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Efficient Approach to Mesoionic Triazolo[5,1-*a*]isoquinolium through Rhodium-Catalyzed Annulation of Triazoles and Internal Alkynes

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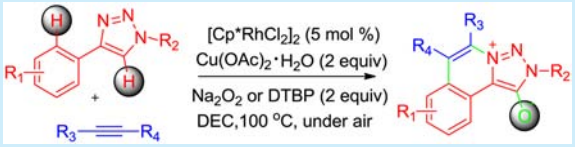
Supporting Information

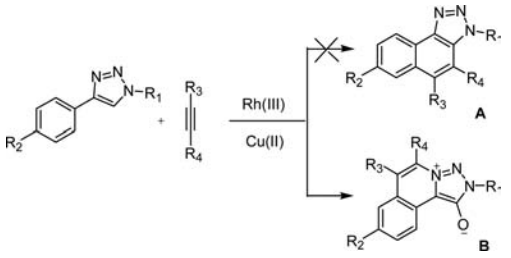
ABSTRACT: Rhodium-catalyzed annulation reactions between triazoles and internal alkynes, leading to various mesoionic isoquinoliums, are described. The reaction involves sequential triazole-directed C−H activation and C−C, C−N, and C−O bond formation processes in a one-pot manner. The starting materials and catalysts are easily available. The reaction offers a facile and practical approach to mesoionic isoquinolium derivatives.



Transition-metal-catalyzed C−H bond activation and annulation has emerged as a powerful tool for the assembly of N-containing heterocycles in biologically active molecules from readily available starting materials, which is generally difficult to achieve using traditional synthetic methods.[1] Rh(III)-catalyzed directed C−H activation and subsequent annulation resulting from the condensation of an aromatic ring with an alkyne unit have received attention because various fused aromatic rings can be efficiently constructed. Recent reports include oxidative C−H activation and annulation of 2-phenylpyridine, leading to isoquinolinium salts using O_2 as the oxidant;[2] [3 + 2] annulation of 5-aryl-2,3-dihydro-1*H*-pyrroles with internal alkynes using a $Cu(OAc)_2$ oxidant, resulting in the formation of the spiro[indene-1,2′-pyrrolidine] architectures;[3] a formal [5 + 2] cycloaddition between *o*-vinylphenols and alkynes, which is a practical route to benzoxepines;[4] and annulation of aryl thiocarbamates with internal alkynes with access to 3,4-disubstituted coumarin derivatives.[5] Highly popular N-heterocyclic carbenes derived from imidazolium also involve cascade double aromatic C−H activation and annulation, affording a variety of polycyclic heteroaromatic molecules containing benzo[*ij*]imidazo[2,1,5-*de*]quinolizinium architectures.[6] *N*-Alkoxyamide contains a reactive internal oxidant/directing group and can promote the formation of a wide variety of isoquinolones at room temperature and quite low catalyst loadings. Both terminal alkynes and alkenes are compatible over the redox-neutral strategy.[7]

1,2,3-Triazoles are essential skeletons of many biologically active organic compounds that have found wide applications in pesticides, medicines, and functional materials.[8] Direct functionalization of triazoles through a triazole-directed C−H activation strategy would be one of the most efficient approaches to access more complex triazoles since many simple triazoles can be easily obtained via click reaction. Recently, ruthenium-catalyzed triazole vinylation was reported to give double vinylated triazoles through C−H activation and alkyne insertion.[9] We envisioned that, under oxidized conditions, further annulation of the vinylation product would occur to afford naphthalene-fused triazoles **A**. However, as shown in Scheme 1, unexpected mesoionic triazolo[5,1-*a*]isoquinolium derivatives **B** were obtained under our conditions. Isoquinolium compounds are key building units of many natural alkaloids and have found wide applications as dyes, insecticides, and pharmaceuticals.[10] Triazolo[5,1-*a*]isoquinoliums have shown antitumor, antibiosis, and anti-inflammation activities,[11] but their synthetic methodology has been less studied. Mesoionic isoquinolinium derivatives are usually obtained from tetrahydroquinaldic acid and aryl diazonium through multistep reactions in moderate yields.[12]

Scheme 1. Rhodium-Catalyzed Annulation Reaction



In this paper, we report the oxidative annulation between triazole and internal alkynes catalyzed by $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2{\cdot}H_2O$, affording a number of mesoionic isoquinolium derivatives. The present reaction is an atom- and step-economic synthetic approach to the triazolo[5,1-*a*]isoquinolium moiety.

