An unusual Rh/Cu-catalyzed synthesis of pyrido[2,1-a]indoles starting from 1-(pyridin-2-yl)-1H-indoles and \( \gamma \)-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 have 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 the literature 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, the 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 alkenes,\(^9\) alkynylhalides\(^10\) as well as benziodoxolone-based hypervalent iodine reagents\(^11\) have been used as alkynylation 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 worth noting that \( \gamma \)-tert-propargyl alcohols have been involved in Sonogashira-type reactions as masked terminal alkynes.\(^12\) Moreover, Miura discovered that \([\text{Rh(OH)(COD)}]_2\) could catalyze regio- and stereo-selective homo-coupling of \( \gamma \)-arylated tert-propargyl alcohols via \( \beta \)-carbon elimination with liberation of 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 \( \gamma \)-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 the 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 unusual 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.\(^16\)

We initiated our study by choosing 1-(pyridin-2-yl)-1\( H \)-indole 1a and 2-methyl-4-phenyl-3-butyne-2-ol 2a as model substrates. Surprisingly, when \([\text{Cp}^*\text{RhCl}_2]\) and Cu(OAc)\(_2\) \( \cdot \)H\(_2\)O 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-\textit{a}]indole products 3af, 3ag (\textit{vide infra, see ESIf}), 3la (Scheme 3), and 3jga (Scheme 3). To the best of our knowledge, efficient strategies for the construction of pyrido[2,1-\textit{a}]indoles, a recurring structural motif found in many pharmaceuticals and functional materials, have rarely been reported.\textsuperscript{17,18} After screening of a variety of rhodium precatalysts, [RhCl(COD)], was found to be the best choice and 3aa was obtained in 78\% isolated yield (entries 2–5). Investigation of solvent effects indicated that toluene was the most suitable solvent (entries 2a, 6). Yield of isolated products based on 1a. \textsuperscript{a} Yield of isolated products based on 2a. \textsuperscript{d} 2 equiv. of K\textsubscript{2}CO\textsubscript{3} was added. \textsuperscript{e} Phenacyl chloride instead of 2a. Substrates bearing methoxy groups at the \textit{meta} and \textit{para} positions on the phenyl ring proceeded well (3ag, 3ah), while that with a methoxy group at the \textit{ortho} position on the phenyl ring failed to yield the desired product 3ai, possibly due to the steric hindrance. It is worth noting that the methodology could be further extended to thiophene containing substrate 2j to afford 3aj in 76\% yield, while \gamma-furan tert-propargyl alcohol 2k did not work at all. Moreover, aliphatic 2-methyl-3-yn-2-ol 2l was also investigated to produce 3ai in 41\% yield, which represents the first example of C(alkyl)–C(alkynyl) single bond cleavage.\textsuperscript{19}

Subsequently, the scope of 1-(pyridin-2-yl)-1H-indoles was further investigated (Table 3). Gratifyingly, reactions of 1b with \gamma-arylated tert-propargyl alcohols 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). In contrast, 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-1H-pyrrrole-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.\textsuperscript{18b,c}

With these optimized reaction conditions in hand, the scope of this reaction was extensively studied. First, a series of \gamma-substituted tert-propargyl alcohols were investigated (Table 2). To our satisfaction, \gamma-arylated tert-propargyl alcohols with electron-donating or electron-withdrawing substituents, such as Me, Et, Cl, CF\textsubscript{3}, and Ph, at the \textit{para} position on the phenyl ring were well tolerated to provide the corresponding products in moderate to good yields (3aa–3af, 41–78\% yield).
pyridin-2-yl to 6-methylpyridin-2-yl significantly affected the reactivity and only the alkylation product 3oa was isolated. The steric hindrance of the Me group at the C-6 position may account for this difference. Isolation of the alkylation product 3oa indicated that the alkylation step was possibly involved in the catalytic cycle for the formation of pyrido[2,1-\text{a}]indoles 3.

To get some mechanistic insights into this transformation, several experiments were carried out (Scheme 2). First, addition of 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 reaction of 2a with [RhCl(COD)]\_2 was performed and no reaction could be observed indeed, even if an excess of NaOAc was added (eqn (1)). Notably, it was found that the Glaser coupling product 4a was generated quantitatively when Cu(OAc)\_2.H\_2O was mixed with 2a at 125 °C (eqn (2)). These results indicated that it is Cu(OAc)\_2.H\_2O rather than [RhCl(COD)]\_2 that is responsible for the C–C bond cleavage of substrate 1a, and only the alkylation product 3oa was isolated. The steric hindrance of the Me group at the C-6 position may account for this difference. Isolation of the alkylation product 3oa indicated that the alkylation step was possibly involved in the catalytic cycle for the formation of pyrido[2,1-\text{a}]indoles 3.

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)-1H-indoles with Rh\textsuperscript{III} species.
Transmetalation of the alkynyl group from the acetylide copper species generated in situ to Rh followed by a reductive elimination yields the alkynylation product (see ESI†), 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 bond cleavage and formation, giving rise to a practical approach for the construction of pyrido[2,1-d]indoles. Remarkably, the highly selective cleavage of several types of extremely inert chemical bonds such as C(aryl)–C(alkynyl), C(alkyl)–(Calkynyl), 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.

We thank the National Basic Research Program of China (973 Program 2012CB821600), the National Natural Science Foundation of China (21072161), and Program for Changjiang Scholars and Innovative Research Team (PCSIRT) in the University.

Notes and references


Scheme 3 Cross reactions.