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Ruthenium(II)-Catalyzed Oxidative Double C−H Activation and Annulation Reaction: Synthesis of Indolo[2,1-*a*]isoquinolines

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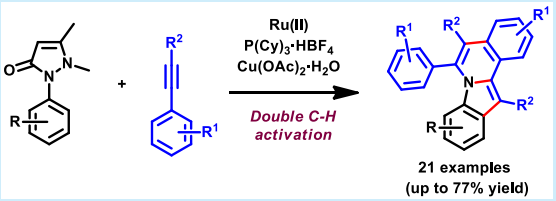
Supporting Information

ABSTRACT: The first metal-catalyzed double aryl C(sp^2)−H bond activation of antipyrine and alkyne annulation reaction is reported. This Ru(II)-catalyzed reaction was accomplished in the presence of 20 mol % phosphine ligand tricyclohexylphosphine tetrafluoroborate to afford indolo[2,1-*a*]isoquinolines that are very important compounds because of their bioactivity and interesting optical properties.



In past few decades, the transition metal-catalyzed activation of the aryl C(sp^2)−H bond followed by alkyne annulation reactions has emerged as an excellent method for the efficient synthesis of various important heteroaromatic compounds, which are otherwise difficult to synthesize by using conventional synthetic methods.[1] There are several examples of the metal-catalyzed reactions for the synthesis of heterocyclic scaffolds that proceed via C−H/N−H bond or C−H/O−H bond activation and alkyne annulation.[1] Very recently, the metal-catalyzed double activation of C(sp^2)−H bonds and alkyne annulation reactions have also proven to be potential tools for the efficient synthesis of polyheteroaromatic compounds. In the recent past, the polyaromatic and polyheteroaromatic compounds have been considered as very useful compounds for the development of organic semiconductors and luminescent materials because of the exceptional p-conjugation of these cyclic compounds.[2] These stable polycyclic compounds with condensed aromatic rings have the ability to enhance the transport of charges, and they exhibit intense fluorescence. Among these polyheteroaromatic compounds, the indolo[2,1-*a*]isoquinolines have in particular attracted a considerable amount of attention from both synthetic chemists and medicinal chemists because of their presence as the key scaffold in several biologically active compounds and pharmaceuticals and their utility in organic light-emitting diodes as hole-transporting materials (HTMs) (Figure 1).[3,4]

Transition metal-catalyzed double C(sp^2)−H activation and alkyne annulation reaction is an excellent route for the efficient synthesis of polyheteroaromatic compounds. However, despite the importance of these polyheteroaromatic compounds, examples of such metal-catalyzed routes for their synthesis are very limited. For example, recently, Cheng, Chuang, and co-workers developed a Rh(III)-catalyzed double C−H activation reaction of (*Z*)-*N*-hydroxybenzamidines and alkyne annulation to synthesize 1*H*-benzo[*de*][1,8]naphthyridine

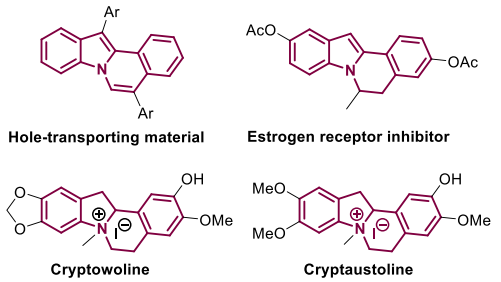


Figure 1. Examples of important indolo[2,1-*a*]isoquinolines.

derivatives (Scheme 1, eq 1).[5] A Rh(III)-catalyzed synthesis of polyarylated naphthyls and anthrylazoles by the double C−H activation of phenylazoles and alkyne annulation reaction was also developed (Scheme 1, eq 2).[6] To pursue our interest in the development of new metal-catalyzed C−H activation reactions,[7] herein, we report a Ru(II)-catalyzed double C(sp^2)−H bond activation of antipyrine and disubstituted alkyne annulation reaction for the synthesis of polyheteroaromatic compound indolo[2,1-*a*]isoquinoline (Scheme 1, eq 3).