The model reaction between 1-octyl-4-phenyltriazole **1a** and 3-hexyne **2a** was performed using different experimental conditions (Table 1). Intermolecular annulation was initiated in the presence of $[Cp^*RhCl_2]_2$ (8 mol %) and $Cu(OAc)_2{\cdot}H_2O$

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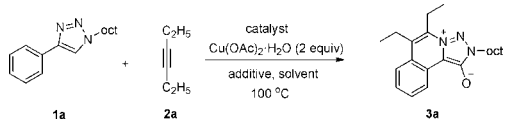
Table 1. Rhodium-Catalyzed C−H Activation and Annulation of 1-Octyl-4-phenyl-1*H*-1,2,3-triazole with 3-Hexyne[a]



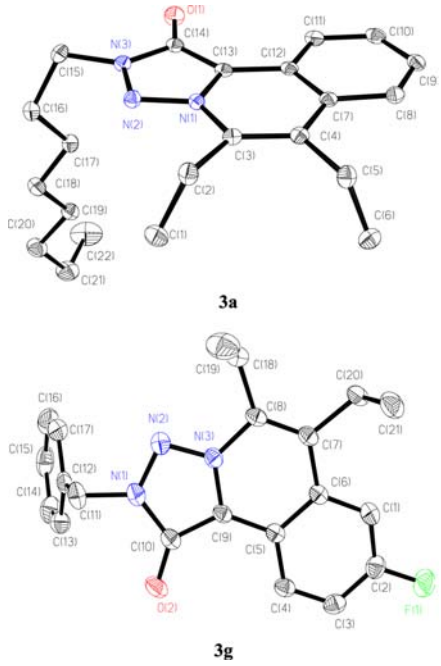
1a 2a 3a

entry	[Rh] (mol %)	additive (equiv)	solvent	yield (%)
1	$[Cp^*RhCl_2]_2$ (8)		DCE	44
2	$[Rh(OAc)_2]_2$ (8)		DCE	nr
3	$Rh(PPh_3)_3Cl$ (8)		DCE	<10
4			DCE	nr
5[b]	$[Cp^*RhCl_2]_2$ (8)		DCE	nr
6	$[Cp^*RhCl_2]_2$ (8)		DMSO	trace
7	$[Cp^*RhCl_2]_2$ (8)		DMF	32
8	$[Cp^*RhCl_2]_2$ (8)		toluene	31
9	$[Cp^*RhCl_2]_2$ (8)		DMAc	37
10	$[Cp^*RhCl_2]_2$ (8)		dioxane	<10
11	$[Cp^*RhCl_2]_2$ (8)		THF	28
12	$[Cp^*RhCl_2]_2$ (8)		CH_3CN	16
13	$[Cp^*RhCl_2]_2$ (8)	Cs_2CO_3 (0.6)	DCE	41
14	$[Cp^*RhCl_2]_2$ (8)	Cs_2CO_3 (1.0)	DCE	27
15	$[Cp^*RhCl_2]_2$ (8)	K_2CO_3 (0.6)	DCE	47
16	$[Cp^*RhCl_2]_2$ (8)	K_2CO_3 (1.0)	DCE	21
17	$[Cp^*RhCl_2]_2$ (8)	NaOAc (0.3)	DCE	trace
18	$[Cp^*RhCl_2]_2$ (8)	KOAc (0.5)	DCE	46
19	$[Cp^*RhCl_2]_2$ (8)	KOAc (1.0)	DCE	44
20	$[Cp^*RhCl_2]_2$ (8)	CsOAc (0.5)	DCE	46
21	$[Cp^*RhCl_2]_2$ (8)	AgOAc (0.5)	DCE	<5
22	$[Cp^*RhCl_2]_2$ (8)	HOAc (0.5)	DCE	<5
23	$[Cp^*RhCl_2]_2$ (8)	Na_2O_2 (1.0)	DCE	51
24[c]	$[Cp^*RhCl_2]_2$ (5)	Na_2O_2 (2.0)	DCE	64
25	$[Cp^*RhCl_2]_2$ (8)	DTBP (1.0)	DCE	41
26[c]	$[Cp^*RhCl_2]_2$ (5)	O_2 (1 atm)	DCE	42
27[c]	$[Cp^*RhCl_2]_2$ (5)	N_2	DCE	nr

