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Scope of the Reactions of Indolyl- and Pyrrolyl-Tethered *N*-Sulfonyl-1,2,3-triazoles: Rhodium(II)-Catalyzed Synthesis of Indole- and Pyrrole-Fused Polycyclic Compounds

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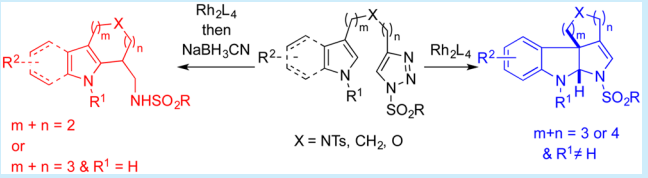
Supporting Information

ABSTRACT: An efficient synthesis of tetrahydrocarboline-type products and polycyclic spiroindolines has been achieved. The transformation proceeds via rhodium(II)-catalyzed intramolecular annulations of indolyl- and pyrrolyl-tethered *N*-sulfonyl-1,2,3-triazoles. The reaction could be tuned toward either the formal [3 + 2] cycloaddition or the C−H functionalization reaction depending on the electronic and structural features of the substrates, leading to the production of a variety of structurally related heterocyclic compounds.



Nitrogen-containing heterocycles are commonly embedded within polycyclic frameworks, among which polycyclic spiroindolines,[1] azepino[4,5-*b*]indoles,[2] and *β*-carbolines[3] are of significant importance because of their wide presence in complex natural products and biologically active compounds (Figure 1).

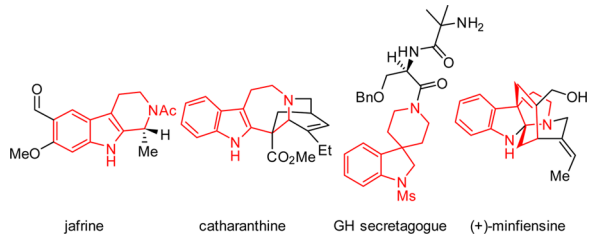


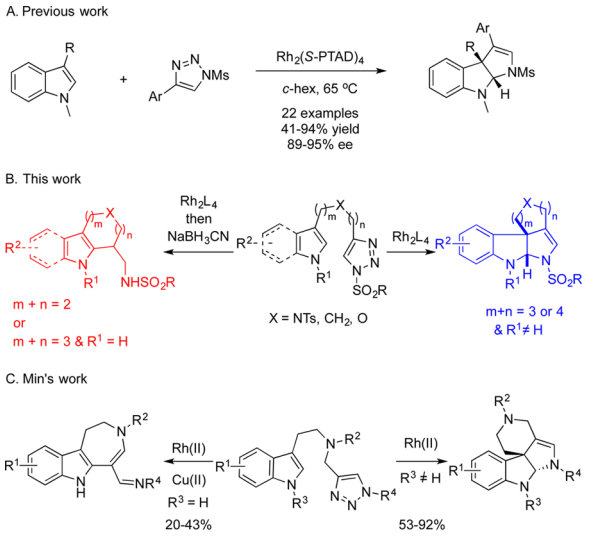
Figure 1. Spiroindoline- and *β*-carboline-containing natural products.

As a result, a variety of methods have been developed to synthesize these classes of compounds.[4−6] However, direct, simple, and effective approaches for their synthesis still remain relatively challenging, and the development of general and divergent methods for their synthesis would be desirable.

