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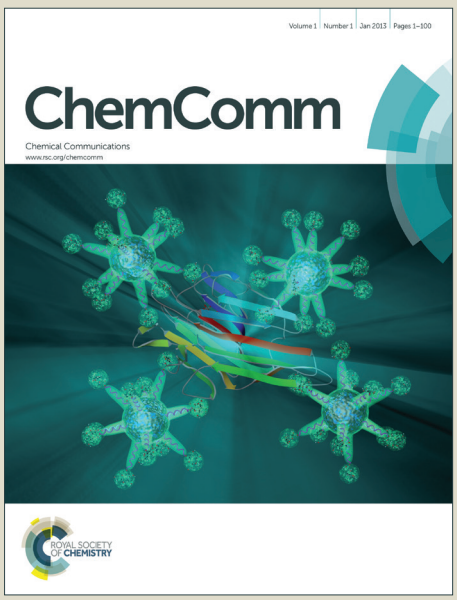

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ARTICLE TYPE

Rh/Cu-Catalyzed Multiple C-H, C-C, and C-N Bonds Cleavage: Facile Synthesis of Pyrido[2,1-a]indoles from 1-(Pyridin-2-yl)-1*H*-indoles and *γ*-Substituted Propargyl Alcohols

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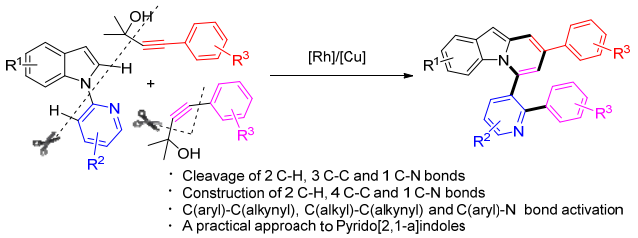
An unusual Rh/Cu-catalyzed synthesis of pyrido[2,1-a]indoles starting from 1-(pyridin-2-yl)-1*H*-indoles and *γ*-substituted propargyl alcohols was presented. The multi-step cascade transformations formally involve the cleavage of two C-H, three C-C, and one C-N bonds with concomitant construction of two C-H, four C-C, and one C-N bonds with excellent chemoselectivity in one-pot reaction.

The selective cleavage and construction of chemical bonds has always been a central topic in modern synthetic organic chemistry.[1] In recent decades, transition metal-catalyzed direct cleavage of inert chemical bonds such as C-H, C-C and C-N bonds, and thus associated transformations has garnered increasing attention by the synthetic community. In particular, significant developments have been acquired in the area of C-H activation.[2] However, reports of C-C activation are less prominent in literatures probably owing to the thermodynamic stability of these bonds and the kinetic factors arising from the greater steric hindrance as well as the competing C-H activation.[3,4] Therefore, examples for C-C bond activation are still mostly limited to strained C-C bonds, decarboxylation reactions, or performed with the help of strong chelation assistants.[3,4] Similarly, due to the high C-N bond dissociation energy, catalytic transformations involving selective cleavage of C-N bonds have been scarce so far.[5,6] Not surprisingly, simultaneous cleavage of both C-C and C-N bonds under one set of conditions would be even more challenging, which is limited to a few reports.[7]