[a]Unless otherwise mentioned, all reactions were carried out using **1** (0.2 mmol), **2** (0.24 mmol), and $Cu(OAc)_2·H_2O$ (0.4 mmol) at 100 °C for 14 h. [b]Without $Cu(OAc)_2·H_2O$. [c]Reaction time was 24 h.

(2.0 equiv) in DCE at 100 °C under air. 5,6-Diethyl-2-propyl-2*H*-[1,2,3]triazolo[5,1-*a*]isoquinolin-4-ium-1-olate **3a** was isolated in 44% yield, and no vinylation products were observed (entry 1). The structures of **3a** and **3g** were confirmed by NMR spectroscopy and X-ray single-crystal diffraction, and the molecular structures are given in Figure 1.

Other Rh catalysts such as $[Rh(OAc)_2]_2$ and $Rh(PPh_3)_3Cl$ were also examined. Under the same conditions as presented in Table 1, the Rh(II) dimer is totally inactive, whereas $Rh(PPh_3)_3Cl$ showed much poorer activity than $[Cp^*RhCl_2]_2$ (entries 2 and 3). $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2·H_2O$ are crucial for this annulation reaction, and $[Cp^*RhCl_2]_2$ or $Cu(OAc)_2·H_2O$ alone is not effective (entries 4 and 5). Screening of the solvents revealed that DCE is the best solvent. Other solvents such as toluene, THF, DMF, etc. afforded **3a** in lower yields (entries 6−12). Additional bases such as K_2CO_3, KOAc, and CsOAc were found to have little impact on this reaction (entries 13−21). Increased base can hinder the reaction. Addition of HOAc inhibits the reaction, and the yield of **3a** sharply decreased to <5% (entry 22). When the annulation of triazole was performed under N_2, no products were observed, and the starting materials could be recovered (entry 27). When the reaction was conducted under 1 atm O_2, the yield of **3a** was almost identical to that found in air (entry 26). Unexpectedly, the annulation was



3a **3g**

Figure 1. Molecular structures of **3a** and **3g**.

remarkably enhanced by addition of Na_2O_2, and the yield of **3a** increased to 64% (entry 24). However, organic peroxide such as DTBP (di-*tert*-butyl peroxide) did not show the same effect (entry 25).

Under the optimized reaction conditions, we examined the generality and restrictions of the annulation reactions between various 1,2,3-triazoles **1a−k** and **2a**. The results are summarized in Scheme 2. Reactions of **2a** with triazoles bearing an electron-withdrawing group such as F and Cl at the *para* position of the phenyl ring provided the corresponding products **3b**, **3c**, **3f**, and **3g** in >70% yield. Triazoles bearing an electron-donating substituent gave the mesoionic isoquinoliums **3d** and **3h** in lower yields of ∼60%. These results illustrate that the electron-deficient triazoles favor the annulation reaction probably because the orthopalladation is relatively easier. The electron-donating substituent at the *meta* position of the phenyl ring inhibits the annulation, and **3j** was isolated in 50% yield. Variation of the N-substituents of the triazole moiety has little impact on the reactions. When *N*-octyl was replaced with benzyl and 2-phenylethyl groups, corresponding products **3g−3k** were isolated in almost identical yields as the *N*-octyl derivatives.