The chemistry of rhodium-stabilized donor/acceptor carbenes has long been a central theme of research in our group. Traditionally, diazo compounds have been most commonly used as the carbene precursors.[7] Gevorgyan and Fokin showed that *N*-sulfonyl-1,2,3-triazoles are capable of undergoing ring-to-chain isomerization to expose the diazo moiety.[8] As a result, these reagents can act as masked diazo compounds and serve as an alternative source of carbene precursors.[9] Since these initial reports, several groups have demonstrated the utilitiy of triazoles as carbene precursors for the development of useful transformations,[10] including transannulation reactions for the direct synthesis of heterocycles.[11]

Previously, we developed an enantioselective synthesis of pyrroloindolines via intermolecular formal [3 + 2] cycloaddition of 3-substituted indoles with 4-aryl-*N*-sulfonyl-1,2,3-triazoles (Scheme 1, A).[4b] Here we describe the intramolecular version of this reaction with indoles and pyrroles (Scheme 1, B). During preparation of this manuscript, a related study was reported by Shi and co-workers in which polycyclic pyrroloindolines and azepino[4,5-*b*]indoles could be formed in intramolecular reactions of indolyltriazoles (Scheme 1, C).[12] Our study goes beyond the Shi study and shows that the transformation has broader scope and flexibility: in addition to azepino[4,5-*b*]indoles, tetrahydrocarbolines and a range of polycyclic spiroindolines with different ring sizes and tether groups could

Scheme 1. Rhodium-Catalyzed Annulation of Indoles



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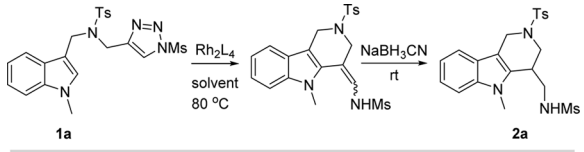
also be generated. Furthermore, pyrrolyltriazoles were demonstrated to be viable substrates.

The optimum conditions for the proposed reaction were determined using a tethered-indolyl triazole **1a** as the model substrate. The $Rh_2(OOct)_4$-catalyzed reaction of **1a** in 1,2-dichloroethane (DCE) at 80 °C gave a *Z*/*E* mixture of the annulated products, which were subsequently reduced with $NaBH_3CN$ in a one-pot fashion to give the sulfonamide **2a** in 81% yield (Figure 2, entry 1).[10e] A series of achiral dirhodium



entry	catalyst	solvent	yield (%)
1	$Rh_2(OOct)_4$	DCE	81
2	$Rh_2(TPA)_4$	DCE	48
3	$Rh_2(Piv)_4$	DCE	76
4	$Rh_2(OAc)_4$	DCE	70
5	$Rh_2(esp)_2$	DCE	71
6	$Rh_2(OOct)_4$	toluene	38
7	$Rh_2(OOct)_4$	$CHCl_3$	60
8	$Rh_2(OOct)_4$	*c*-hex	<5

Figure 2. Optimization of reaction conditions for tetrahydrocarboline formation.

catalysts and solvents were examined, and the combination of $Rh_2(OOct)_4$ and DCE was found to be the optimal combination (entry 1). Specifically, other achiral catalysts such as $Rh_2(TPA)_4$, $Rh_2(Piv)_4$, $Rh_2(OAc)_4$, and $Rh_2(esp)_2$ (Figure 3) proved to be

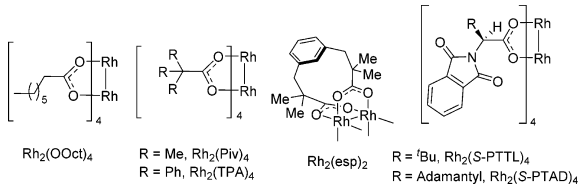
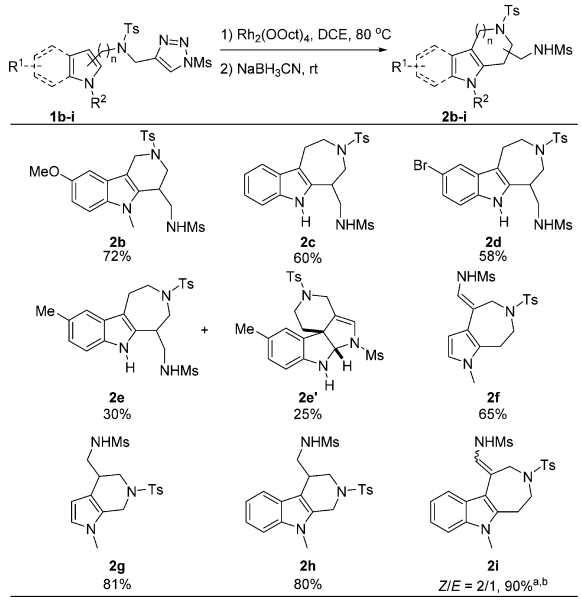