On the other hand, transition-metal mediated direct C-H alkynylation for the introduction of the alkynyl functionality has received much attention recently.[8] Although terminal alkynes,[9] alkynylhalides[10] as well as benziodoxolone-based hypervalent iodine reagents[11] have been used as the alkynyl coupling partners to achieve direct C-H alkynylation of intrinsically different arenes, the substrate scope remains limited. It is still necessary to develop highly efficient and general alkynylation methods for broadly defined arenes via a C-H activation pathway. In this context, it is worthy to note that *tert*-propargyl alcohols have been involved in Sonogashira-type reactions as masked terminal alkynes.[12] Moreover, Miura discovered that $[Rh(OH)(COD)]_2$ could catalyze regio- and stereo-selective homo-coupling of *γ*-arylated *tert*-propargyl alcohols via *β*-carbon elimination with liberation of a ketone, in which, an alkynyl rhodium generated in situ was proposed as the key intermediate.[13] Furthermore, given the great success and advantages of rhodium catalysis in the construction of C-X bonds (X = C, N, O, etc.) based on C-H activation in recent years,[14,15] we were prompted to design the Rh-catalyzed direct C-H alkynylation of arenes utilizing *γ*-substituted *tert*-propargyl alcohols as the alkynyl coupling partner. Following this idea, we have thus examined the reactions of 1-(pyridin-2-yl)-1*H*-indoles with *tert*-propargyl alcohols under Rh/Cu catalyst system, which, serendipitously led to the formation of pyrido[2,1-a]indoles instead of the expected alkynylation products (Scheme 1). Herein, we communicate this unsual cascade reaction, whereby at least six bonds, including two C-H, three C-C and one C-N bonds, were cleaved and seven bonds (two C-H, four C-C and one C-N bonds) were constructed in one pot. The reaction reported here is unprecedented especially when the efficiency is considered.[16]

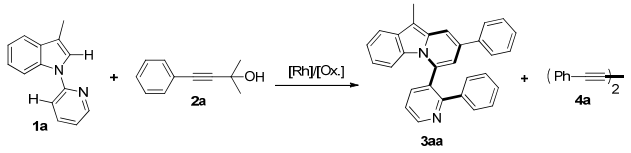


Scheme 1 Rh/Cu-catalyzed facile synthesis of pyrido[2,1-a]indoles via multiple C-H, C-C, and C-N bonds cleavage.

We initiated our study by choosing 1-(pyridin-2-yl)-1*H*-indole **1a** and 2-methyl-4-phenyl-3-butyn-2-ol **2a** as model substrates. Surprisingly, when $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2{\cdot}H_2O$ were employed as the catalytic system, the unexpected product **3aa**, which contains a pyrido[2,1-a]indole skeleton, was isolated in 24% yield (Table 1, entry 1). The definite structures of **3** came from the X-ray crystallographic studies of a series of pyrido[2,1-a]indole products **3af**, **3ag** (*vide infra*, See SI), **3la** (Table 3), and **3jga** (Scheme 3). To the best of our knowledge, efficient strategies for the construction of pyrido[2,1-a]indoles, a recurring structural motif found in many pharmaceuticals and functional materials, have rarely been reported.[17,18] After screening of a variety of rhodium precatalysts, $[RhCl(COD)]_2$ was found to be the best choice and **3aa** was obtained in 78% isolated yield

(entries 2-5). Investigation on solvent effects indicated that toluene was the most suitable solvent (entries 5-8). Control experiments revealed that no desired product **3aa** was detected in the absence of either $[RhCl(COD)]_2$ or $Cu(OAc)_2{\cdot}H_2O$ (entries 9-10). Notably, the reaction was suddenly shut down in the presence of an extra basic additive K_2CO_3 (entry 11). The use of other common oxidants such as AgOAc or Ag_2CO_3 did not provide **3aa** at all (entries 12-13). 125 °C was found to be the optimal temperature (entries 14-15). We have also examined the possibility to employ simple terminal alkyne instead of **2a** for this transformation, which gave **3aa** in only 21% yield accompanied with a large amount of Glaser coupling product **4a** in 71% yield (entry 16). This result clearly showed that Glaser coupling was inhibited effectively in this reaction by using *tert*-propargyl alcohol as the alkynylating reagent instead of phenylacetylene.

