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One-Pot Protocol to Functionalized Benzopyrrolizidine Catalyzed Successively by $Rh_2(OAc)_4$ and $Cu(OTf)_2$: A Transition Metal–Lewis Acid Catalysis Relay

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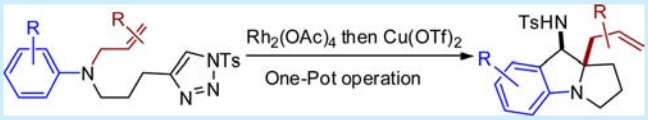
Ⓢ *Supporting Information*



ABSTRACT: 4-*N*-Allylarylpropylamino-1-sulfonyl triazoles are converted to structurally unique benzopyrrolizidinyl sulfonamides in a one-pot operation. Intramolecular capture of rhodium carbene with arylamino nitrogen gives rise to the formation of an ammonium ylide immediate. A [2,3]- or [1,2]-rearrangement occurs to give a 2-allylpyrrolidinyl-2-carbimine intermediate which undergoes $Cu(OTf)_2$ catalyzed aza-Friedel–Crafts cyclization to finish a highly functionalized tricyclic system decorated with a synthetically difficult quaternary carbon center, a sulfonamide group, and an allyl segment.

Nitrogen-containing heterocycles are present in numerous bioactive natural products and synthetic agents. Accordingly, this class of molecules is highly popular in the pharmaceutical industry, medicinal chemistry, and chemical biology. The N-heterocyclic motif very often serves as either/both the core framework or/and the key pharmacophore in a bioactive molecule.[1] The benzo-fused pyrrolizidine motif has received continuous interest[2] because it has been found in numerous biologically important natural products such as isatisine **A**,[3] mitomycins,[4] flinderoles,[5] and yuramamine[6] (Figure 1). In an era of wide application of high throughput bioassay to identify potential pharmaceutical leads,[7] synthetic methodologies that can provide facile and quick entries to highly functionalized N-herterocycles which can be easily elaborated to diverse structures that are extremely desired. We wish to report an efficient construction of a benzopyrrolizidine skeleton with versatile functional groups.

We have previously reported a divergent approach to *N*-heterocycles 3-indolyl aldehyde **2** and 3-azabicyclo[3,1,0]hexyl aldehyde **3** from **1** (Scheme 1a)[8] by the combined virtues of versatile carbene reactivities[9] and the convenient carbene precursor of 1-sulfonyl 1,2,3-triazole.[10] In line with this direction, we were in a position to ask what will be the succeeding event for the in situ generated reactive azavinyl carbenoid **5a** formed via the rhodium promoted decomposition of corresponding precursor 4-(*N*-allyl-*N*-phenylaminopropyl)-1-sulfonyl-1,2,3-triazole **4**, given the fact that there are four potential reacting sites for the carbenoid in proximity (Scheme 1b; shown in **5**: (i) insertion into the π-bond;[11] (ii) C–H insertion;[12] (iii) attack on heteroatom n-electron pair;[13] and (iv) attack on aromatic ring[14]).

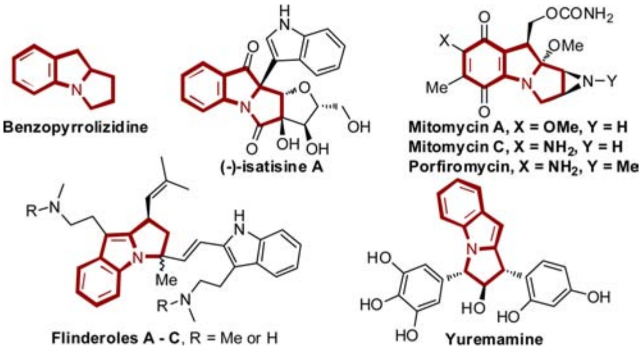
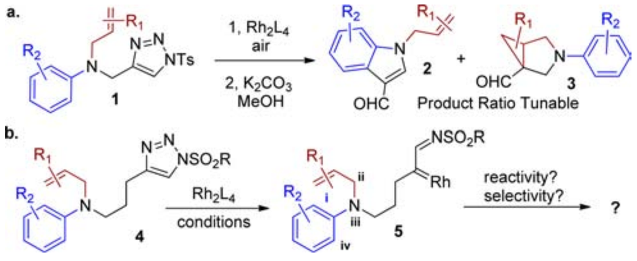


Figure 1. Benzopyrrolizidine framework in biologically active natural products.