Figure 3. Dirhodium carboxylate catalysts used in this study.

less effective compared to $Rh_2(OOct)_4$ (entries 2–5). A solvent screen (entries 6–8) revealed that nonpolar solvents such as toluene and *c*-hexane were less effective for the system. Another chlorinated solvent chloroform was also a reasonably effective solvent in the reaction, though not as efficient as DCE.

The substrate scope for this transformation was then examined under the optimized reaction conditions, and a variety of carboline-type products could be synthesized (Scheme 2). The reaction of methoxy derivative **1b** generated the tetrahydrocarboline **2b**. Similar to Shi's observation,[12] the homologated and NH-unprotected substrates **1c–e** gave the formal C–H functionalization products azepino[4,5-*b*]indoles (**2c–e**). Interestingly, substrate **1d** with an electron-withdrawing bromo substituent gave exclusively tetrahydrocarboline **2d**, whereas substrate **1e** with an electron-donating methyl group at the 5-position gave a mixture of the spiroindoline and tetrahydrocarboline products (**2e** and **2e′**). Our studies further show that the transformation could be extended to substrates beyond the indolyl structure explored by Shi.[12] The reactions of pyrrole-tethered triazoles gave the desired formal C–H functionalization tetrahydropyrrolopyridine and tetrahydropyrrolo[2,3-*d*]azepine

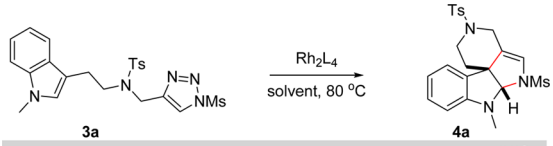
Scheme 2. Substrate Scope for the Intramolecular Formal C–H Functionalization with *N*-Sulfonyl-1,2,3-triazoles



[a]The products were not reduced with $NaBH_3CN$. [b]Combined yield of two isomers.

products in excellent yield (**2f,g**). The flexibility of the transformation was further demonstrated by using substrates with the tethers at C(2), and the product containing *β*-tetrahydrocarboline and *β*-azepine derivatives could be efficiently synthesized (**2h,i**).

When an *N*-methyl-homologated substrate **3a** was used, the formal C–H functionalization product was not obtained (Figure 4). Instead, only spiro compound **4a** derived from formal



entry	Rh_2L_4	solvent	yield (%)[a]
1	$Rh_2(OOct)_4$	DCE	62
2	$Rh_2(OOct)_4$	toluene	48
3	$Rh_2(OOct)_4$	$CHCl_3$	63
4	$Rh_2(OOct)_4$	*c*-hex	<5
5	$Rh_2(OOct)_4$	EtOAc	65
6	$Rh_2(TPA)_4$	EtOAc	60
7	$Rh_2(Piv)_4$	EtOAc	58
8	$Rh_2(esp)_2$	EtOAc	55
9	Rh_2(*S*-PTTL)$_2$	EtOAc	87[b]
10	Rh_2(*S*-PTAD)$_2$	EtOAc	86

[a]Isolated yield. [b]ee is 31% as determined by chiral HPLC analysis.

