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Rh(II)-Catalyzed Transannulation of *N*-Sulfonyl-1,2,3-Triazoles with 2,1-Benzisoxazoles or 1,2-Benzisoxazoles

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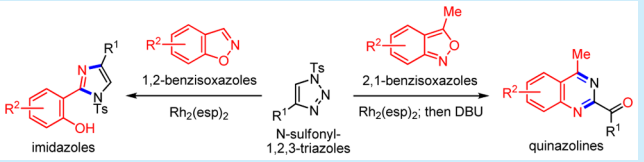
Supporting Information

ABSTRACT: A Rh(II)-catalyzed transannulation of *N*-sulfonyl-1,2,3-triazoles with 2,1-benzisoxazoles has been developed, which affords an efficient method for the synthesis of quinazoline derivatives. The transformation represents an unprecedented example which utilizes *N*-sulfonyl-1,2,3-triazole as an aza-[2C]-component in cycloadditions. Meanwhile, a Rh(II)-catalyzed formal [3 + 2] cycloaddition of *N*-sulfonyl-1,2,3-triazoles with 1,2-benzisoxazoles is also presented, which enables the rapid synthesis of functionalized imidazole derivatives.



Quinazoline and related scaffolds (e.g., quinazolin-4-one) are widespread structural units in bioactive natural products, therapeutic agents, and agrochemicals.[1] For example, gefitinib and erlotinib are known drugs for the treatment of lung cancer (Figure 1).[2] Prazosin, an α-adrenergic blocker, is used to treat high blood pressure, anxiety, and panic disorder.[3] Rutaecarpine, an alkaloid isolated from *Evodia rutaecarpa*, displays diverse therapeutic effects including anticancer, anti-inflammatory, and analgesic activities.[4] Not surprisingly, in view of their importance in organic synthesis and drug research, the development of a novel method to access quinazoline and related scaffolds has been a subject of intense interest in organic chemistry.[5]

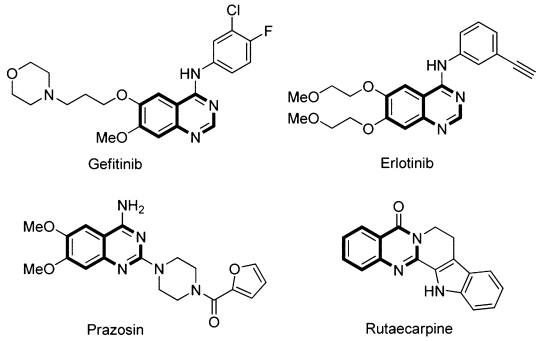
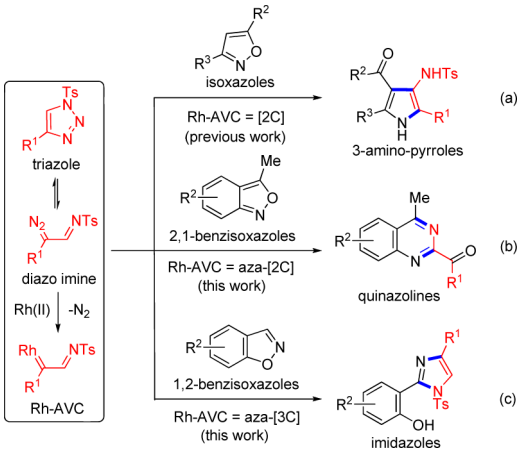


Figure 1. Representative quinazoline-containing compounds.