Table 1 Optimization of reaction conditions[a]

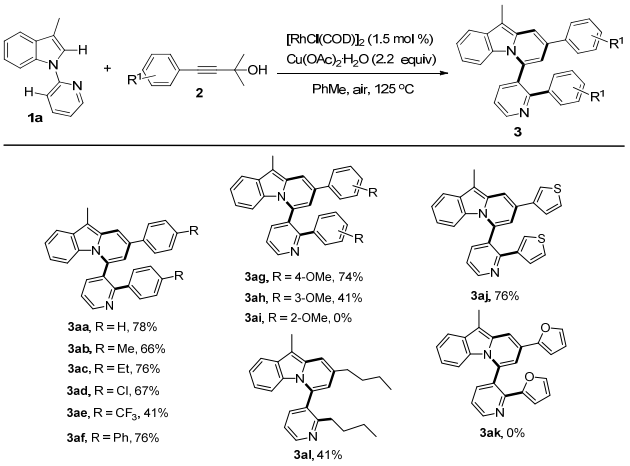


Entry	[M]	Oxidant	Solvent	Temp. (°C)	Yield (%) 3aa[b]
1	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	PhMe	125	24/(**4a** 64[c])
2	$[Cp^*Rh(CH_3CN)_3][SbF_6]_2$	$Cu(OAc)_2{\cdot}H_2O$	PhMe	125	32
3	$Cp^*Rh(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	PhMe	125	40
4	$[RhOH(COD)]_2$	$Cu(OAc)_2{\cdot}H_2O$	PhMe	125	57/(**4a** 54)
5	$[RhCl(COD)]_2$	$Cu(OAc)_2{\cdot}H_2O$	PhMe	125	78/(**4a** 41)
6	$[RhCl(COD)]_2$	$Cu(OAc)_2{\cdot}H_2O$	Xylene	125	67
7	$[RhCl(COD)]_2$	$Cu(OAc)_2{\cdot}H_2O$	DCE	125	56
8	$[RhCl(COD)]_2$	$Cu(OAc)_2{\cdot}H_2O$	Dioxane	125	20
9	$[RhCl(COD)]_2$	NO	PhMe	125	0
10	NO	$Cu(OAc)_2{\cdot}H_2O$	PhMe	125	0/(**4a** 98)
11	$[RhCl(COD)]_2$	$Cu(OAc)_2{\cdot}H_2O$	PhMe	125	trace[d]
12	$[RhCl(COD)]_2$	AgOAc	PhMe	125	0
13	$[RhCl(COD)]_2$	Ag_2CO_3	PhMe	125	0
14	$[RhCl(COD)]_2$	$Cu(OAc)_2{\cdot}H_2O$	PhMe	110	0/(**4a** 84)
15	$[RhCl(COD)]_2$	$Cu(OAc)_2{\cdot}H_2O$	PhMe	140	trace
16	$[RhCl(COD)]_2$	$Cu(OAc)_2{\cdot}H_2O$	PhMe	125	21/(**4a** 71)[e]

[a] Reaction Conditions: **1a** (0.20 mmol), **2a** (0.80 mmol, 4 equiv), [M] (1.5 mol %), oxidant (2.2 equiv) and solvent (2 mL) under air for about 6 h. [b] Yield of isolated products based on **1a**. [c] Yield of isolated products based on **2a**. [d] 2.0 equiv of K_2CO_3 was added. [e] Phenylacetylene instead of **2a**.

With these optimized reaction conditions in hand, the scope of this reaction was extensively studied. First, a series of *γ*-substituted *tert*-propargyl alcohols were investigated (Table 2). To our satisfaction, *γ*-arylated *tert*-propargyl alcohols with electron-donating or electron-withdrawing substituents, such as Me, Et, Cl, CF_3, and Ph, at the *para* position on the phenyl ring were well tolerated to provide the corresponding products in moderate to good yields (**3aa**-**3af**, 41-78% yield). Substrates bearing a methoxy group at the *meta* and *para* position on the phenyl ring proceeded well (**3ag**, **3ah**), while that with a methoxy group at the *ortho* position on the phenyl ring failed to yield the desired product **3ai**, possibly due to the steric hindrance. It is worthy to note that the methodology could be further extended to thiophene containing substrate **2j** to afford **3aj** in 76% yield, while *γ*-furan *tert*-propargyl alcohol **2k** did not work at all. Moreover, aliphatic 2-methyloct-3-yn-2-ol **2l** was also investigated to produce **3al** in 41% yield, which represent the first example of C(alkyl)-C(alkynyl) single bond cleavage.[19]