The scope of aliphatic alkynes was examined in this annulation reaction. When **1c** and **1d** reacted with 2-butyne **2b**, the corresponding isoquinoliums **3l** and **3m** were obtained in 33 and 44% yields. An unsymmetric internal alkyne was also applied to the annulation reaction. Reactions of 1,2,3-triazoles with 2-hexyne **2c** gave the corresponding products **3n** and **3o** in 39 and 30% yields. Isoquinoliums **3n** and **3o** were isolated as mixtures of two isomers. Unfortunately, we did not get any annulation products when bis(trimethylsilyl)acetylene, 1,4-dibromo-2-butyne, and 2-butyne-1,4-diol were used as the starting materials.

Unexpectedly, the annulation reaction of aromatic internal alkynes did not occur under the conditions described above. Instead, double vinylation of 1,2,3-triazoles took place smoothly, giving **5a−5k** (Scheme 3). Treatment of 1-octyl-4-(4-chlorophenyl)-1*H*-1,2,3-triazole **1b** with 1,2-diphenylacetylene **4a** (1:1.2) in the presence of $[Cp^*RhCl_2]_2$ (8 mol %) and $Cu(OAc)_2·H_2O$ (2.0 equiv) in DCE at 100 °C for 14 h afforded

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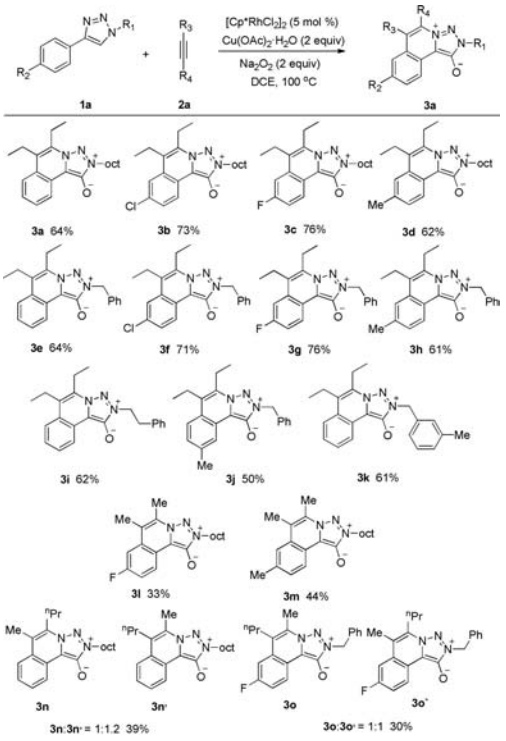
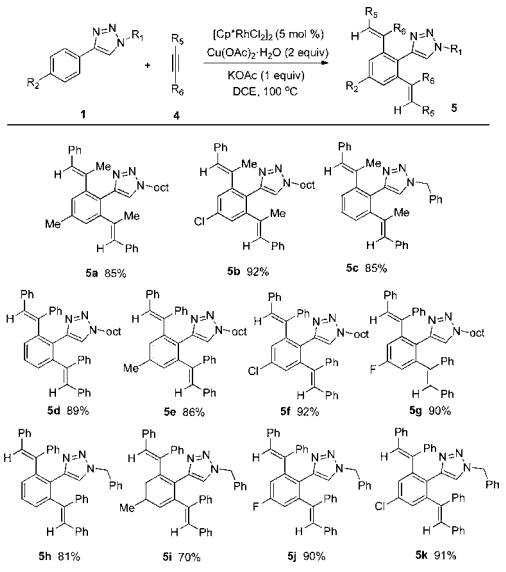
Scheme 2. Variation of Internal Alkynes[a]



[a]Reactions were carried out using **1** (0.2 mmol), **2** (0.24 mmol), $Cu(OAc)_2·H_2O$ (0.4 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), and Na_2O_2 (0.4 mmol) at 100 °C for 24 h.

