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Rh-Catalyzed [3 + 2] Cycloaddition of 1-Sulfonyl-1,2,3-triazoles: Access to the Framework of Aspidosperma and Kopsia Indole Alkaloids

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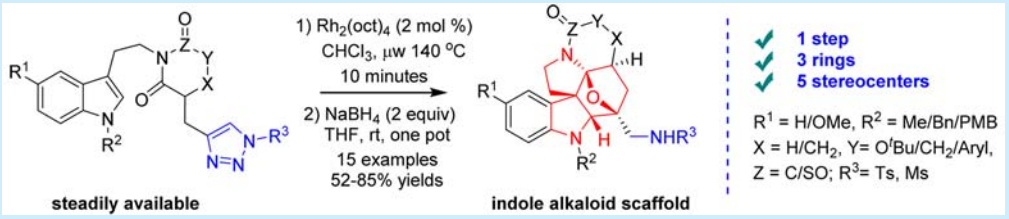
Supporting Information



ABSTRACT: A Rh(II)-catalyzed dearomative intramolecular [3 + 2] dipolar cycloaddition involving the indolic C2−C3 carbon−carbon double bond has been developed. The reaction was launched from the triazole moiety within the substrate and proceeded efficiently under mild conditions. A wide range of functional groups could be tolerated. These features render the current reaction a highly useful tool for the synthesis of polycyclic indole alkaloids, as showcased by a rapid assembly of the core structure of Aspidosperma and the related alkaloids.

Indole alkaloids represent a plethora of small molecules with unparalleled structural diversity.[1] Because of their intriguing chemical structures and significant biological properties[2] exemplified by strychnine, tubotaiwine, and vindoline (Figure 1), indole alkaloids are broadly considered to be attractive

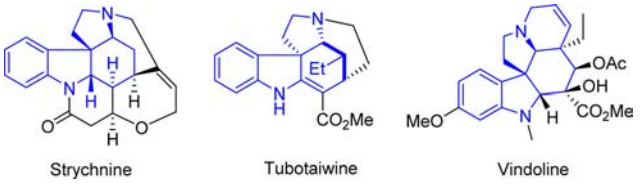


Figure 1. Some bioactive indole alkaloids.

synthetic targets. Many effective approaches for the stereoselective construction of various annulated indoline arrays[3] have thus been developed. In this regard, we were attracted to the idea of using an intramolecular [3 + 2] cycloaddition approach to access such structures in a single operation. Herein, we report a novel 1-sulfonyl-1,2,3-triazole-triggered intramolecular dipolar cycloaddition of indole which provides a rapid and practical entry to Aspidosperma and Kopsia alkaloid core structures to represent a useful complement to existing elegant studies.[4]

1-Sulfonyl-1,2,3-triazoles are readily prepared from terminal alkynes and *N*-sulfonyl azides by copper-catalyzed 1,3-dipolar cycloaddition. These compounds could serve as convenient precursors of α-imino metallocarbenes on treatment with rhodium(II) salts which were originally reported by Fokin and Gevorgyan.[5] The resulting α-imino metallocarbenes are very electrophilic and can undergo a variety of useful transformations.[6] In most cases, such species (A_1) act as a formal N,C 1,3-dipole equivalent[7] (Scheme 1, route a) in the reactions with nitriles,[5] aldehydes,[8] imines,[8] alkynes,[9] isocyanates,[10] indoles,[11] allenes,[12] or aromatic rings[7] to form a five-membered ring system.

It is conceivable that trapping of the electrophilic α-imino carbene with a carbonyl group properly located within the same molecule would lead to an oxonium ylide,[13] which could serve as a C,C 1,3-dipole (A2) capable of generating a substituted tetrahydrofuran through a cycloaddition with an olefin (Scheme 1, route b). In contrast to the oxonium ylide generated from α-diazo keto derivatives, reported previously by Padwa and coworkers,[4e,13a,c] the current imido oxonium ylide-based reaction could have two advantages. (1) The resulting imine motifs would facilitate their further transformation into the corre-

