Rhodium-Catalyzed Annulative Coupling of Isothiazoles with Alkynes through N–S Bond Cleavage

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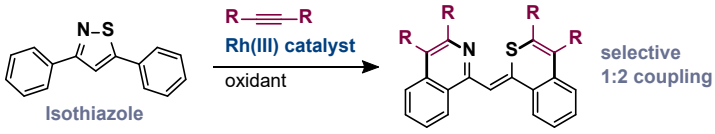
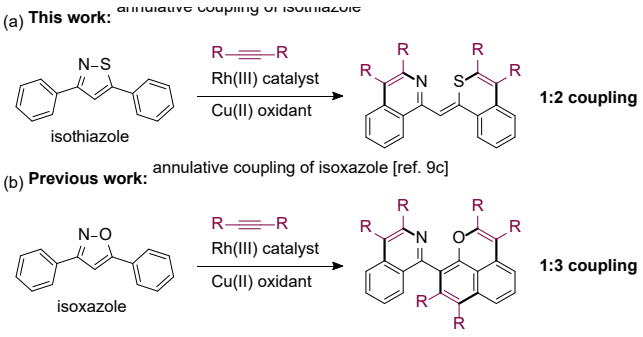


ABSTRACT: A Rh(III)-catalyzed annulative coupling of 3,5-diarylisothiazoles and alkynes is reported. The N–S bond in the isothiazole ring acts as an internal oxidant to regenerate the Rh(III) species in combination with an external Cu(II) oxidant, and the corresponding 1:2 coupling products are obtained. The remarkable difference in the reaction outcome between isothiazoles and the relevant isoxazoles has been investigated by DFT calculations, revealing that the relative stability of the enolate intermediates dictates the product selectivity.

Polycyclic heteroaromatic scaffold is ubiquitous in many natural compounds and has been a key motif in a wide range of manufactured functional molecules. The past decades witnessed a tremendous achievement in the field of transition-metal-catalyzed C–H activation[1] and subsequent oxidative annulation (annulative coupling) with alkynes or their equivalents,[2] allowing us to assemble various fused-ring systems with operational simplicity. In this reaction system, particularly using group 9 metal complexes (Co, Rh, Ir), catalytically active high-valent species are regenerated by external oxidants to ensure the catalyst turnover. Alternatively, some coordinating functionalities may act as two electron oxidants through heterolytic bond cleavage within them.[3,4] Fagnou *et al.* reported a seminal Rh(III)-catalyzed isoquinolone synthesis utilizing the N–O bond of hydroxamic acids as internal oxidants.[4b] Afterward, a series of catalytic coupling protocols based on such an N–O oxidizing directing group strategy has been developed by many research groups involving Glorius, Hartwig, Yu, and Chiba.[4,5] Furthermore, N–N,[6] N–S,[7] and C–N[8] bonds have also been adopted to establish redox-neutral coupling protocols.

Most of these reactions employed the oxidizing groups (-OR, -NR, -SR) as leaving counterparts. Our group,[9] Zhu,[10a,10b] and Dong[10c] recently developed Rh(III)-catalyzed 1-substututed isoquinoline synthesis via the cleavage of N–O bonds embedded in the aromatic ring systems of isoxazoles[11] and oxadiazoles. In each of the reactions, the whole of the directing groups is incorporated into the product skeleton. Upon our continuous investigation in such ring-to-ring transformations, we turned our interest in developing an annulative coupling of isothiazoles whose N–S bond may act as an internal oxidant. The use of oxidizing N–S bond in catalysis has rarely been successful to this date after the first report by Dong et al. who applied *N*-sulfinylimines to the synthesis of substituted pyridines.[7a]

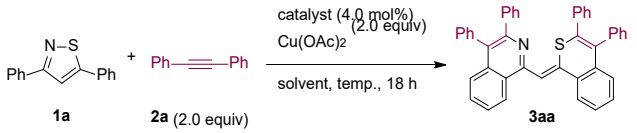
Scheme 1. Rh-catalyzed annulative coupling of isoxazole/isothiazole with alkyne



Herein, we report that 3,5-diarylisothiazoles selectively undergo cascade oxidative annulation with the incorporation of two equivalents of alkynes in the presence of an additional Cu(II) oxidant to construct isoquinoline and isothiochromene rings conjugated by a methine moiety in one pot manner (Scheme 1a). This is contrasting to the reaction of 3,5-diarylisoxazoles, which gives the 1:3 coupling products exclusively (Scheme 1b).[9c] In order to rationalize the outcome, preliminary DFT calculations have been carried out for the relative stability and reactivity of the corresponding enolate intermediates.