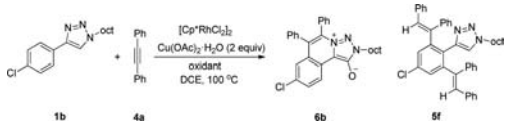
Scheme 3. Rhodium-Catalyzed Double Vinylation of Triazoles with Internal Alkynes[a]



[a]Reactions were carried out using **1** (0.2 mmol), **4** (0.4 mmol), $Cu(OAc)_2·H_2O$ (0.4 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), and KOAc (0.2 mmol) at 100 °C for 14 h.

5f in 29% yield, resulting from double vinylation of **1b**. The same reaction catalyzed by $[Ru(p\text{-cymene})Cl]_2$ was reported recently.[9] Monovinylation product and mesoionic isoquinolinium **6b** were not observed. Results are summarized in Scheme 3 and Table 2.

Table 2. Rhodium-Catalyzed C−H Activation and Annulation of 4-(4-Chlorophenyl)-1-octyl-1*H*-1,2,3-triazole with Diphenylacetylene[a]



entry	additive (equiv)	yield of **6b** (%)	yield of **5f** (%)
1[b]		nr	29
2		nr	51
3	K_2CO_3 (1.0)	nr	68
4	KOAc (1.0)	nr	92
5	Na_2O_2 (1.0)	trace	47
6	$K_2S_2O_8$ (1.0)	<5	29
7	$(NH_4)_2S_2O_8$ (1.0)	trace	31
8	TEMPO (1.0)	nr	40
9	DTBP (1.0)	25	18
10	*m*CPBA (1.0)	trace	27
11	H_2O_2 (30%) (1.0)	<5	15
12[c]	DTBP (2.0)	56	17
13[d]	DTBP (1.0)	90	trace
14[c,e]	DTBP (2.0)	nr	16
15[c,f]	DTBP (2.0)	<10	<10

[a]Unless otherwise mentioned, all reactions were carried out using **1b** (0.2 mmol), **2d** (0.4 mmol), $Cu(OAc)_2·H_2O$ (0.4 mmol), and $[Cp^*RhCl_2]_2$ (8 mol %) at 100 °C for 14 h. [b]**2d** (0.24 mmol). [c]$[Cp^*RhCl_2]_2$ (5 mol %) for 24 h. [d]$[Cp^*RhCl_2]_2$ (15 mol %). [e]$Cu(OAc)_2·H_2O$ (0.4 mmol) was replaced with CuI (0.4 mmol). [f]$Cu(OAc)_2·H_2O$ (0.4 mmol) was replaced with CuCl (0.4 mmol).

For 4-(4-chlorophenyl)-1-octyl-1*H*-1,2,3-triazole, when the molar ratio of triazole and alkyne increased from 1:1.2 to 1:2, the yield of **5f** sharply increased to 51% from 29% (entries 1 and 2, Table 2). Bases such as KOAc and K_2CO_3 can further improve the double C−H activation processes, and the yield of **5f** increased to 92 and 68% in the presence of 1 equiv of KOAc and K_2CO_3, respectively (entries 3 and 4). A few other triazoles and alkynes were also examined. The efficiency of the double vinylation reaction is also affected by the substituents of triazoles. Scheme 3 illustrates that electron-deficient triazoles are more reactive, and **5f**, **5g**, **5j**, and **5k** were isolated in >90% yield, whereas the electron-rich triazoles gave slightly lower yields. The influence of N-substituents can be neglected. In the presence of 1 equiv of KOAc, unsymmetric alkynes are also reactive, and the corresponding vinylation products **5a**−**5c** were isolated in comparable yields. In all cases, no monovinylation products were observed when <1 equiv of alkynes was used.