Scheme 1. (a) Divergent Synthesis of *N*-Heterocycles 3-Indolyl Aldehyde and 3-Azabicyclo[3,1,0]hexyl Aldehyde; (b) Queries on the Reactivity/Selectivity of a Multifunctionalized Rhodium Carbene Intermediate



Our studies began with 4-[*N*-allyl-*N*-(3-methoxylphenyl)-aminopropyl]-1-tosyltriazole **4a** (Table 1). When a solution of **4a** in toluene (tol) was heated to 80 °C in the presence of a catalytic amount of rhodium acetate dimer ($Rh_2(OAc)_4$), benzopyrrolizidine derivative **6a** was isolated as the sole

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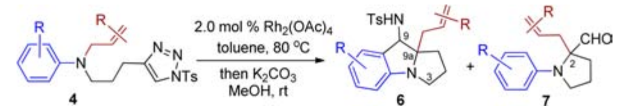
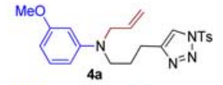
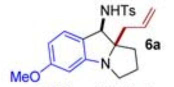
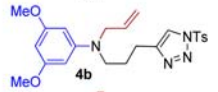
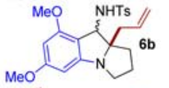
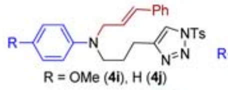
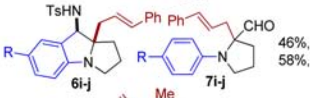
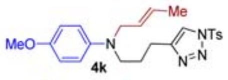
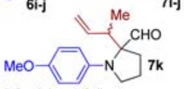
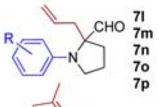
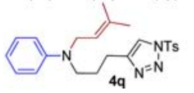
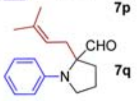
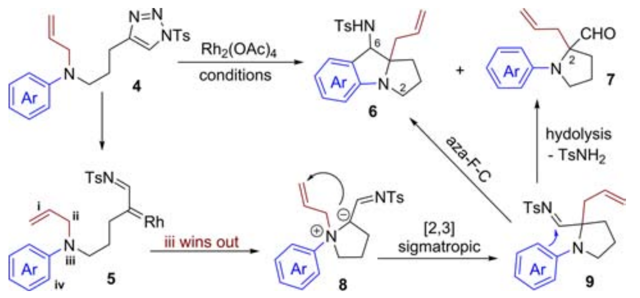
Table 1. $Rh_2(OAc)_4$ Catalyzed Reaction of 4-[3-(*N*-Allyl-*N*-aryl-amino)propyl]-1-tosyl-1*H*-1,2,3-triazoles[a]



substrate	product	yield[b], ratio
 4a	 6a	68%
 4b	 6b	66% *cis*/*trans*: 1.2/1
 R = Me (4c), Cl (4d), Br (4e)	 6c-e 7c-e	60%, 7c/6c: 2.1/1 63%, 7d/6d: > 20/1 64%, 7e/6e: 4.8/1
 R = Ph (4f), Cl (4g), Br (4h)	 6f-h 7f-h	64%, 7f/6f: 5.4/1 67%, 7g/6g: 2.3/1 65%, 7h/6h: > 20/1
 R = OMe (4i), H (4j)	 6i-j 7i-j	46%, 6i (trace 7i) 58%, 6j/7j: < 1/20
 4k	 7k 2/3 mixture of diastereomers	64%
 R = 4-MeO (4l), H (4m), 4-Me (4n), 4-Cl (4o), 3-Cl (4p)	 7l 7m 7n 7o 7p	66% 64% 65% 68% 45%
 4q	 7q	46%

[a] Reaction conditions: (step 1) **4** (0.3 mmol), $Rh_2(OAc)_4$ (2.0 mol %), tol (4 mL); then (step 2) K_2CO_3 (0.4 mmol), MeOH (4 mL), rt, overnight. [b] Isolated yield.