At the outset, we carried out an optimization study for the model reaction of 3,5-diphenylisothiazole (**1a**) with diphenylacetylene (**2a**) (Table 1). The corresponding 1:2 coupling product **3aa** was obtained in 93% yield using a $[Cp^*Rh(MeCN)_3][SbF_6]_2$ catalyst (4.0 mol%) and a $Cu(OAc)_2$ oxidant (2.0 equiv) at 100 °C in dioxane solvent (entry 1). The structure of **3aa** was unambiguously determined by X-ray crystallographic analysis,[12] where the isoquinoline and isothiochromene fragments are lying in almost the same plane with a small torsion angle of 11.6°. Both the rhodium catalyst and the copper oxidant were essential for the reaction (entries 2 and 3). Analogous neutral Rh(III) complexes (entries 4 and 5), $Cp^*CoI_2(CO)$ (entry 6), and $[(p\text{-cymene})RuCl_2]_2$ (entry 7) were totally inactive for the present transformation. Among the tested solvents, DCE afforded the highest 93% isolated yield at a lower temperature of 60 °C (entries 8-11). Notably, the reaction proceeded efficiently even at 40 °C (entry 12). The reaction could be conducted in 1.0 mmol scale (Scheme 2).

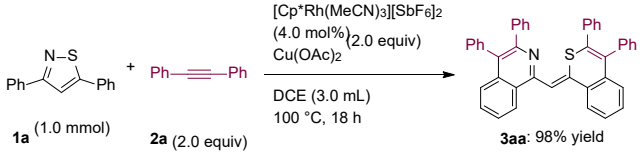
Table1. Optimization study [a]



entry	catalyst	solvent	temp	yield [b]
1	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	dioxane	100 °C	93%
2 [c]	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	dioxane	100 °C	trace
3	--	dioxane	100 °C	n.d.
4	$[Cp^*RhCl_2]_2$	dioxane	100 °C	n.d.
5	$[Cp^ERhCl_2]_2$	dioxane	100 °C	n.d.
6	$Cp^*CoI_2(CO)$ with $AgSbF_6$ (8.0 mol%)	dioxane	100 °C	n.d.
7	$[(p\text{-cymene})RuCl_2]_2$ with $AgSbF_6$ (8.0 mol%)	dioxane	100 °C	n.d.
8	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	dioxane	60 °C	93%
9	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	toluene	60 °C	76%
10	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	^{t}AmOH	60 °C	65%
11	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	DCE	60 °C	98% (93%)
12	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	DCE	40 °C	77%

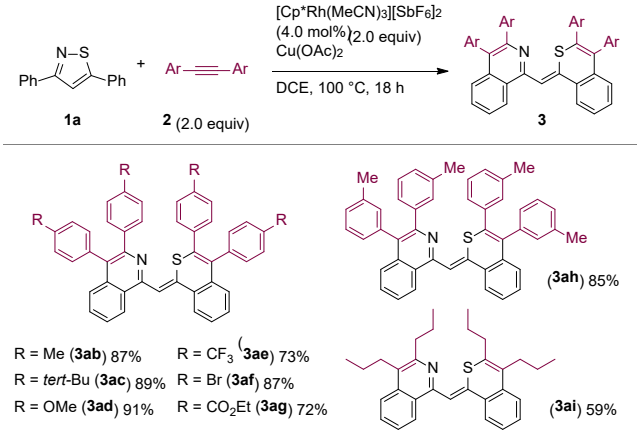
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), catalyst (4.0 mol% metal), $Cu(OAc)_2$ (0.2 mmol), solvent (1.5 mL).
[b] Determined by NMR analysis. Isolated yield in parentheses.
[c] Without $Cu(OAc)_2$. n.d. = not detected.