Table 2 Reaction scope of *γ*-substituted *tert*-propargyl alcohols

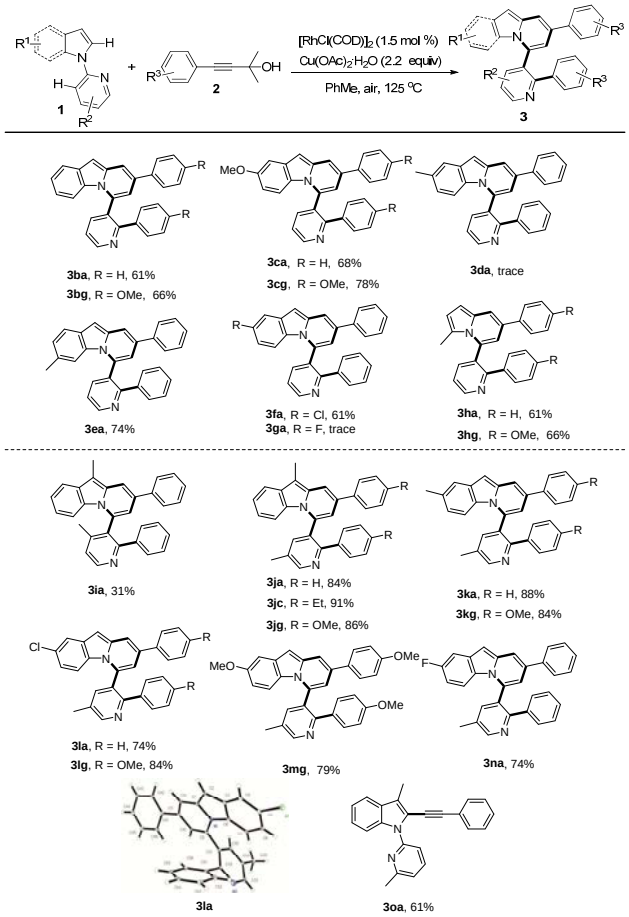


General reaction conditions: **1a** (0.2 mmol), **2** (0.8 mmol), $[RhCl(COD)]_2$ (1.5 mol %), $Cu(OAc)_2{\cdot}H_2O$ (2.2 equiv), PhMe (2 mL), 125 °C, air, 6 h. Yield of isolated products based on **1a**.

Subsequently, the scope of the 1-(pyridin-2-yl)-1*H*-indoles was further investigated (Table 3). Gratifyingly, reactions of **1b** with *γ*-arylated *tert*-propargyl achohols worked well to yield **3ba** and **3bg** in good yields. Other indoles with a substituent group such as OMe or Cl at the C-5 position on the indole ring were also compatible with this transformation, thus affording the corresponding products **3ca**, **3cg**, and **3fa**, while substrates with Me or F at the C-5 position on the indole ring did not work (**3da**, **3ga**). Contrastly, when the Me group was at the C-6 position, the reaction proceeded smoothly to give **3ea** in 74% yield. More importantly, when 2-(2-methyl-1*H*-pyrrol-1-yl)pyridine **1h** was used as the substrate, indolizine derivatives **3ha** and **3hg** could be obtained in 61% and 66% yields respectively, which represent the rare examples of indolizine synthesis starting from pyrrole.[18b,c]