Scheme 2. Pathways Corresponding to the Formation of Benzopyrrolizidine and 2-Allyl-1-phenylpyrrolidine-2-carbaldehyde



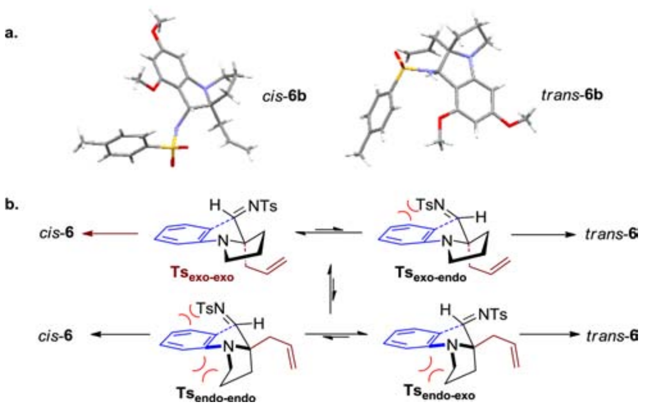


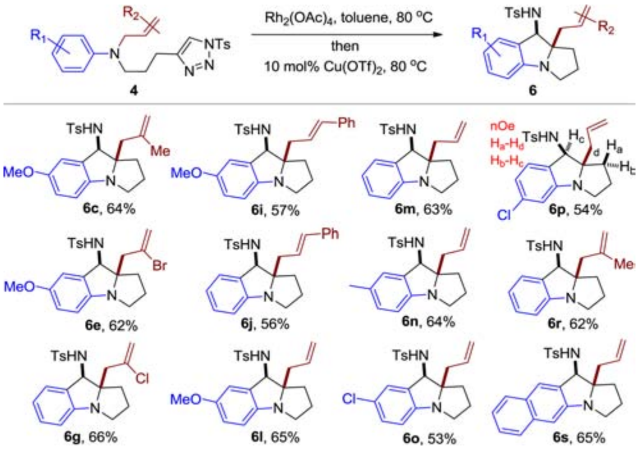
Figure 2. (a) X-ray crystal structure of *cis*-**6b** and *trans*-**6b**; (b) proposed transition states for the aza-Friedel–Crafts cyclization.

Table 2. Brief Lewis Acid Screening for Aza-Friedel–Crafts Cyclization[a]

additive	yield[b]	6l/7l
$BF_3 \cdot OEt_2$	24%	>20/1
$Sc(OTf)_3$	66%	1/2.3
$Cu(OTf)_2$	65%	>20/1

[a] Procedure and conditions: (step 1) **4l** (0.4 mmol), $Rh_2(OAc)_4$ (2.0 mol %), tol (4 mL), 80 °C, N_2, 2 h; then (step 2) 10 mol % Lewis acid was introduced directly at 80 °C and the reaction was stirred at this temperature for 2 h. [b] Isolated yields.

Scheme 3. Substrate Scope for Two-Step–One-Pot Synthesis of Benzopyrrolizidines[a,b]



[a] Procedure and conditions: (step 1) **4** (0.4 mmol), $Rh_2(OAc)_4$ (2.0 mol %), tol (4 mL), 80 °C, N_2, 2 h; then (step 2) 10 mol % Lewis acid was introduced directly at 80 °C and the reaction was stirred at this temperature for 2 h. [b] Isolated yields.

product in good yield after a hydrolysis operation. This selective formation of a valuable tricyclic system prompted further investigations. Substrate **4b** with a more electron-rich aniline group gave a 1.2/1 *cis*/*trans* diastereomeric mixture of tricyclic **6b**. Interestingly, when the same protocol was applied to compounds **4l**–**4q**, pyrrolidinyl aldehydes **7l**–**7q** were obtained in 46–68% yields.[15] Moreover, substrates (**4c**–**4h**) with a 2-substituted allyl group delivered mixtures of corresponding tricyclic benzopyrilidinyl sulfonamide and pyrrolidinyl aldehyde in favor of the latter (**4c**, **4e**–**4g** → **6c**:**7c**, **6e**:**7e**–**6g**:**7g**) except that only the aldehydes **7d** and **7h** were observed from the reactions of **4d** and **4h**. In contrast to the exclusive conversion of **4j** and **4k** to aldehyde **7j** and **7k**, their close analogue **4i** was transformed to tricyclic N-heterocycle **6i** in 46% isolated yield accompanied by a trace amount of pyrrolidinyl aldehyde **7i** according to NMR analysis of the crude reaction mixture, indicating that the aromaticity of a phenyl substituent on the allyl group at the terminal position and the nucleophilicity of the N-aryl group favor the formation of a benzopyrrolizidine framework (Table 1). Further studies proved that the hydrolyzing step is not necessary for the isolation of tricyclic compounds in cases the sulfonamides **6** were majorly formed.