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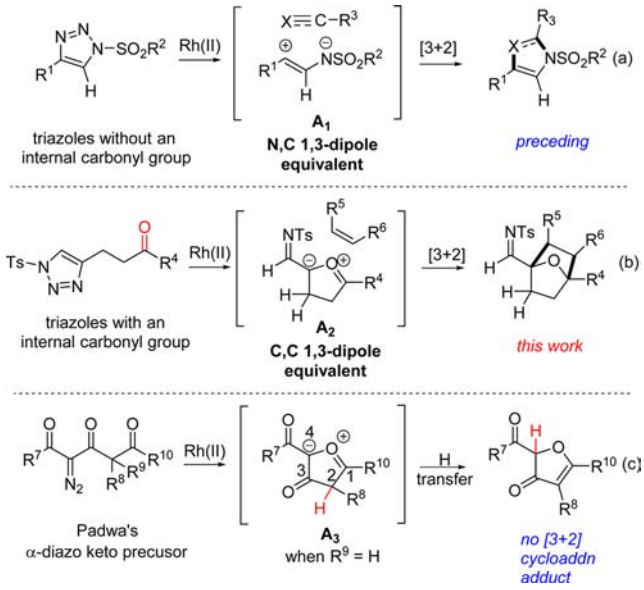
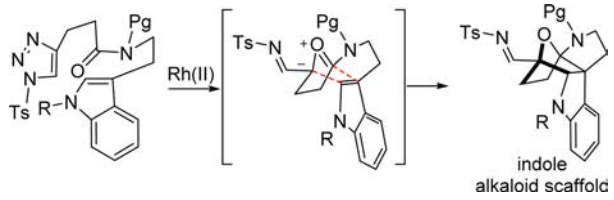
Scheme 1. Formal [3 + 2] Cycloaddition of Metallocarbenes



sponding aldehydes or sulfonamides, which would greatly expand the structural diversity of the products. (2) Without the extra carbonyl present in ylide A2 in our case, the ylide would be more reactive and prefer dipolar cycloaddition rather than undergoing an intramolecular 1,3-hydrogen transfer to afford a furanone, a product generated from ylide A3 (route c, the 3 + 2 cycloaddition does not occur if a hydrogen atom exists at C2 in the α-diazoketo substrate).[14]

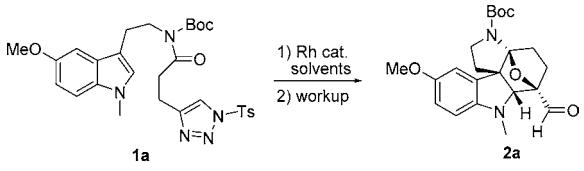
It is well-known that intramolecular cycloaddition reactions can offer a quick assembly of structural complexities. We envisioned that tryptamine-derived indolyl-1-tosyl-1,2,3-triazoles might provide the tetracyclic scaffolds of aspidosperma and kopsia alkaloids upon treatment with rhodium(II) salts if the imido oxonium ylide could be successfully generated (Scheme 2). These promising features promoted us to evaluate the feasibility of this synthetic method in our lab.

Scheme 2. Rh-Catalyzed Intramolecular Dipolar Cycloaddition



Our investigations began with the reaction of **1a** in the presence of a rhodium catalyst. Although with $Rh_2(OAc)_4$ as the catalyst no desired cyclization product was detected in DCM at room temperature (Table 1, entry 1), the cycloaddition[15] did proceed at a higher temperature (90 °C) in $CHCl_3$ to give the expected **2a** as a single isomer in 62% yield (entry 2). The structure of **2a** was secured by both NMR data and an X-ray crystallographic analysis of **3n**.[16] Further examinations of the reaction conditions showed that $CHCl_3$ was the best solvent, while $Rh_2(oct)_4$ was a more effective catalyst, especially at higher temperatures (see Table 1). Notably, the yield could be further improved to 87% under microwave irradiation at 140 °C in a sealed tube (entry 7). Use

Table 1. [3 + 2] Cycloaddition of 1a[a]



entry	catalyst	solvent	temp (°C)	yield[b] (%)
1	$Rh_2(OAc)_4$	DCM	25	NR
2	$Rh_2(OAc)_4$	$CHCl_3$	90	62
3	$Rh_2(OAc)_4$	hexane	90	20
4	$Rh_2(OAc)_4$	1,2-DCE	90	45
5	$Rh_2(OAc)_4$	PhMe	120	42
6	$Rh_2(oct)_4$	$CHCl_3$	90	73
7[c]	$Rh_2(oct)_4$	$CHCl_3$	140	87

[a]All reactions were performed with 0.1 mmol of triazole **1a** and 2 mol % of the Rh catalyst. [b]Isolated yield. [c]Performed in a microwave reactor.

of anhydrous solvent and high dilution (0.02 M) proved essential for the reaction.