Recently, Rh-azavinylcarbene (Rh-AVC) has emerged as a versatile intermediate for the synthesis of nitrogen-containing heterocycles.[6] Readily generated from *N*-sulfonyl 1,2,3-triazoles through denitrogenation with the action of a Rh(II)-catalyst, Rh-AVC has been successfully employed as a [1C]-, [2C]-, or aza-[3C]-component in various transformations.[7−9] Our group has also shown keen interest in this emerging area of research, and several mechanistically interesting and synthetically useful cycloaddition reactions have been developed by us.[9a,b,10] For example, we recently disclosed a novel Rh(II)-catalyzed cycloaddition of *N*-sulfonyl 1,2,3-triazoles with isoxazoles, which enables the efficient synthesis of polysubstituted 3-aminopyrroles (Scheme 1a).[9b] In continuation of the above-mentioned study, we present herein another interesting Rh(II)-catalyzed cycloaddition of *N*-sulfonyl-1,2,3-triazoles with 2,1-benzisoxazoles, which results in the formation of functionalized quinazoline derivatives (Scheme 1b). Of note, in this reaction the *N*-sulfonyl-1,2,3-triazole formally serves as an aza-[2C]-

Scheme 1. Rh(II)-Catalyzed Cycloadditions of *N*-Sulfonyl-1,2,3-triazoles with Isoxazoles and Benzisoxazoles



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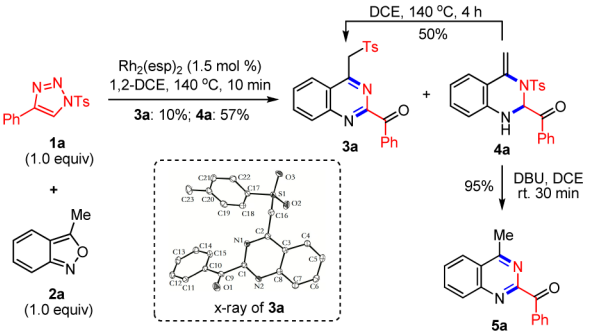
component instead of the commonly seen [1C]-, [2C]-, or aza-[3C]-component. In addition, a formal [3 + 2] cycloaddition of *N*-sulfonyl-1,2,3-triazoles with 1,2-benzisoxazoles is also presented, which provides a rapid entry to imidazole derivatives (Scheme 1c).

Our study was initiated from a seminal discovery depicted in Scheme 2. When 1,2,3-triazole **1a** and 2,1-benzisoxazole **2a**

Scheme 2. Initial Discovery



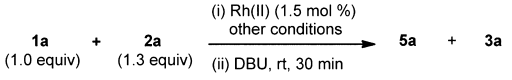
were treated with the conditions (1.5 mol % $Rh_2(esp)_2$, 1,2-DCE, 140 °C, 10 min) employed in the previous work,[9b] the expected cycloadduct was not observed (for details, see Scheme S-1, Supporting Information). Instead, two new products were detected, among which the minor one was determined to be **3a** by X-ray crystallographic study (Scheme 2),[11] and the major one was assigned to be **4a** on the basis of extensive spectroscopic study. **4a** was unstable and readily transformed to **3a** upon exposure to high temperature (140 °C, 4 h). Besides, **4a** could also convert to the quinazoline derivative **5a** in nearly quantitative yield upon treatment with DBU. The above discoveries appeared encouraging, since the resulting quinazoline derivative represents an important class of heterocycles in organic and medicinal chemistry. Moreover, in the reaction *N*-sulfonyl-1,2,3-triazole formally serves as an aza-[2C]-component, which represents a mechanistically interesting reaction that has not been fully explored.

To improve the efficiency of the reaction, we conducted a systematic condition screening (Table 1). In consideration of the fragile nature of **4a**, we chose to convert it to the more stable and synthetically useful product **5a** through a two-step one-pot procedure. As shown, among the several commonly used Rh(II)-catalysts, $Rh_2(esp)_2$ exhibited superior reactivity by affording the best yield of **5a** (entries 1−5). This observation was in agreement with our previous results.[9b] The solvent effect was also examined. Both $CHCl_3$ (entry 6) and toluene (entry 7) were less effective than DCE. A notable improvement was obtained when the reaction was conducted at 160 °C (entry 8), which afforded **5a** in 80% yield. In contrast, the lower reaction temperature (entries 9 and 10) gave inferior results.

