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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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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.

Graphical Abstract

Nitrogen-containing heterocycles are commonly embedded within polycyclic frameworks, among which polycyclic spiroindolines,¹ azepino[4,5-*b*]indoles,² and β -carboline³ are of significant importance because of their wide presence in complex natural products and biologically active compounds (Figure 1). 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

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Notes

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, characterization data, NMR spectra, and X-ray crystallography

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 utility 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 the course of preparation of the manuscript, a related study was reported by Shi and coworkers 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 also be generated. Furthermore, pyrrolyltriazoles were demonstrated to be viable substrates.

The optimum conditions for the proposed reaction was determined, using a tethered-indolyl triazole **1a** as the model substrate. The Rh₂(OOct)₄-catalyzed reaction of **1a** in 1,2-dichloroethane (DCE) at 80 gave a *Z/E* mixture of the annulated products, which were subsequently reduced with NaBH₃CN in a one-pot fashion to give the sulfonamide **2a** in 81% yield (Figure 2, entry 1).^{10e} A series of achiral dirhodium catalysts and solvents were examined and the combination of Rh₂(OOct)₄ and DCE was found to be the optimal combination (entry 1). Specifically, other achiral catalysts such as Rh₂(TPA)₄, Rh₂(Piv)₄, Rh₂(OAc)₄, and Rh₂(esp)₂ (Figure 3) proved to be less effective compared to Rh₂(OOct)₄ (entries 2–5). A solvent screen (entries 6–8) revealed that non-polar solvents such as toluene and *n*-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 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 a *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 intramolecular [3 + 2] cycloaddition was observed in 62% yield. This behavior was also observed by Shi and coworkers.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, Rh₂(OOct)₄ was found to be optimal among all the achiral catalysts (entries 6–8), but inferior to the chiral catalyst Rh₂(*S*-PTTL)₄.¹³ The best conditions described by Shi were Rh₂(*S*-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 Rh₂(*S*-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 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–3l**). The optimized conditions used in our system (Rh₂(*S*-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, *iso*-propyl sulfonyl, tosyl, and *para*-chlorobenzenesulfonyl were all tolerated (**4a–4d**). Furthermore, reactions of substrates with different sulfonyl groups on the tether: X = NTs, NMe_s, and NB_s 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–4l**).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**); a similar 1,2-hydride shift was observed by Shi and coworkers¹² 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 desired product was observed based on 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 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**, **2e–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 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 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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13. For more detailed attempts to improve the enantioselectivity of the transformation, see 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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Figure 1.
Spiroindoline and β -carboline containing natural products

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

Figure 2.
Optimization of reaction conditions for tetrahydrocarboline formation

Figure 3.
Dirhodium carboxylate catalysts used in this study

entry	Rh_2L_4	solvent	yield (%) ^a
1	$\text{Rh}_2(\text{OOct})_4$	DCE	62
2	$\text{Rh}_2(\text{OOct})_4$	toluene	48
3	$\text{Rh}_2(\text{OOct})_4$	CHCl_3	63
4	$\text{Rh}_2(\text{OOct})_4$	<i>c</i> -hex	<5
5	$\text{Rh}_2(\text{OOct})_4$	EtOAc	65
6	$\text{Rh}_2(\text{TPA})_4$	EtOAc	60
7	$\text{Rh}_2(\text{Piv})_4$	EtOAc	58
8	$\text{Rh}_2(\text{esp})_2$	EtOAc	55
9	$\text{Rh}_2(\text{S-PTTL})_2$	EtOAc	87^b
10	$\text{Rh}_2(\text{S-PTAD})_2$	EtOAc	86

^aIsolated yield. ^bee is 31% as determined by chiral HPLC analysis.

Figure 4.
Optimization of reaction conditions for spiroindoline formation

A. Previous work

B. This work

C. Min's work

Scheme 1.
Rhodium-catalyzed annulation of indoles

^aThe products were not reduced with NaBH₃CN. ^bCombined yield of two isomers.

Scheme 2.

Substrate scope for the intramolecular formal C-H functionalization with *N*-sulfonyl-1,2,3-triazoles

^aFormation of byproduct derived from 1,2-hydride shift was observed. ^bPerformed at 120 °C.

Scheme 3.

Substrate scope of the intramolecular [3+2] annulation

Scheme 4.
Test of substrate with an ester as the tether

Scheme 5.
Proposed mechanistic pathways