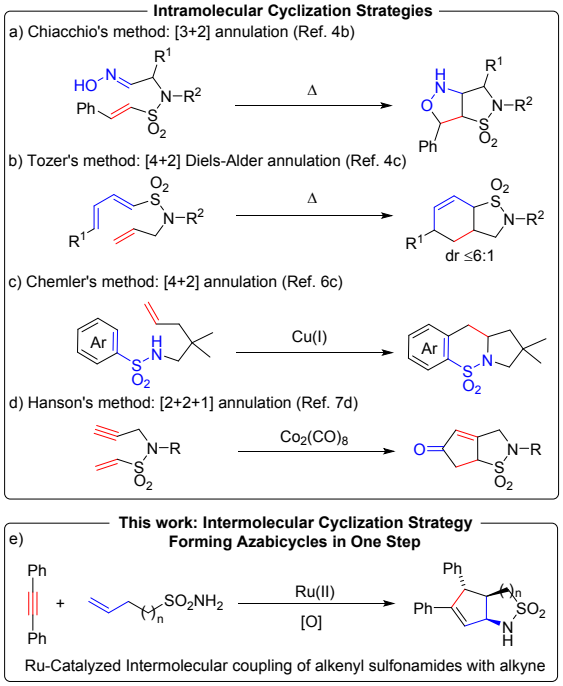


Figure 1. Representative bicyclic sultams.

Despite these advances, from the viewpoint of step- and atom-economy, it would be highly demanded to develop an intermolecular annulation to elaborate bicyclic sultams. To the best of our knowledge, the bimolecular assembly of such important motif still remains underexploited.



Scheme 1. General strategies for constructing bicyclic sultams in one step.

Transition-metal-catalyzed direct C–H annulations with nitrogen atom is arguably one of the most efficient strategy to access *N*-heterocycles.[10] For example, intramolecular allylic/benzylic C–H aminations of unsaturated sulfamate esters[11] and *N*-sulfonamides[12] have been well studied. Notably, Rovis and co-workers disclosed a Rh(III)-catalyzed intermolecular annulation of *N*-alkenyl sulfonamides with alkynes for the synthesis of azabicycles.[13] Inspired by these precedents[13,14] and our continuing interests in developing new annulations,[15] we envisioned that alkenyl sulfonamides possibly could undergo allylic C–H activation and alkyne insertion to yield bicyclic sultams under ruthenium catalysis (Scheme 1e).

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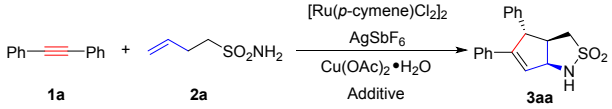
Results and discussion

Initially, 1,2-diphenylethyne (**1a**) and but-3-ene-1-sulfonamide (**2a**) were selected as model substrates to test our hypothesis (Table 1). The expected annulation of **1a** and **2a** indeed occurred using $[Ru(p\text{-cymene})Cl_2]_2$ as catalyst precursor and $Cu(OAc)_2{\cdot}H_2O$ as oxidant, albeit with a low yield of **3aa** (entry 1). The relative stereochemistry of **3aa** was unequivocally determined by X-ray diffraction analysis.[16] A screening of the solvents and temperature indicated that the best result was obtained when the reaction was conducted in DCE at 80 °C (entries 2-10). Moreover, the influences of base and acid additives were surveyed. The employment of HOAc as additive resulted in an apparent improvement on the reactivity (entries 11-13). Gratifyingly, the yield of **3aa** was further enhanced to 74% upon increasing the catalyst loading and the amount of **1a** (entries 14-15).

Table 1. Optimization of the reaction conditions[a]