With the optimal conditions in hand, the scope of triazole was examined. As illustrated in Scheme 3, a wide range of 4-aryl-triazoles reacted smoothly with **2a** to afford the corresponding quinazolines in good yields. Substrates possessing electron-rich (**5b−d**) or electron-deficient (**5e−f**) aryl substitutes at the C4 position showed comparable efficiency.[11] The orientation of the substituents exerted notable impact on the reaction. While both the para- and meta-substituted substrates provided satisfying results (**5b−i**), the ortho-substituted ones displayed inferior reactivity (e.g., **5l**). Moreover, some other aryl- or heteroaryl-substituted triazoles were tolerated well in the reaction (**5m** and **5n**).

Next, we examined the scope of the 2,1-benzisoxazole partner. As shown in Scheme 4, a range of substrates bearing electron-deficient or electron-rich substituents worked effectively with **1a** under the standard conditions, providing the

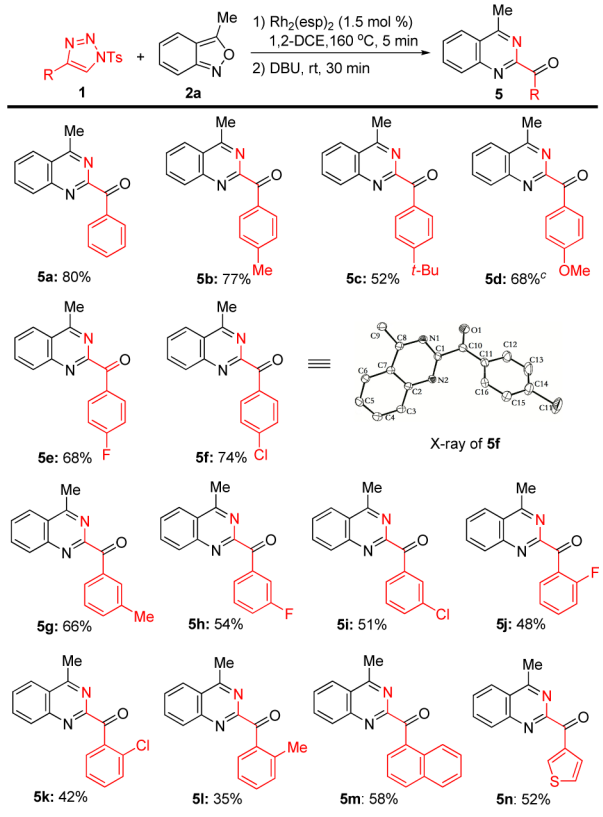
Table 1. Optimization of Reaction Conditions



entry	catalyst	other conditions[a]	yield (%)[b] 5a	3a
1	$Rh_2(oct)_4$	DCE, 140 °C, 40 min	46	17
2	$Rh_2(OAc)_4$	DCE, 140 °C, 90 min	30	29
3	Rh_2(*S*-DOSP)$_4$	DCE, 140 °C, 40 min	trace	trace
4	Rh(*S*-PTAD)$_4$	DCE, 140 °C, 40 min	trace	trace
5	$Rh_2(esp)_2$	DCE, 140 °C, 10 min	63	11
6	$Rh_2(esp)_2$	$CHCl_3$, 140 °C, 90 min	21	9
7	$Rh_2(esp)_2$	PhMe, 140 °C, 10 min	35	34
8	$Rh_2(esp)_2$	DCE, 160 °C, 5 min	80	–
9	$Rh_2(esp)_2$	DCE, 120 °C, 30 min	59	24
10	$Rh_2(esp)_2$	DCE, 60 °C, 12 h	trace	trace

[a]Reaction conditions: **1a** (0.20 mmol), **2a** (0.26 mmol), and Rh(II)-cat. (3.0 μmol) in 1,2-DCE (1.0 mL); DBU (1.5 equiv). [b]Isolated yield. DCE = dichloroethane, oct = octanoate, (*S*)-DOSP = 4-(dodecylphenyl)sulfonyl-(2*S*)-prolinate, (*S*)-PTAD = *N*-phthaloyl-(*S*)-adamantylglycine, esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropanoate.