Facile formation of the tetracyclic moiety present in many indole alkaloids from readily available triazole **1a** prompted us to further study the scope of the current rhodium-catalyzed intramolecular [3 + 2] cycloaddition. As shown in Figure 2, this

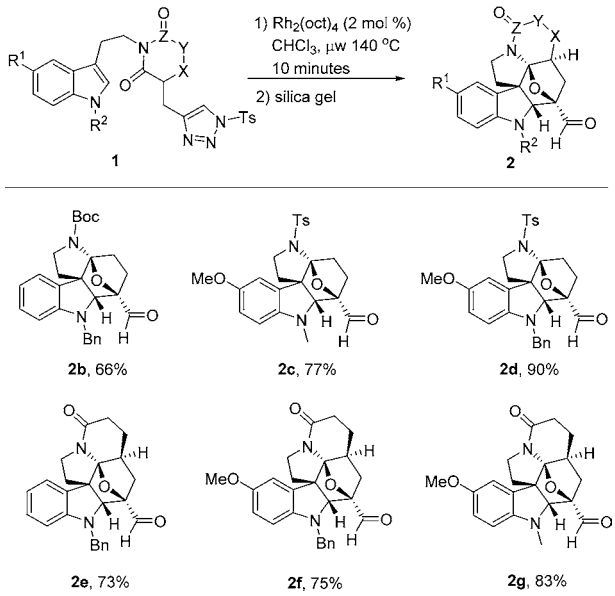


Figure 2. Rh-catalyzed cycloaddition of triazoles. Reactions performed (in a sealed tube) with **1** (0.1 mmol) and $Rh_2(oct)_4$ (2 μmol) in $CHCl_3$ (5 mL) at 140 °C for 10 min in a microwave reactor unless otherwise noted, with yields referring to isolated yields after chromatography on silica gel.

protocol tolerated a variety of functionalities on both the indole moiety and the amido tether. Considering the commercial availability, trypitamine and its C5-methoxyl derivative were chosen as the starting material of the substrates, the reaction results revealed the substituents on the indole N1 (Me, Bn) and C5 positions (H, MeO) had little influence on the reaction. The reactants with an *N*-tosyl group on the nitrogen atom within the amide tether also gave good to excellent yields (**2c,d**). The substrates with a cyclic imido tether (**1e−g**) were

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also transformed smoothly into the pentacyclic Aspidosperma skeleton in good yields (**2e**–**g**).

It was found that the [3 + 2] cycloaddition products (aldehydes after hydrolysis) were not so stable. Therefore, direct reduction before reaction workup and product purification appeared to be more appropriate. After several sets of reaction conditions were screened,[17] $NaBH_4$ in THF containing 1% MeOH was found to give the best results, providing the more stable secondary sulfonamides as a single isomer in reasonable to good yields. As shown in Figure 3, a more extensive scope exploration was then conducted by adopting the one-pot cyclization–reduction process. In general, the reaction displayed good functional group tolerance, and in all cases, the resulting indolines were obtained as a single isomer. A variety of substituents on the indole, the amido tether, and triazole moieties were extensively evaluated. The

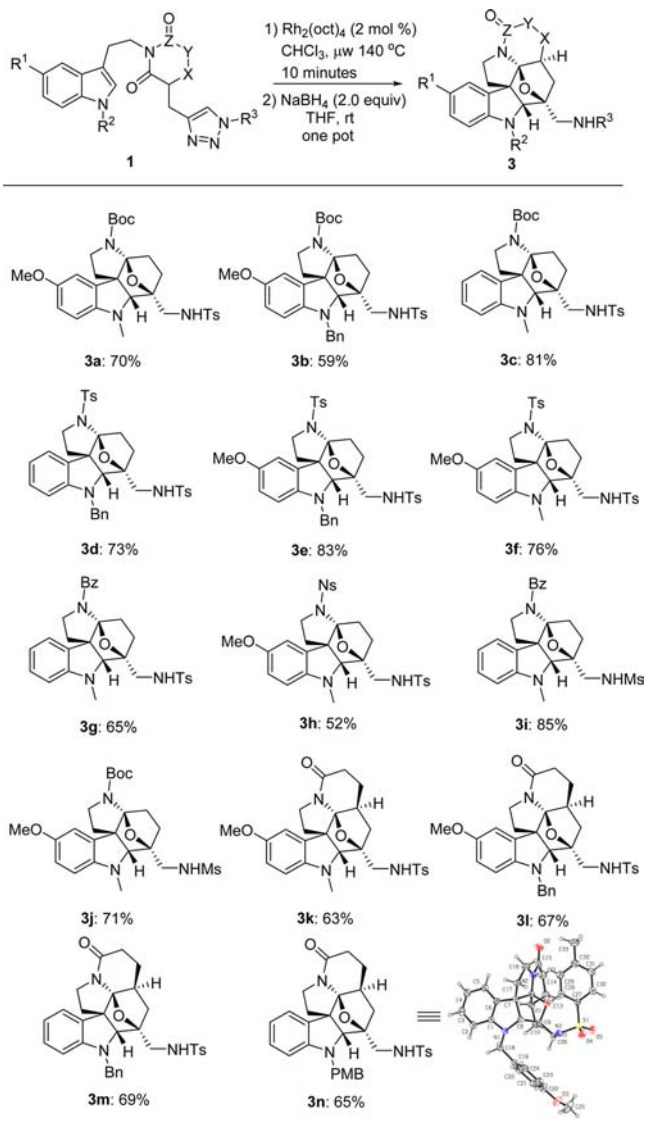
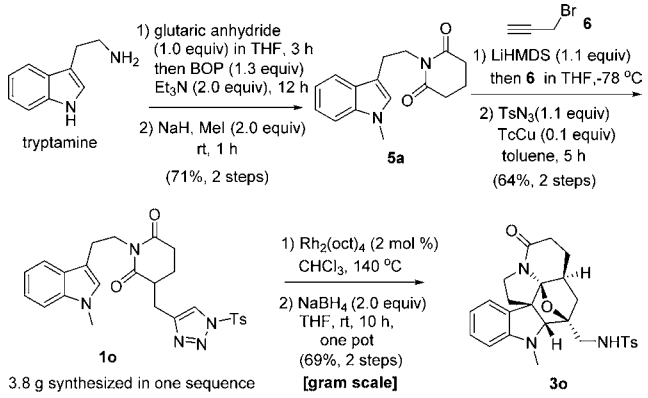