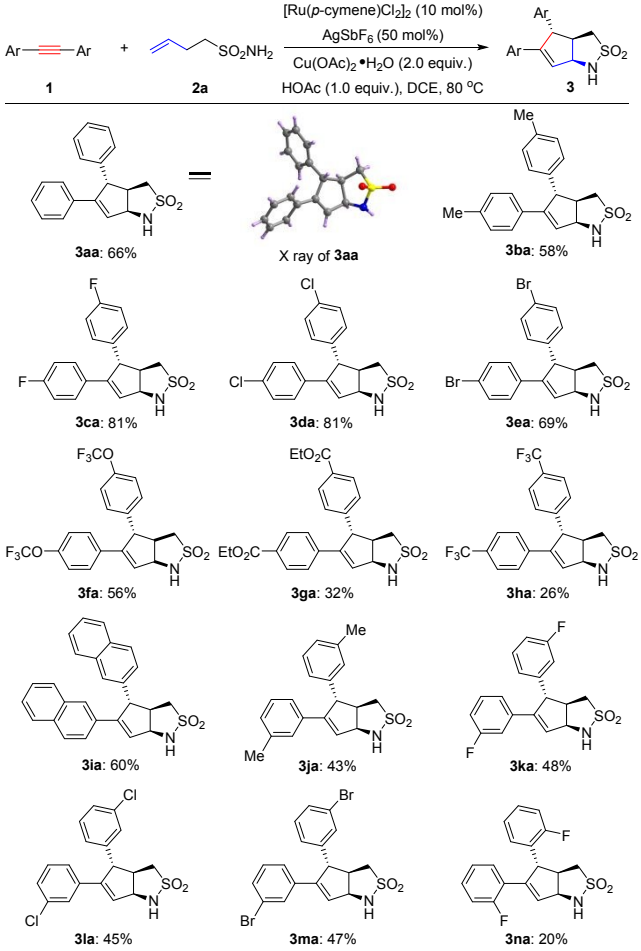
1a 2a 3aa

Entry	Solvent	T (°C)	Additive	Yield (%)[b]
1	Dioxane	120	None	7
2	PhCl	120	None	8
3	DCE	120	None	18
4	Et_2O	120	None	5
5	DMSO	120	None	NR.
6	DCE	140	None	5
7	DCE	100	None	24
8	DCE	80	None	30
9	DCE	60	None	27
10	DCE	40	None	21
11	DCE	80	K_2CO_3	16
12	DCE	80	PivOH	30
13	DCE	80	HOAc	42
14[c]	DCE	80	HOAc	60
15[c,d]	DCE	80	HOAc	74

[a]Conditions: **1a** (0.10 mmol), **2a** (0.10 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (0.005 mmol), $AgSbF_6$ (0.025 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.20 mmol), additive (0.10 mmol), solvent (2 mL), 16 h; [b]Determined by HPLC with naphthalene as internal standard; [c]$[Ru(p\text{-cymene})Cl_2]_2$ (0.01 mmol), $AgSbF_6$ (0.05 mmol), DCE (4 mL); [d]**1a** (0.20 mmol).

With the optimal reaction conditions established, we subsequently explored the substrate generality (Table 2). Alkyne **1b** bearing electron-donating (4-Me) substituent on phenyl ring reacted with homoallylic sulfonamide **2a** smoothly to furnish bicyclic sultam **3ba** in 58% yield. The halide groups including -F, -Cl, and -Br were all well tolerated, affording the corresponding products in 69-81% yields (**3ca**-**3ea**). Trifluoromethoxy derived alkyne was readily transformed into **3fa** in 56% yield. Electron-withdrawing substituents such as $-CO_2Et$ (**3ga**) and CF_3 (**3ha**) were compatible with the process, albeit with slightly decreased yields. Remarkably, bulky 2-naphthyl alkyne was also a suitable substrate. The process could be further extended to various meta-substituted alkynes, and the electronic properties of the substituents had minimal influence on the reaction (**3ja**-**3ma**). The annulation of 2-F derived alkyne with **2a** led to the desired bicyclic sultam **3na** in a relatively low yield, which was presumably ascribed to the steric hindrance.

Table 2. Construction of [3.3.0] azabicyclic sultams[a]

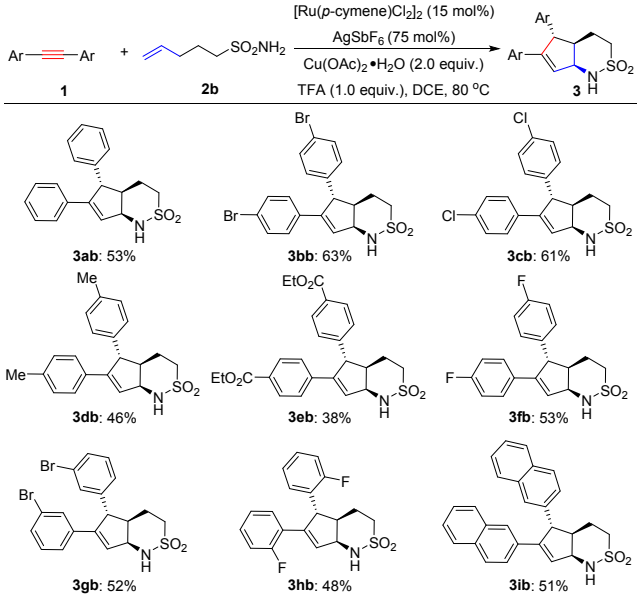


[a]Reaction conditions: **1** (0.30 mmol), **2a** (0.60 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (0.03 mmol), $AgSbF_6$ (0.15 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.60 mmol), HOAc (0.30 mmol), 80 °C, 16 h.

When alkenyl sulfonamide **2b** with longer carbon chain was employed as substrate, the annulation could proceed efficiently to deliver [4.3.0] azabicyclic sultam **3ab** in 53% yield (Table 3). The halide substituents, regardless of their positions, were all amenable to the protocol (**3bb**, **3cb**, **3fb**, **3gb**), and even 2-F substituted alkyne also led to product **3hb** in an acceptable yield (53%). In the cases of electron-donating 4-Me and electron-withdrawing $4\text{-}CO_2Et$ derived alkynes, the reactions afforded the corresponding sultams (**3db**, **3eb**) in

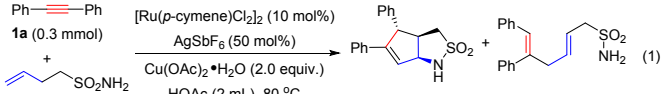
46% and 38% yield, respectively. Treatment of 2-naphthyl alkyne with standard conditions resulted in the formation of **3ib** in a moderated yield (51%).