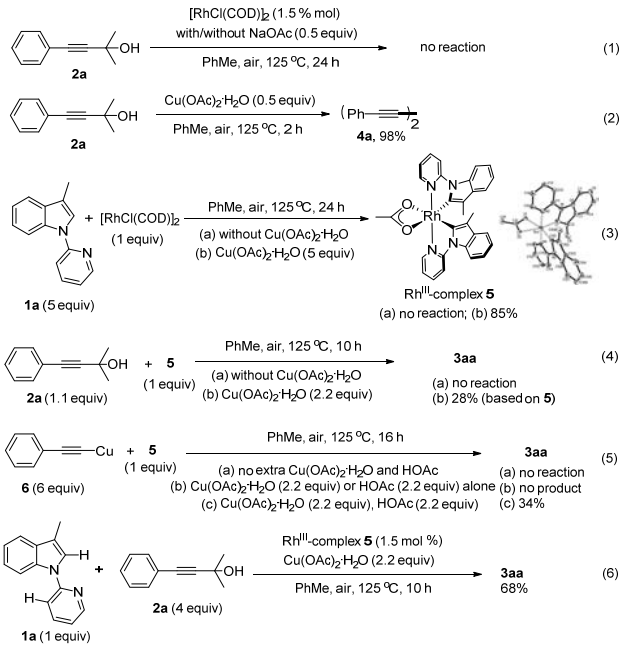
We next examined the influences of the substituent at the pyridyl directing groups for the reaction (Table 3). Firstly, when the C-3 position of the pyridyl group, which is subject to the consequent C-C bond formation, was blocked with a Me group, the reaction was completely suppressed to yield **4a** only. In addition, installation of the Me substituent on the pyridyl C-4 position furnished product **3ia** in only 31% yield. Further studies revealed that the 5-methylpyridin-2-yl directing group gave the best result, providing the target products in particularly high yields (**3ja**-**3na**, 74%-91%) and even substrates with Me or F at the C-5 position on the indole ring were converted into the corresponding target products **3ka**, **3kg**, and **3na** effectively. It should be noted that changing the directing group from pyridin-2-yl to 6-methylpyridin-2-yl significantly affected the reactivity and only the alkynylation product **3oa** was isolated. The steric hindrance of the Me group at the C-6 position may account for this difference. Isolation of the alkynylation product **3oa** indicated that the alkynylation step was possibly involved in the catalytic cycle for the formation of pyrido[2,1-a]indoles **3**.

Table 3 Reaction scope of the 1-(pyridin-2-yl)-1*H*-indoles

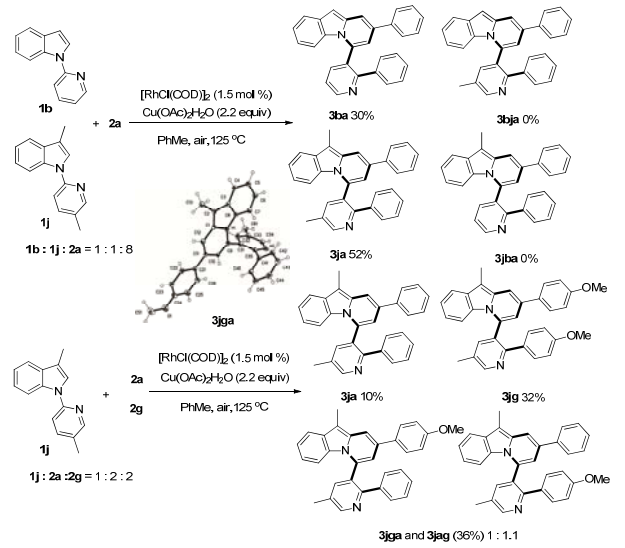


General reaction conditions: **1** (0.2 mmol), **2** (0.8 mmol), $[RhCl(COD)]_2$ (1.5 mol %), $Cu(OAc)_2{\cdot}H_2O$ (2.2 equiv), PhMe (2 mL), 125 °C, air, 6 h. Yield of isolated products based on **1**.