At the beginning, the annulation reaction was studied to construct indolo[2,1-*a*]isoquinoline **3aa** using antipyrine **1a** and alkyne **2a** as the starting compounds (Table 1). Screening of some of the catalysts using $Cu(OAc)_2$ as the additive revealed the $[\{RuCl_2(p\text{-cymene})\}_2]$ catalyst to be the most efficient catalyst that afforded a 30% yield of **3aa** (entry 3 and Table SI-1). Further studies of the additives provided an inferior yield of **3aa** (entries 5−7). Fortunately, after a variety of phosphine ligands had been surveyed, the $P(Cy)_3{\cdot}HBF_4$ ligand provided the highest yield of **3aa** (entry 9 and Table SI-1). Then, these standardized reaction conditions were first examined with various substituted antipyrine derivatives **1b−m**

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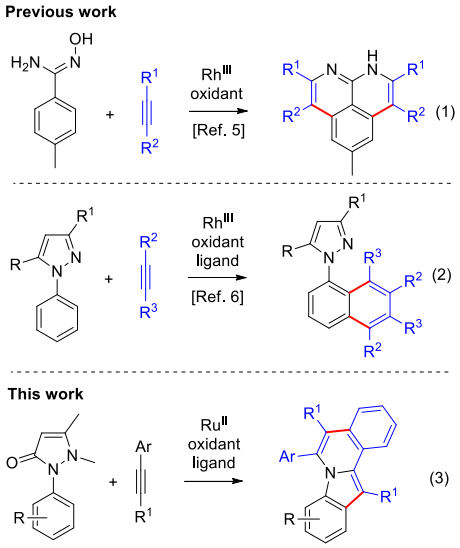
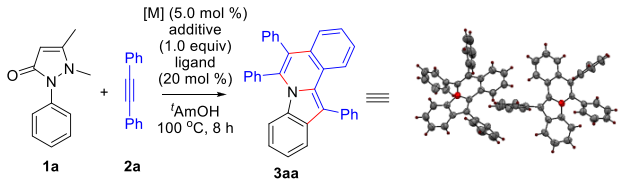
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Examples of Double C(sp^2)−H Activation and Alkyne Annulation Reactions



with alkyne **2a** to afford the corresponding indolo[2,1-*a*]isoquinoline derivatives **3ba**−**ma**, respectively (Scheme 2). The antipyrines substituted at the *para* position of the phenyl ring with substituents such as methyl (**1b**), isopropyl (**1c**), methoxy (**1d**), fluoro (**1e**), chloro (**1f**), and trifluoromethyl (**1g**) afforded **3ba**−**ga**, respectively, with **2a** in good yields. Similarly, the antipyrines possessing substituents such as methyl (**1h**), fluoro (**1i**), and chloro (**1j**) at the *meta* position of the antipyrine phenyl ring also reacted smoothly with **2a** to provide products **3ha**−**ja**, respectively. These annulation reactions of **1h**−**j** with **2a** were found to be highly regioselective owing to the selective less sterically hindered C(sp^2)−H bond activation. The antipyrines possessing two substituents at positions 3 and 4 (**1k** and **1m**) and positions 3 and 5 (**1l**) of the phenyl ring were also tested to provide the desired products **3ka**−**ma**, respectively, with **2a** in good yields. The reactions of **1k** and **1m** with alkyne **2a** were highly regioselective. Subsequently, the standard Ru(II)-catalyzed reaction conditions were studied for the annulation of alkynes **2a**−**i** with antipyrine (**1a**). All of the representative diaryl-substituted symmetrical alkynes possessing substituents such as methyl (**2b**), methoxy (**2c**), and fluoro (**2d**) at the *para* position of the phenyl rings turned out to be suitable starting compounds for this reaction to provide products **3ab**−**ad**, respectively, with **1a** in moderate to good yields (Scheme 3). The unsymmetrically substituted diaryl alkynes bearing substituents methyl and fluoro (**2e**) and methyl and methoxy (**2f**) at the *para* position of the phenyl ring provided a mixture of isomers **3ae** and **3af** with **1a**, which could not be separated by normal silica gel column chromatography. The reaction of unsymmetrical aryl alkyl group-containing alkyne **2g** with antipyrine (**1a**) provided only one isomer, **3ag**. However, similar unsymmetrical disubstituted alkynes **2h** and **2i** provided a mixture of products **3ah** (10:1) and **3ai** (2.5:1), respectively, with **1a**. The dialkyl-substituted alkynes and terminal alkynes were not good starting compounds for the performance of this annulation reaction. The tested heterocycle-containing alkyne 1,2-di(thiophen-3-yl)ethyne, the ester-containing alkyne ethyl 3-phenylpropiolate, and the silyl group-containing alkyne trimethyl(phenylethynyl)silane could not afford the corresponding annulated products. At the same time, the readily available acetanilide afforded only 12% of product **3aa** with **2a** under the optimized conditions. The structures of all of the synthesized indolo[2,1-*a*]isoquinolines were clearly established by NMR spectroscopy and X-ray crystallography studies of **3aa**.[8] The regioselectivity of compounds **3ag**−**ai** were determined by comparing the ^{1}H NMR spectra of these compounds with those of some other synthesized compounds (Supporting Information). The regioselectivity of the cyclization of unsymmetrical alkynes **2g**−**i** follows the reported metal-catalyzed alkyne annulation reactions, where, in the alkyne insertion step in the C−M bond, the metal preferentially forms a bond with the electron rich carbon center of the alkyne.[9]