To explore the possibility of a one-pot synthesis of mesoionic isoquinolium from triazole and aromatic alkynes, we further optimized the reaction conditions. We examined the role of a few inorganic and organic oxidants (entries 5−12, Table 2). The presence of 1.0 equiv of Na_2O_2, $K_2S_2O_8$, $(NH_4)_2S_2O_8$, H_2O_2 (30%), TEMPO, and *m*CPBA did not promote the formation of isoquinolium. Bases usually retarded the vinylation of triazoles. DTBP can efficiently boost the annulation reaction, and **6b** was isolated in 25% yield with the vinylation product in 18% yield (entry 9). When 15 mol % of $[Cp^*RhCl_2]_2$ and 1 equiv of DTBP were employed, the yield of **6b** sharply increased to 90% (entry 13). Treatment of **1b** with **4a** in the presence of $[Cp^*RhCl_2]_2$ (5 mol %), $Cu(OAc)_2·H_2O$ (2.0 equiv), and DTBP (2.0 equiv) in DCE at 100 °C for 24 h afforded **6b** in 56% yield (entry 12).

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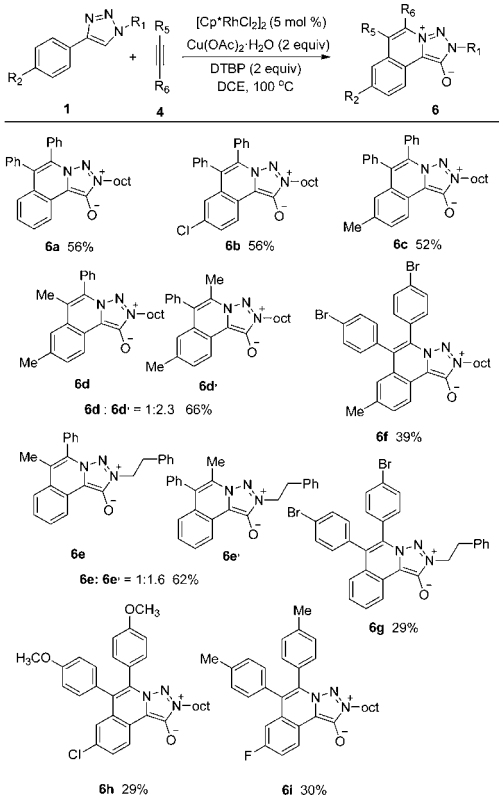
Replacement of $Cu(OAc)_2·H_2O$ by another copper salt or oxide did not improve the reaction (entries 14 and 15).

Annulation reactions of various aromatic alkynes and triazoles in the presence of 5 mol % of $[RhCp^*Cl_2]_2$ and 2.0 equiv of DTBP were further investigated, and the results are listed in Scheme 4. Reactions of diphenylacetylene with triazoles with

Scheme 4. Annulation of Triazoles with Various Aryl Alkynes[a]



[a]Reactions were carried out using **1** (0.2 mmol), **4** (0.4 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $Cu(OAc)_2·H_2O$ (0.4 mmol), and DTBP (0.4 mmol) at 100 °C for 24 h.

electron-donating or electron-withdrawing substituents took place, giving corresponding mesoionic isoquinoliums **6a**−**6c** in moderate yields. Annulation reaction of unsymmetric alkyne with triazole afforded a mixture of **6e** and **6e′** (1:1.6) in a total yield of 62%. Substituted alkynes are generally inert, and their corresponding isoquinoliums **6g**−**6i** were obtained in lower yields.

In conclusion, we described a simple and practical protocol for the synthesis of mesoionic isoquinolium through Rh-catalyzed annulation of triazoles and internal alkynes. The reaction involves sequential triazole-directed C−H activation and C−C, C−N, and C−O bond formation processes in one pot. Although there are many precedents involving C−H activation and alkyne insertion, studies of the detailed mechanism of functionalization through C−H activation are still needed, and the origin of oxygen is not clear at present.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and spectra of ^1H NMR, ^{13}C NMR, and HRMS for new products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01247.

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Notes

The authors declare no competing financial interest.

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