Scheme 3. Scope of 1,2,3-Triazoles[a,b]



[a]Reaction conditions: **1** (0.20 mmol), **2a** (0.26 mmol), and $Rh_2(esp)_2$ (3.0 μmol) in 1,2-DCE (1.0 mL) at 160 °C; then DBU (1.5 equiv). [b]Isolated yield. [c]120 °C, 10 min.

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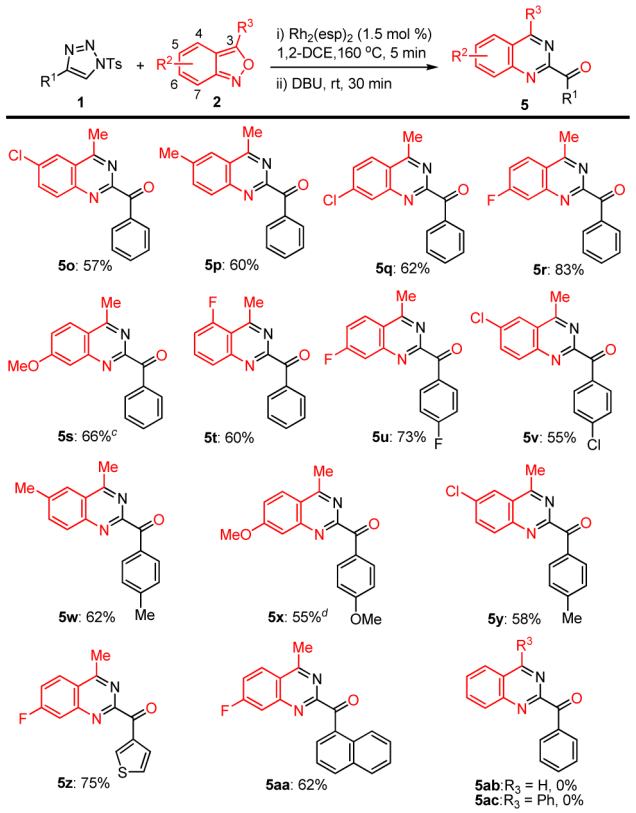
Scheme 4. Scope of 2,1-Benzisoxazoles[a,b]

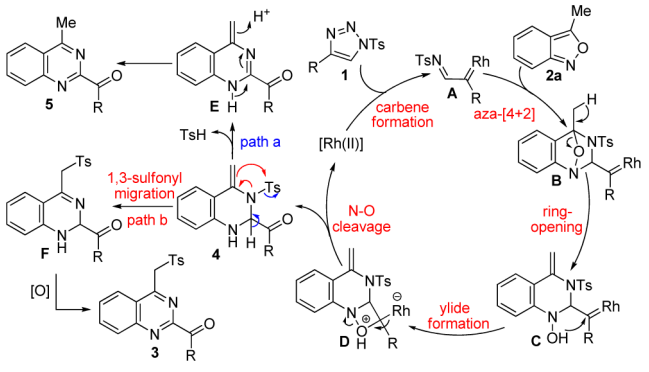


[a]Reaction conditions: **1** (0.20 mmol), **2** (0.26 mmol), and $Rh_2(esp)_2$ (3.0 μmol) in 1,2-DCE (1.0 mL) at 160 °C; then DBU (1.5 equiv). [b]Isolated yield. [c]120 °C, 15 min. [d]120 °C, 5 min.

corresponding quinazolines (**5o−t**) in good yields. The orientation of the substituents has little influence on the outcomes. The transformation could also be applied to the synthesis of a variety of quinazolines bearing two substituted aromatic rings (**5u−z** and **5aa**). However, the reaction was sensitive to the R_3-substituent of 2,1-benzisoxazoles **2**. Actually, both substrates bearing a H atom or a phenyl group at the C-3 position failed to give the desired products (**5ab** and **5ac**).