Table 1. Optimization of the Reaction Conditions for 3aa[a]



entry	catalyst	additive	ligand	3aa (%)[b]
1	$Pd(OAc)_2$	$Cu(OAc)_2·H_2O$	–	0
2	$[RuCl_2(PPh_3)_3]$	$Cu(OAc)_2·H_2O$	–	0
3	$[\{RuCl_2(p\text{-cymene})\}_2]$	$Cu(OAc)_2·H_2O$	–	30
4	$[(Cp^*RhCl_2)_2]$	$Cu(OAc)_2·H_2O$	–	14
5	$[\{RuCl_2(p\text{-cymene})\}_2]$	CsOAc	–	13
6	$[\{RuCl_2(p\text{-cymene})\}_2]$	$CuBr_2$	–	0
7	$[\{RuCl_2(p\text{-cymene})\}_2]$	AgOAc	–	11
8	$[\{RuCl_2(p\text{-cymene})\}_2]$	$Cu(OAc)_2·H_2O$	$P(Cy)_3$	42
9	$[\{RuCl_2(p\text{-cymene})\}_2]$	$Cu(OAc)_2·H_2O$	$P(Cy)_3·HBF_4$	77
10	$[\{RuCl_2(p\text{-cymene})\}_2]$	$Cu(OAc)_2·H_2O$	DCYPE	28
11	$[\{RuCl_2(p\text{-cymene})\}_2]$	$Cu(OAc)_2·H_2O$	(±)-BINAP	54
12	$[\{RuCl_2(p\text{-cymene})\}_2]$	$Cu(OAc)_2·H_2O$	(±)-BINOL	43

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), catalyst (5.0 mol %), additive (0.5 mmol), ligand (20 mol %), and ^{t}AmOH (5.0 mL) heated at 100 °C for 8 h under air. [b]Isolated yields.