Scheme 2. Scale-up reaction



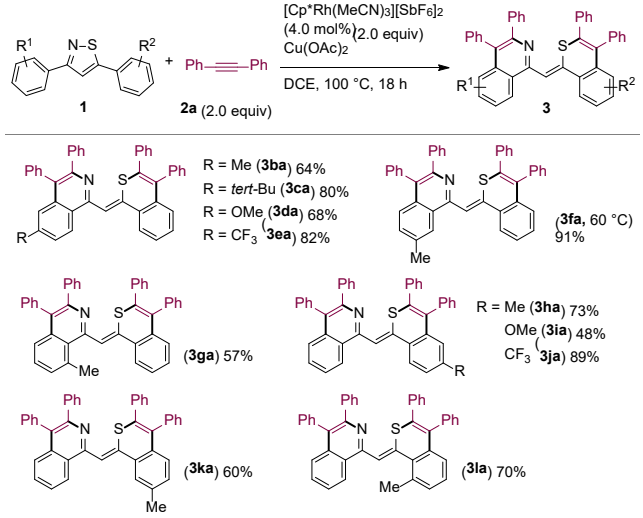
With the optimized reaction conditions, we evaluated the substrate scope with respect to alkynes **2** (Scheme 3). For aromatic alkynes **2b**–**2h**, the desired 1:2 coupling products **3ab**–**3ah** were obtained in high to excellent yields. The structures of **3ab**, **3ac**, and **3af** were confirmed by the X-ray analysis.[12] Bromo (**3af**) and ester (**3ag**) functionalities were remained intact during the reaction. An aliphatic alkyne (4-octyne, **2i**) was also applicable to the present reaction to give the corresponding product **3ai** in 59% yield.

Scheme 3. Substrate scope for alkynes



We next examined the annulative coupling of various 3,5-diarylisothiazoles **1b**–**1l** with the alkyne **2a** (Scheme 4). Apparently, substituents on the 3-aryl ring (**1b**–**1g**) and on the 5-aryl ring (**1h**–**1l**) did not significantly affect the reaction outcome, and they respectively fall into the isoquinoline and the isothiochromene subunits of the products. Both the electron-donating (**1c**, **1d**, **1i**) and -withdrawing (**1e**, **1j**) groups were tolerated. It is noteworthy that, for the reaction of **1f** and **1k**, the C–H activation took place only at the sterically more accessible positions to produce **3fa** and **3ka** exclusively. The position of the methyl protrusion in the coupling products (**3ba**, **3fa**, **3ga**, **3ha**, **3ka**, **3la**) were all determined by the X-ray analysis.[12]

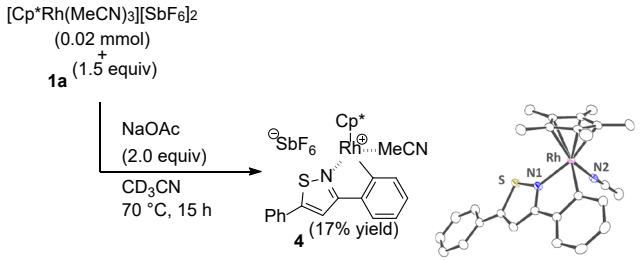
Scheme 4. Substrate scope for isothiazoles



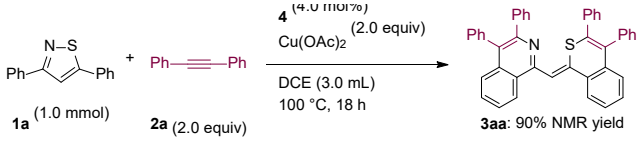
The isothiazole ring inherently offers two coordination sites, i.e. nitrogen and sulfur atoms. In order to elucidate which atom participates in the initial C–H activation event, we carried out a stoichiometric reaction of **1a** with the Rh(III) complex (Scheme 5). According to the literature procedure,[13] **1a** was treated with $[Cp^*Rh(MeCN)_3][SbF_6]_2$ in the presence of NaOAc as an acetate source. The corresponding metallacycle complex **4** was isolated in 17% yield, and the X-ray measurement revealed its

structure as a nitrogen-coordinated species.[12] This result indicated that the annulative coupling firstly proceeded at the nitrogen side to furnish the isoquinoline ring; thereby the second alkyne molecule constructed the sulfur heterocycle. The complex **4** served as an active catalyst to give **3aa** in 90% yield under the standard conditions (Scheme 6).