Figure 3. Scope of the Rh-catalyzed cycloaddition. Reactions performed (in a sealed tube) with **1** (0.1 mmol) and $Rh_2(oct)_4$ (2 μmol) in $CHCl_3$ (5 mL) at 140 °C for 10 min in a microwave reactor. The crude product after removal of the solvent was then treated with $NaBH_4$ (0.2 mmol) in THF (2 mL) and MeOH (20 μL) at rt for 5 h, with yields referred to two-step isolated ones after chromatography on silica gel.

substituent on the indole C5 position showed only a negligible influence on the cyclization. However, an electronic-rich group (such as methyl or benzyl) on the indolic nitrogen N1 position was essential for the success of the cyclization, while carbomethoxy derivatives did not form any desired products at all. On the other hand, the substitution at the amido nitrogen atom with an acyl or sulfonyl group (Boc, Bz, Ts, Ns) only had a minor influence on the reaction. The substrates with different groups at the amido tether reacted smoothly to deliver the corresponding products (**3a**–**h**) in yields ranging from 52% to 85%. As expected, triazoles containing either a tosyl or a mesyl behaved similarly (**3i**, **3j**). The substrates with a cyclic 6-membered tether (**3k**–**n**) generally gave the products in higher yields, while their counterparts with a 5-membered imido tether led only to a complex mixture, presumably due to the steric strain.

To test the practicality of our protocol, a gram-scale preparation of **3o** was executed. Triazole **1o** was prepared (3.8 g for a single synthetic sequence) from tryptamine via a four-step straightforward synthesis[18] (Scheme 3). Compound

Scheme 3. Gram-Scale Synthesis of 3o



1o was heated in the presence of 2 mol % of $Rh_2(oct)_4$ in $CHCl_3$, and this was followed by reduction with $NaBH_4$ to afford **3o** in 69% yield (1.2 g-scale). It is noteworthy that the above-mentioned cycloaddition showed distinct diastereoselectivitiy; the transition state TS1 (see the Supporting Information) seemed to be more favored and therefore gave the desired product.

In conclusion, we have developed a rhodium-catalyzed intramolecular [3 + 2] cycloaddition with *N*-sulfonyl-1,2,3-triazoles as the 1,3-dipole precursor, which showed excellent stereoselectivity and allowed for a quick access to the scaffold of Aspidosperma- and Kopsia-related alkaloids. In contrast to previously reported *N*-sulfonyl-1,2,3-triazole-based [3 + 2] cycloaddition reactions, the present protocol generates in situ a C,C-1,3 dipole synthon for the subsequent cycloaddition and thus provides a new entry to the polysubstituted tetrahydrofurans. Based upon its operational simplicity and the mild reaction conditions, the current approach may open up a new and efficient access to an array of valuable indole alkaloid analogues.

■ ASSOCIATED CONTENT

Supporting Information

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Synthetic procedures; ^{1}H and ^{13}C NMR spectra for all organic products (PDF)
X-ray data of compound **3n** (ZIP)

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Notes

The authors declare no competing financial interest.

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(15) The innate generated sulfonyl imine product could be identified by the ^{1}H NMR spectrum (see the SI) using the directly concentrated resulting reaction mixture. However, the sole product changed to corrresponding aldehyde after the sillica gel chromatography with elution containing 5% triethylamine.

(16) CCDC1463221 (**3n**) contains the supplementary crystallographic data for this paper. Data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

(17) Reduction of the resulting sulfonyl imines with $NaBH_4$, $NaBH(OAc)_3$, or $Na(CN)BH_3$ in classical protic solvents such as MeOH, EtOH or *i*-PrOH led to total decomposition of product, while DABAL or $LiAl(O^tBu)_3H$ in THF gave low yields.

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