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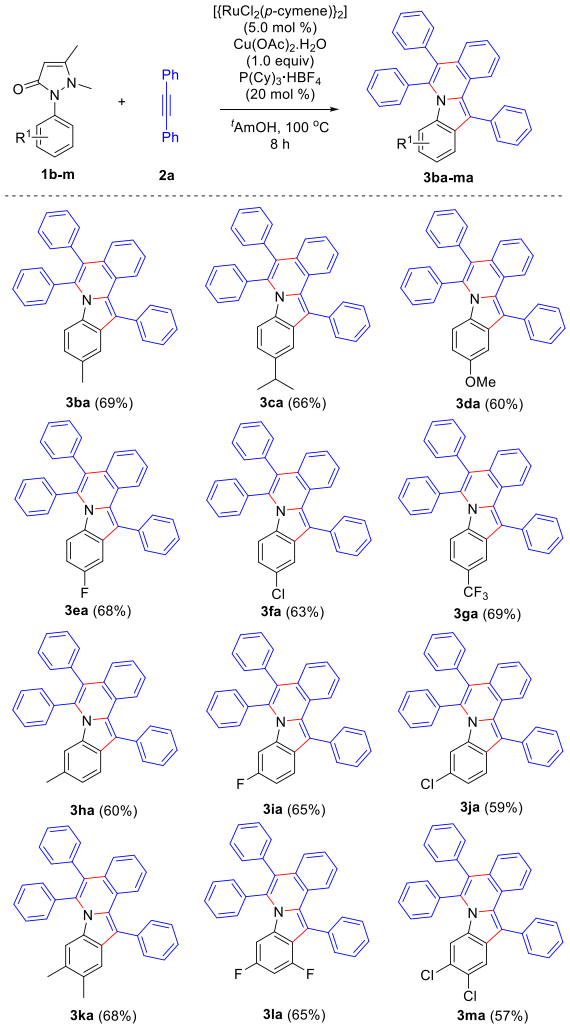
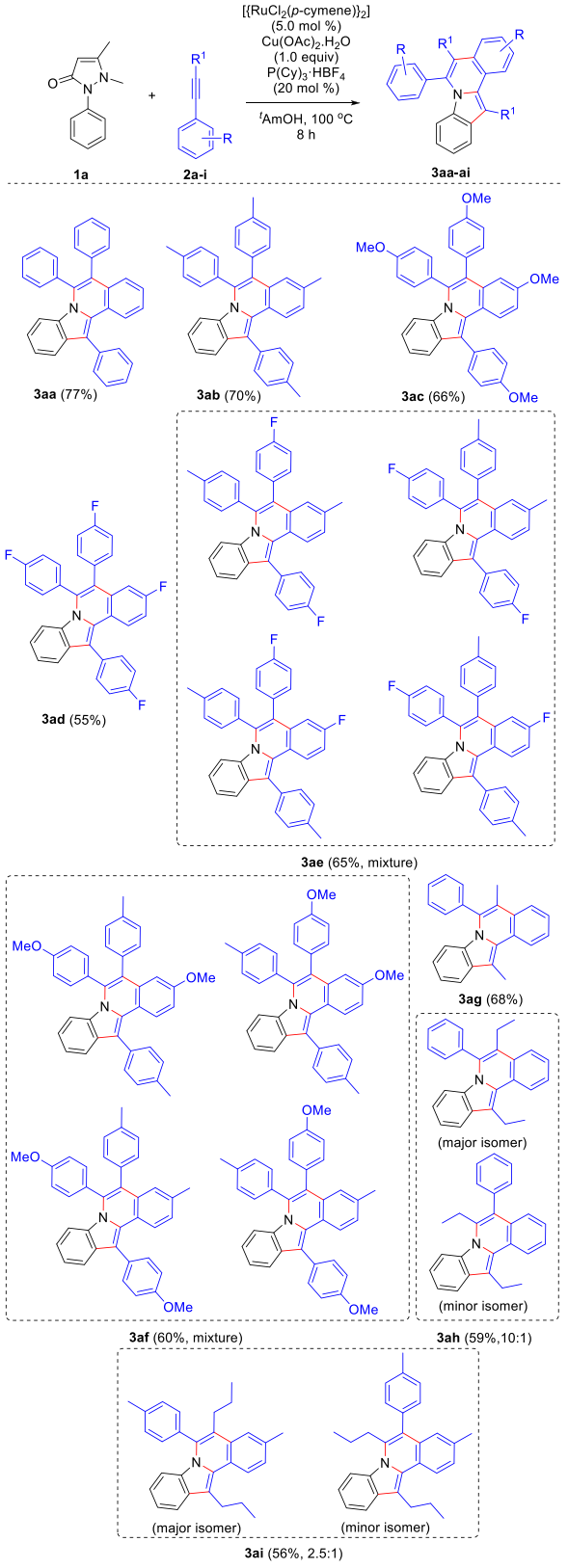
Scheme 2. Reactions of Antipyrenes 1b−m with Alkyne 2a[a]



[a]Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), Ru(II) catalyst (5.0 mol %), $P(Cy)_3{\cdot}HBF_4$ (20 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.5 mmol), and ^{t}AmOH (5.0 mL) heated at 100 °C for 8 h under air.

Scheme 3. Reactions of Antipyrine (1a) with Alkynes 2a−i[a]



[a]Reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), Ru(II) catalyst (5.0 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.5 mmol), $P(Cy)_3{\cdot}HBF_4$ (20 mol %), and ^{t}AmOH (5.0 mL) heated at 100 °C for 8 h under air.

The deuterium labeling experiment of antipyrine (**1a**) without using the alkyne, performed under the optimized conditions using CD_3OD as the solvent, could not provide the deuterium−hydrogen exchanged compound **1a-D$_2$**, which is shown in Scheme 4 (eq 1). This reaction indicates the nonreversible cycloruthenation step of this Ru-catalyzed reaction. Moreover, the intermolecular and competitive parallel kinetic isotope effect experiments provided a k_H/k_D of 4.0 and a k_H/k_D of 3.4, respectively (Scheme 4, eqs 2 and 3). These experiments indicate the metal-catalyzed C(sp^2)−H bond activation step to be the rate-limiting step of this reaction.