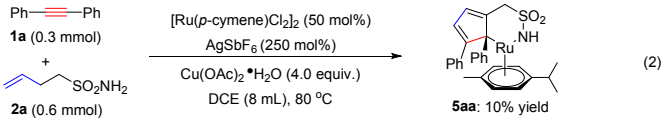
Table 3. Construction of [4.3.0] azabicyclic sultams[a]



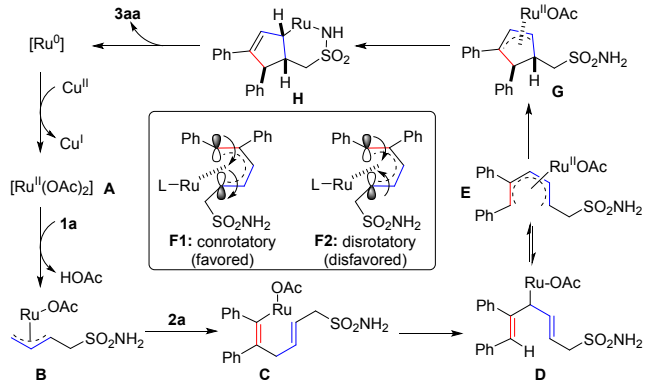
[a]Reaction conditions: **1** (0.30 mmol), **2b** (0.60 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (0.045 mmol), $AgSbF_6$ (0.225 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.60 mmol), TFA (0.30 mmol), 80 °C, 16 h.

In order to isolate some potential reaction intermediates for proposed mechanism, HOAc was used as solvent to promote the protodemetalation (Eq. 1). Besides sultam **3aa**, the control experiment also generated a skipped diene **4aa** as side-product which was not observed under the standard conditions. These results revealed that a migratory insertion of alkyne **1a** into π-allyl ruthenium complex is probably involved in the process. An interestingly cyclometallated ruthenium complex **5aa** was isolated when increase the loading of ruthenium precursor [Ru(*p*-cymene)Cl_2]$_2$ (Eq. 2). This Ru complex has been fully characterized by ^{1}H NMR, ^{13}C NMR, ^{1}H-^{13}C HMQC, ^{1}H-^{13}C HMBC and HRMS (See Supporting Information).





On the basis of these observations and previous report,[13] a plausible mechanism was shown in Scheme 2. First, allylic C(sp^3)–H bond of **2a** is activated by an *in-situ* formed cationic Ru(II) catalyst, generating a π-allyl ruthenium complex **B**. Subsequent a migratory insertion of alkyne **1a** into ruthenium complex **B** gives vinyl Ru(II) **C**. A vinyl-to-allyl 1,3-Ru shift of intermediate **C** furnishes the bis(allyl)ruthenium species **D** in equilibrium with intermediate **E**. Side-product **4aa** (Eq. 1) could be obtained *via* an enhanced protodemetalation of ruthenium complex **C** or **D**.[17] A 4π-conrotatory electro-cyclization of **E** yields a five-membered π-allyl ruthenium **G** via model **F1**. The high diastereoselectivity can be rationalized from the requirements of the Woodward–Hoffmann rules (Disrotatory model **F2** is disfavored). Intermediate **G** undergoes ligand exchange and reductive elimination to produce bicyclic sultam **3aa**. The resulting Ru(0) species is ultimately oxidized by $Cu(OAc)_2$ to regenerate the Ru(II) catalyst. In the presence of excess oxidant $Cu(OAc)_2$, cyclometallated ruthenium complex **5aa** (Eq. 2) could be generated from intermediate **H** through oxidation and subsequent 1,3-Ru shift. Therefore, the observation of Ru complex **5aa** supports the proposed mechanism.



Scheme 2. Proposed mechanism.

Conclusions

In conclusion, we have successfully developed a direct synthesis of bicyclic sultams *via* ruthenium-catalyzed intermolecular coupling of alkenyl sulfonamides with alkynes, involving a ruthenium(II)-catalyzed tandem cyclization reactions/amination progress. The high diastereoselectivity for [3.3.0] and [4.3.0] bicyclic sultams resulted from steric factors during 4π-conrotatory electrocyclization. The alkenyl sulfonamide acted as a ternary-composition for cycloaddition with alkynes in this protocol. Further studies on the biological activity of these bicyclic sultams are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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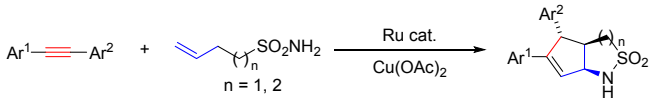

High diastereoselective formation two cycles and three new bonds in one step

A ruthenium-catalyzed allylic C(sp3)−H activation strategy has been employed to develop an intermolecular coupling of alkenyl sulfonamides with alkynes. This protocol features the diastereoselective construction of [3.3.0] and [4.3.0] bicyclic sultams in one step.