Figure 4. Optimization of reaction conditions for spiroindoline formation.

intramolecular [3 + 2] cycloaddition was observed in 62% yield. This behavior was also observed by Shi and co-workers.[12] The efficiency of the reaction was found to be dependent on the nature of dirhodium catalyst and the solvent. Interestingly, ethyl acetate was found to be the optimal solvent for the transformation (entries 2–5). After systematic exploration of the dirhodium catalysts for the reaction, $Rh_2(OOct)_4$ was found to be optimal among all of the achiral catalysts (entries 6–8) but

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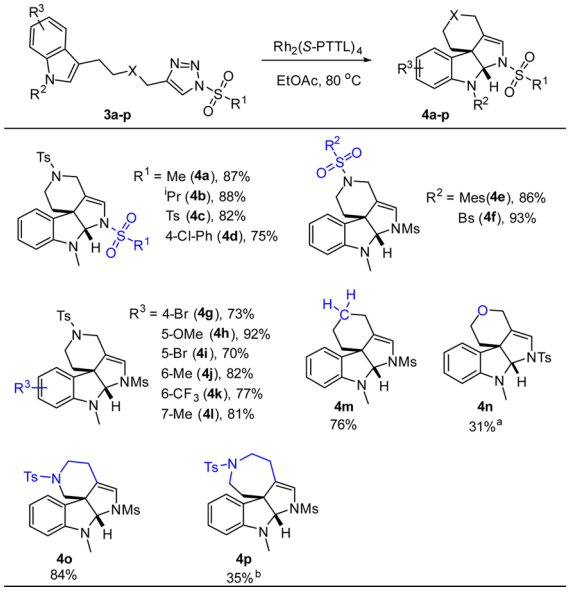
inferior to the chiral catalyst $Rh_2(S\text{-PTTL})_4$.[13] The best conditions described by Shi were $Rh_2(S\text{-PTTL})_4$ as the catalyst and *c*-hex/DCM as a solvent mixture.[12] Our results showed that ethyl acetate was a superior solvent for the reaction (87% vs 66% yield). The diastereoselectivity was routinely high (>19:1), but the chiral catalysts all gave relatively low levels of enantioselectivity (up to 31% ee with $Rh_2(S\text{-PTTL})_4$).

Having established the optimal conditions for the transformation, the scope of this reaction was subsequently explored and was found to be very general (Scheme 3). Similar to Shi's

Scheme 3. Substrate Scope of the Intramolecular [3 + 2] Annulation

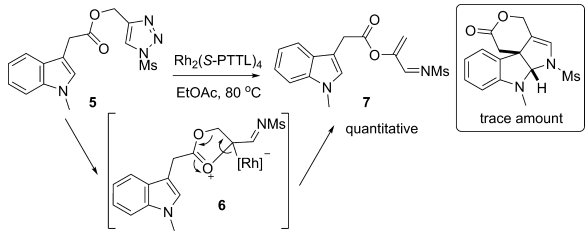


[a]Formation of byproduct derived from 1,2-hydride shift was observed. [b]Performed at 120 °C.

observations,[12] variation of sulfonyl groups on either the tethering nitrogen atom or the triazole moiety and substitutions on the indole ring were well tolerated (**3a**–**l**). The optimized conditions used in our system ($Rh_2(S\text{-PTTL})_4$/EtOAc) gave similar but generally improved yields compared to Shi's system (70–93% (average 82%) vs 53–92% (average 73%) yields). Specifically, a variety of sulfonyl groups on the triazole ring including mesyl, isopropylsulfonyl, tosyl, and *p*-chlorobenzenesulfonyl were all tolerated (**4a**–**d**). Furthermore, reactions of substrates with different sulfonyl groups on the tether, X = NTs, NMes, and NBs, all proceeded smoothly to afford the corresponding products (**4a**, **4e**, and **4f**). Different types of substitutions on the indole ring were tolerated, and the desired products were obtained in good to excellent yields regardless of the electronic nature of the substitutions (**4g**–**l**).[14] Our exploration also demonstrated that the transformation could be extended to more diverse substrates. Tethering groups other than nitrogen were examined: carbon-tethered substrate gave the desired product in good yield (**4m**); the oxygen-tethered analogue gave lower yield, with the observation of an undesired 1,2-hydride shift byproduct (**4n**); and a similar 1,2-hydride shift was observed by Shi and co-workers[12] in their intramolecular annulations. The position of the nitrogen tether could be moved closer to the indole ring (**4o**). Substrate **3p** with the tether homologated by one carbon also reacted, even though higher temperature was required for this transformation, and the 7-membered ring product **4p** was obtained in decreased yield. The substituent on the indole nitrogen has significant influence on the reactivity: the reaction of *N*-Boc substituted substrate gave a complex mixture, and the desired product was not observed.