To get some mechanism insights into this transformation, several experiments were carried out (Scheme 2). First, addition TEMPO to the reaction mixture had a negligible effect on the reaction, which suggested that a free-radical pathway might be ruled out. Next, stoichiometric reactions of **2a** with $[RhCl(COD)]_2$ was performed and no reaction could be observed indeed, even if an excess of NaOAc was added (eq 1). Notably, it was found that the Glaser coupling product **4a** was generated quantitatively when $Cu(OAc)_2{\cdot}H_2O$ was mixed with **2a** at 125 °C (eq 2). These results indicated that it is $Cu(OAc)_2{\cdot}H_2O$ rather than $[RhCl(COD)]_2$ that is responsible for the C-C bond cleavage of **2a** via *β*-carbon elimination.[13] Reaction of $[RhCl(COD)]_2$ with **1a** was also investigated and no appreciable reaction could be observed when the reaction was performed in the absence of $Cu(OAc)_2{\cdot}H_2O$. However, the biscyclometalated Rh(III) complex **5** was obtained in 85% yield when the reaction was performed in the presence of $Cu(OAc)_2{\cdot}H_2O$ (eq 3), which clearly indicated that the Csp^2-H bond cleavage of substrate **1a** was enforced by the Rh^{III} species. The structure of **5** was confirmed by a single-crystal X-ray diffraction. Further on, the reactivity of complex **5** was tested. Again, no reaction took place when complex **5** was mixed with **2a** at 125 °C (eq 4). In sharp contrast, the reaction of **5** and **2a** in ratio of 1:1.1 in the presence of $Cu(OAc)_2{\cdot}H_2O$ did proceed to yield the target product **3aa** (eq 4). Further efforts to isolate intermediates from the reaction mixtures by adjusting the ratio of **5** and **2a** failed, however. Reaction of **5** with copper phenylacetylide **6** was also investigated to give product **3aa**, albeit in 34% yield. Of note, the addition of extra $Cu(OAc)_2{\cdot}H_2O$ as an oxidant and HOAc was essential to promote the reaction. No desired product could be observed in the absence of $Cu(OAc)_2{\cdot}H_2O$ or HOAc (eq 5). These observations implied that the acetylide copper species generated from the reaction of **2a** with $Cu(OAc)_2{\cdot}H_2O$ could undergo transmetalation of the alkynyl group to rhodium to afford the acetylide rhodium, which then participated in the subsequent transformations. The catalytic activity of complex **5** under the standard conditions was also tested to provide **3aa** in 68% yield, which indicated that complex **5** could be a possible intermediate in the catalytic cycle (eq 6).



Scheme 2 Mechanism studies.



Scheme 3 Cross reactions.

The possibility of cross reactions between two different indoles

or propargyl alcohols was also investigated (Scheme 3). The reaction of indole substrates **1b** and **1j** with **2a** afforded the corresponding **3ba** and **3ja** only, while the crossover products **3bja** and **3jba** were not detected at all, clearly indicating that the C-N bond cleavage and the concomitant transformations proceeded in an intramolecular manner. In contrast, reaction of **1j** with a mixture of **2a** and **2g** led to the isolation of the products **3ja**, **3jg** as well as the expected crossover products **3jga** and **3jag** with the latter two as a mixture.

Given the results of the above control experiments, it is reasonable to believe that the reaction is presumably initiated by the cyclometallation of 1-(pyridin-2-yl)-1*H*-indoles with Rh^{III} species**.** Transmetalation of the alkynyl group from the in situ generated acetylide copper species to Rh followed by a reductive elimination yield the alkynylation product (See SI), which then proceeds to undergo a series of transformations to afford the target product finally. The mechanistic details for the further transformation of the alkynylation product to give the pyrido[2,1-a]indole skeleton are unclear yet.

In conclusion, we have discovered a novel Rh/Cu catalyzed cascade reaction involving multiple C-H, C-C, and C-N bonds cleavage and formation, giving rise to a practical approach for the construction of pyrido[2,1-a]indoles. Remarkably, the highly selective cleavage of several types of extremely inert chemical bonds such as C(aryl)-C(alkynyl), C(alkyl)-C(alkynyl), and C(aryl)-N bonds was realized in this transformation. Further studies aimed at revealing the detailed mechanism of this complicated reaction and applications of this protocol are currently being investigated in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental and crystallographic details. CCDC 1032403 (**3af**), CCDC 1032402 (**3ag**), CCDC 1032405 (**3ia**), CCDC 1032406 (**3jga**), and CCDC 1032404 (**5**). See DOI: 10.1039/b000000x/.

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