Scheme 5. Stoichiometric reaction of **1a** with Cp*Rh(III) complex; the structure of **4** is drawn with 40% thermal ellipsoid, hydrogen atoms and the counter anion are omitted for clarity

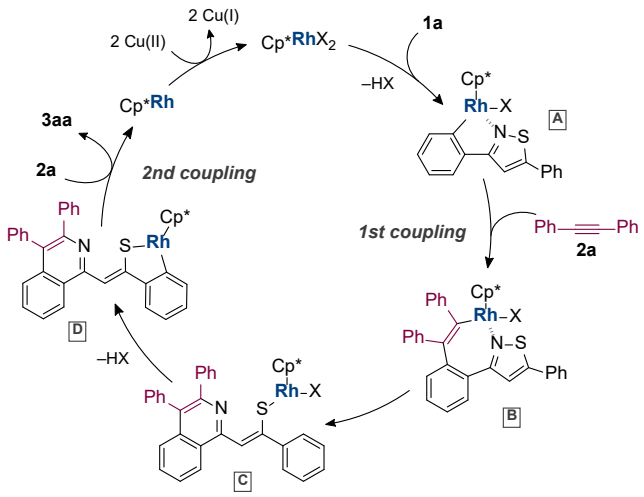


Scheme 6. Catalytic reaction with the complex **4**



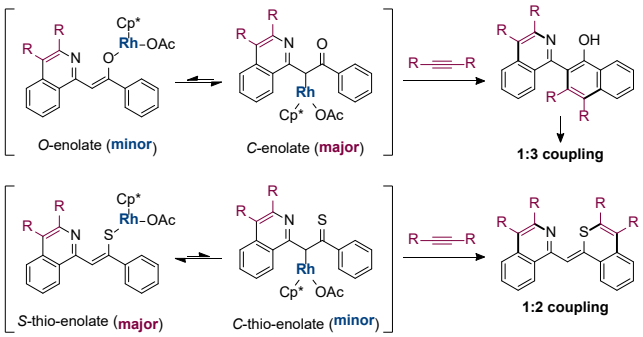
A proposed reaction mechanism for the 1:2 annulative coupling of **1a** and **2a** is illustrated in Scheme 7. The isothiazole ring coordinates to a cationic Cp*Rh(III) species to form a rhodacycle complex **A** through the proximal C–H bond activation. After the alkyne insertion into the Rh–C bond, sequential C–N reductive elimination and N–S oxidative addition generate an *S*-thioenolate (thiolate) complex **C**.[14] Following second C–H activation, alkyne insertion, and reductive elimination assemble the isothiochromene ring to give the product **3aa**. The liberated Rh(I) species is oxidized by $Cu(OAc)_2$ to regenerate the catalytically active Rh(III) species, closing the catalytic cycle.

Scheme 7. A proposed reaction mechanism



The difference in the product selectivity between the isoxazoles and the relevant isothiazoles would be dictated by the relative stabilities of the enolate intermediates. We previously found that the reaction of the isoxazole with alkyne proceeded via tautomerization from the *O*-enolate intermediate, which is structurally relevant to the complex **C** in Scheme 7, to the corresponding *C*-enolate (Scheme 8, top). Therefore, the isoxazoles selectively produced the 1:3 coupling products. In sharp contrast, this is not the case for the isothiazoles since the formation of *C*-thioenolate (thioketone) species is thermodynamically much unfavorable (Scheme 8, bottom).[15] Accordingly, the 1:2 coupling products are considered to be dominant for the reaction of the isothiazoles.

Scheme 8. Mechanistic consideration for the selectivity



In order to gain some insight into this speculation, we conducted a computational study (Figure 1).[16] The phenyl groups on the isoquinoline ring were omitted to simplify the calculation. In both cases of isoxazole (Figure 1a) and isothiazole (Figure 1b), the most stable configurations were isoquinoline-coordinated six-membered enol complexes **E-1**. Without the coordination of the nitrogen atom, two metastable states **K-2** (for *C*-enolate and *C*-thio-enolate) and **E-2** (for *O*-enolate and *S*-thioenolate) were obtained. For the isoxazole, the *C*-enolate (**K-2**) exhibited a lower ΔH (+9.6 kcal/mol) as compared to that of *O*-enolate (**E-2**, ΔH = +15.8 kcal/mol). In sharp contrast, for the isothiazole, the *C*-enolate (**K-2**, ΔH = +33.4 kcal/mol) was of much higher energy content than the *S*-thioenolate species (**E-2**, ΔH = +23.1 kcal/mol). Additionally, we calculated the activation enthalpies of the following C–H bond cleavage reactions via the concerted metalation deprotonation (CMD) mechanism from the intermediates **K-2** and **E-2**. The activation barriers for the isoxazole were respectively 20.1 kcal/mol in the keto pathway (**K-2**→**K-TS**→**K-3**) and 20.8 kcal/mol in the enol pathway (**E-2**→**E-TS**→**E-3**). Since there was no significant difference in between the activation energies, it is reasonable to conclude that the reaction outcome is mainly directed by the relative stability of the intermediates (**E-2** vs **K-2**), being consistent with the explanation in Scheme 8. In a similar manner, the barriers for the isothiazole were estimated as 9.0 kcal/mol in the keto pathway and 9.4 kcal/mol in the enol pathway. The enthalpies obtained herein were high considering the fact that the reaction proceeded even at 40 °C (Table 1, entry 12). This is probably because the stabilization effect of isoquinoline coordination is overestimated due to the omission of the phenyl substituents.