The reaction with an ester-tethered substrate **5** led to an unexpected result (Scheme 4). Only a trace amount of the

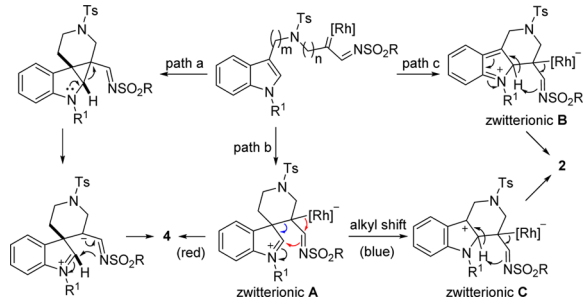
Scheme 4. Test of Substrate with an Ester as the Tether



desired product was observed on the basis of crude ^1H NMR analysis. Instead, product **7** proposed to be derived from rearrangement of the zwitterionic intermediate **6** generated by nucleophilic attack of the oxygen lone pair of the ester toward the electrophilic rhodium carbene was formed in nearly quantitative yield.

Plausible mechanistic pathways are outlined in Scheme 5. Shi and co-workers proposed that when the indole substrates were

Scheme 5. Proposed Mechanistic Pathways



protected by an alkyl group, cyclopropanation of the indole double bond followed by ring expansion gave the formal cycloaddition products.[12] Alternatively, when the indole NH is unprotected, a Friedel–Crafts-like reaction occurs in which the intramolecular hydrogen bonding between the indole NH and the imine group is critical. However, we found that the protected indole substrates (**2a**,**e**–**i**) still gave Friedel–Crafts-type products. Hence, we propose that for the annulation pathway, according to our previous report,[7b] initial cyclopropanation of the C(2)–C(3) double bond of the indole followed by subsequent ring-opening and recombination is the likely pathway (Scheme 5, path a). However, considering that *N*-Boc-indole which was reported to undergo concerted cyclopropanations with Rh(II) carbenes to afford isolable cyclopropylindolines did not work under the reaction conditions[15] and the presence of solvent effect in the reaction, a zwitterionic pathway resulting from substantial polarization of the C(2)–C(3) double bond is also plausible (Scheme 5, path b). On the other hand, when the tether is one carbon shorter, or with NH free indole, a Friedel–Crafts-type reaction takes place. In this case, reaction occurs at C(2) via zwitterionic intermediate **B** (Scheme 5, path c) or undergoes an alkyl shift from zwitterionic intermediate **A** to form

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zwitterionic intermediate **C** to give the formal C−H functionalization products.

In conclusion, a synthesis of tetrahydrocarboline, azepino[4,5-*b*]indoles, tetrahydropyrrolopyridine, and tetrahydropyrrolo[2,3-*d*]azepine by rhodium(II)-catalyzed intramolecular annulations of indolyl- and pyrrolyl-tethered *N*-sulfonyl-1,2,3-triazoles was achieved. During the studies, it was further found that by tuning electronic and structural factors polycyclic spiroindolines could also be synthesized by [3 + 2] cycloaddition reactions. This method features divergent intramolecular reactions of tethered triazole substrates, allowing for facile synthesis of a variety of nitrogen-containing heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

TThe Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00180.

Experimental procedures, characterization data, NMR spectra, and X-ray crystallographic data (PDF)
X-ray data for **4j** (CIF)

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Notes

The authors declare no competing financial interest.

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(13) For more detailed attempts to improve the enantioselectivity of the transformation, see the Supporting Information.

(14) The structure for compound **4j** was unambiguously assigned by X-ray crystallography. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre, and the deposition number CCDC 1427192 has been allocated.

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