The plausible mechanism of the above transformation is illustrated in Scheme 5. Thus, the Rh-azavinylcarbene **A**, once generated from triazole **1** upon treatment with a Rh(II)-catalyst, could react with 2,1-benzisoxazole **2a** to form the intermediate **B** via an aza-[4 + 2] cycloaddition.[12] **B** could undergo ring opening to yield **C** which then evolves to the

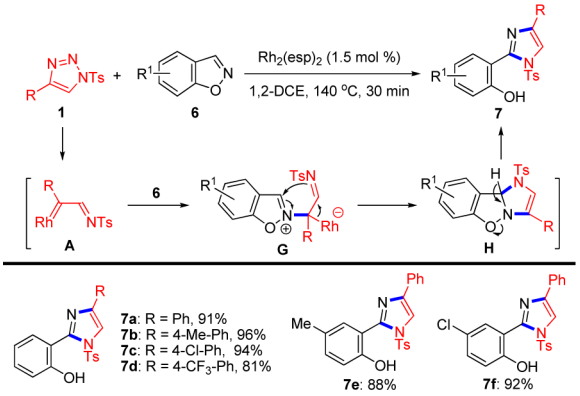
Scheme 5. Plausible Mechanisms



oxonium ylide **D**. Subsequently, the cleavage of the N−O bond would give the intermediate **4** alone with the release of the Rh(II)-catalyst. At this point, **4** could divert to two different products. On one hand, it could convert to the quinazoline **5** via the elimination of TsH followed by tautomerization (path a). This process plays a dominant role in the presence of DBU. On the other hand, **4** could also undergo a formal 1,3-sulfonyl migration[13] to give the intermediate **F**,[14] which, after autoxidation with air, could advance to the quinazoline derivative **4** (path b). Notably, while a concerted intramolecular 1,3-sulfonyl migration could not be completely excluded, a stepwise mechanism involving a close ion pair intermediate more likely accounts for the transformation from **4** to **F** based on the result of crossover experiments (for details, see Scheme S-3, Supporting Information).

As an extension of the above-mentioned study, the cycloaddition of *N*-sulfonyl-1,2,3-triazoles (**1**) with 1,2-benzisoxazoles (**6**) was also investigated (Scheme 6). To our

Scheme 6. Rh(II)-Catalyzed Cycloadditions of 1,2,3-Triazoles with 1,2-Benzisoxazoles[a,b]



[a]Reaction conditions: **1** (0.20 mmol), **6** (0.60 mmol), and $Rh_2(esp)_2$ (3.0 μmol) in 1,2-DCE (1.0 mL) at 140 °C. [b]Isolated yield.

surprise, this type of substrates displayed distinct reactivity from that of 2,1-benzisoxazoles (**2**). Indeed, in all of the examined cases, the imidazole derivatives (**7a−f**) were obtained as major products in excellent yields. Mechanistically, a formal [3 + 2] cycloaddition of *N*-sulfonyl-1,2,3-triazoles (**1**) with 1,2-benzisoxazoles (**6**) would give the dihydroimidazoles **H**, which then readily underwent aromatization via the cleavage of the N−O bond to afford the imidazoles **7**. Of note, a simple survey of the substrate scope indicated that this transformation was amenable to a wide range of triazoles and 1,2-benzisoxazoles, thus offering a useful method for the access of imidazole derivatives.

In summary, a novel Rh(II)-catalyzed transannulation of *N*-sulfonyl-1,2,3-triazoles with 2,1-benzisoxazoles has been developed, which provides an efficient method for the synthesis of quinazoline derivatives. Besides its potential synthetic value, the current work is also conceptually interesting since it represents the first example of utilizing Rh(II)-AVC as an aza-[2C]-component in the related cycloadditions, which further enriches the versatile reactivity of Rh(II)-AVC. In addition, a formal [3 + 2] cycloaddition of *N*-sulfonyl 1,2,3-triazoles with 1,2-benzisoxazoles is also reported, which enables the rapid construction of diverse imidazole derivatives. We anticipate that

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the present chemistry will find broad application in organic or medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02454.

Experimental procedures, spectra data, and copies of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(11) X-ray CCDC 1498773 (**3a**) and CCDC 1498774 (**5f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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(14) While the intermediate F was readily oxidized to F upon exposure to air, its intermediacy was validated experimentally. For details, see Supporting Information.

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