On the basis of our observation and evidence from the literature, a probable mechanism of Ru(II)-catalyzed formation of **3aa** is presented in Scheme 5. Initially, the active Ru(II) catalyst forms Ru complex **B** via amine group-directed irreversible activation of the C(sp^2)−H bond.[10] Then, metal−alkyne coordination, followed by migratory alkyne insertion into the Ru−C bond and subsequent oxidation of the metal Ru(II) to Ru(IV) because of the cleavage of the weak N−N bond, provides a six-membered Ru(IV) complex **C**.[11] Next, reductive elimination of the Ru metal and further C(sp^2)−H activation of the substituted phenyl ring of the resulting indole derivative might have formed a nine-membered Ru complex **D**. Subsequent contraction of the

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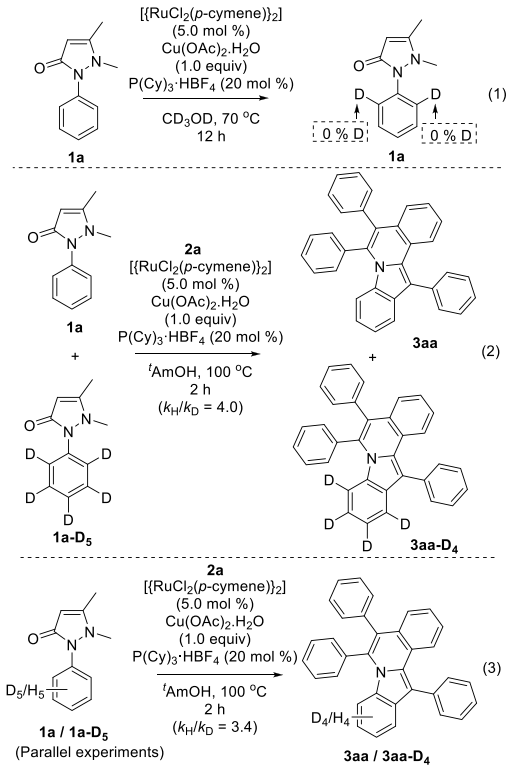
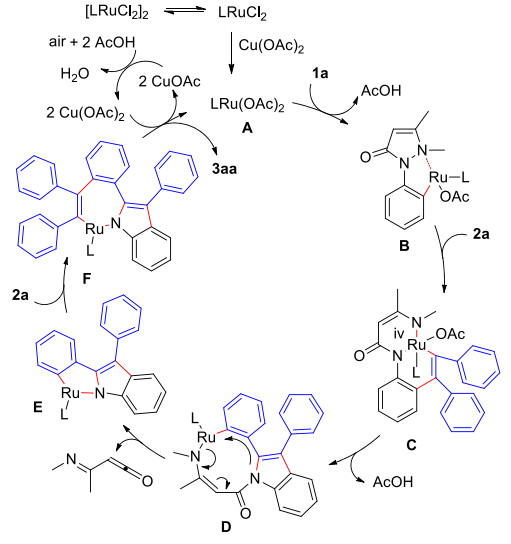
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Isotopically Labeled Experiments



Scheme 5. Possible Mechanism



nine-membered ring by elimination of a ketene type of fragment might have generated Ru(II) complex **E**. However, attempts to detect the ketene intermediate by mass spectroscopy met with failure, which might be due to the reactivity of the intermediate. Again, insertion of another molecule of **2a** into the Ru−C bond of **E** followed by reductive elimination of the Ru metal affords **3aa**. The Ru metal is oxidized to regenerate active catalyst **A** by $Cu(OAc)_2$ and oxygen from air.

In conclusion, a novel ruthenium(II)-catalyzed annulation reaction of antipyrines and alkynes was developed for the efficient synthesis of indolo[2,1-*a*]isoquinoline derivatives. This annulation reaction proceeds through double aryl C(sp^2)−H bond activation and double alkyne insertion to provide indolo[2,1-*a*]isoquinolines with good yields. This ligand-directed reaction has opened up a new synthetic route to access important polyheteroaromatic indolo[2,1-*a*]-isoquinolines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02871.

Experimental procedures, spectroscopic data, and copies of ^{1}H NMR, ^{13}C NMR, and HRMS spectra of the synthesized compounds (PDF)

Accession Codes

CCDC 1547364 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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