The above observations accumulated to evidence that the N-nucleophile (iii) outcompetes the other three reacting sites (i, ii, and iv) for the in situ generated rhodium carbene in complex **5** (Scheme 2), leading to the formation of ammonium ylide **8**, which proceeds to pyrrodinyl sulfonyl imine **9** via a [2,3]-sigmatropic event.[16] The sulfonyl imine **9** would further undergo an aza-Friedel−Crafts reaction[17] with a competent vicinal aromatic ring to afford the tricyclic scaffold **6** in a heated reaction medium, and for those inert to the cyclization process, an additional hydrolysis step would eventually convert them into aldehyde **7**. The ratio of **7** to **6** for a specific substrate must reflect its combined influence of nucleophilicity of the meta carbon of the *N*-phenyl ring and the substituent on the N-allyl group. Interestingly, in cases **4i**, **4j**, and **4q**, a [1,2] Stevens rearrangement[18] occurred in place of its [2,3] counterpart, presumably due to the big conjugation effect and steric hindrance, respectively.

The structures of *cis*-**6b** and *trans*-**6b** were established unequivocally by X-ray analysis (Figure 2a). By analogy, the relative stereochemistry of the rest benzopyrrolizidines **6** in this draft was assigned as a 9,9a-*cis*-configuration which was further supported by ^{1}H−^{1}H NOESY analysis of **7p**. To explain the high *cis*-selectivity, it was proposed that there were four transition states in equilibrium as shown in Figure 2b. Transition state $\mathbf{Ts}_{\mathbf{exoexo}}$ was more stabilized in energy than the rest due to steric interactions found in the latter three. This accounts for the sole observation of the *cis*-configuration in most cases. While for **4b** → **6b**, the high nucleophilicity of the aromatic ring enabled by the three donating groups at the 1,3,5-positions might raise the cyclization rate to a level close to or even greater than the interconverting rates among these transition states, thus causing loss of diastereoselectivity.

Next, efforts were devoted to achieving the general applicability of this facile one-pot protocol for benzopyrrolizidine synthesis. For this end, we reasoned that the issue of low conversion of sulfonyl imine intermediate **9** to tricyclic alkaloid **6** in the reaction mixture had to be addressed. It was further reasoned that Lewis acids could be capable sulfonyl imine activators toward electrophilic attack.[19] Lewis acid screening was carried out using **4l** as a carbene precursor, and quickly, $Cu(OTf)_2$ emerged as a competent catalytic promoter with which full conversion of **9l** was achieved to give **6l** in 65% yield. Comparatively, only 1/3 cyclization occurred under the action of $Sc(OTf)_3$ and a much lower yield of **6l** has been obtained with $BF_3{\cdot}OEt_2$ as an aza-Friedel−Crafts promoter (Table 2). In all these cases, Lewis acid catalysts did not change the *cis*-diastereoselectivity.

With $Cu(OTf)_2$ as the catalytic sulfonyl imine activator, the above two-step−one-pot protocol for benzopyrrolizidinyl sulfonamide synthesis was applicable to a range of triazoles of type 4. The yields fall in the range of 55%−66%, demonstrating the generality of this protocol (Scheme 3).

In summary, a method for the efficient synthesis of structurally unique N-heterocycle benzopyrrolizidine has been developed; the highly functionalized tricyclic system with a synthetically difficult quaternary carbon center, a sulfonamide group, and an allyl segment was efficiently constructed via two relay catalytic reactions in a one-pot operation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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