In summary, we have developed a Rh(III)-catalyzed annulative coupling of 3,5-diarylisothiazoles and alkynes that occurs selectively in a 1:2 manner to furnish structurally intriguing isoquinoline-isothiochromene conjugates. DFT calculations revealed that the difference in the reaction outcome between the isoxazoles and the isothiazoles are dominantly dictated by the relative stabilities of the corresponding keto and enol intermediates.

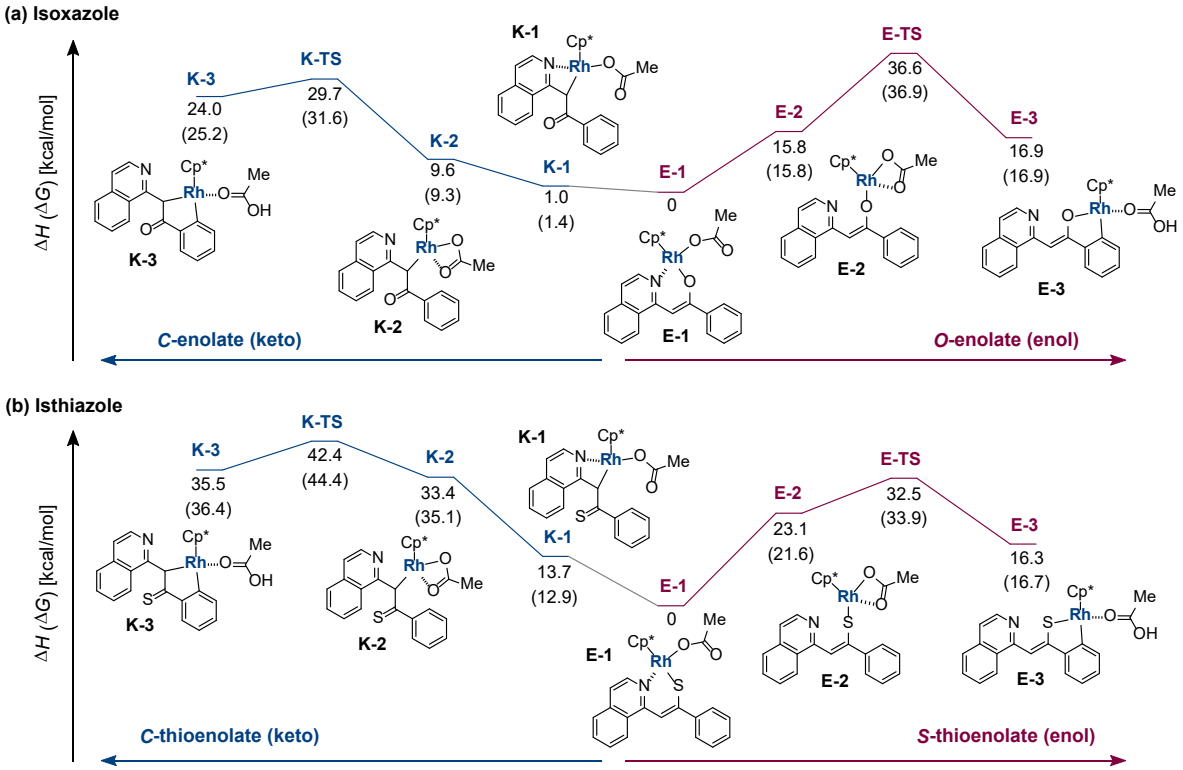


Figure 1. Partial enthalpy profile of the annulative coupling of (a) isoxazole and (b) isothiazole. Values in parenthesis are relative Gibbs energies.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website, including detailed experimental procedures, spectroscopic data, and copy of NMR spectra as a PDF file, and atomic coordinates of all calculated molecules as an XYZ file.

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Notes

The authors declare no competing financial interest.

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