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Sequential one-pot Rh(III)-catalyzed direct C2 and C7 alkylation of (hetero)aromatic C–H bonds of indoles

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ABSTRACT

A simple and versatile method for highly efficient synthesis of various polysubstituted indoles via a sequential one-pot Rh(III)-catalyzed direct C2–H and C7–H alkylation with diazo compounds has been developed. This process features with mild reaction conditions, wide substrate scope, and good functional group tolerance (24 examples, up to 96% yield).

Transition-metal-catalyzed C–H activation has emerged as one of the most powerful tools for forming new C–C and C–heteroatom bonds in terms of step- and atom-economy.[1] With the assistance of directing groups, modification of various arenes and heteroarenes had achieved enormous successes.[2] Among them, a few excellent examples on activation of two identical aromatic or heteroaromatic C–H bonds in the same catalytic system had been well documented (Scheme 1).[3] Although significant progress had been made in this hot area of research, highly efficient activation of two or multiple different C–H bonds under the same catalytic system still remains challenging.

Indoles and their derivatives are commonly occurring structural motifs found in numerous natural products, pharmaceuticals, and biologically active compounds.[4] Therefore, there is a continuing interest in the development of C–H activation to access various functionalized indoles, especially the polysubstituted indoles.[5] A large number of excellent studies had been carried out on functionalization of indoles through selective cleavage of heteroaromatic C2- or C3–H bond of indoles.[6] Nevertheless, the methods that allow for direct selective activation of C–H bond at the C-7 position of indoles are relatively rare.[7] A multi-step synthetic strategy of C–H activation and dehydrogenation of indolines is an efficient protocol for C-7 substituted indoles' synthesis.[8] In this context, acylation, arylation, olefination, alkylation, alkynylation, and amination of indolines at the C-7 position had been actively investigated.[9] Interesting, an atom-economic one-pot method for synthesis of C7-substituted indoles via Rh-catalyzed regioselective olefination of indolines has been developed by Antonchick and coworkers.[10] Over the past few years, diazo compounds had been widely employed as a class of versatile alkylation reagents in metal catalyzed carbenoid insertion of (hetero)aromatic C–H bonds. For example, in 2012, Yu's group elegantly developed the first example of Rh(III)-catalyzed carbenoid ortho C–H cross-coupling reaction with diazomalonates.[11] Shortly after, the groups of Rovis,[12] Glorius,[13] Cramer,[14] Cui,[15] and others[16] also described the successful exploration of diazo compounds as cross-coupling partners of C–H alkylation and tandem C–H alkylation/cyclization. Very recently, Zhou and coworkers had developed a Rh(III)-catalyzed C7–H alkylation of indolines with diazo compounds, followed by dehydrogenation and C2–H alkynylation to prepare the disubstituted indoles.[17] Yi had developed a mild Rh(III)-catalyzed direct carbenoid insertion C2-alkylation of indoles with diazotized Meldrum's acid, and the C2- and C7-functionalized indoles could be highly efficiently synthesized through direct C7–H alkenylation using another Rh(III)/Cu(II) catalytic system.[18] Despite the potential utility of C2- and C7-disubstituted indole derivatives, development of more highly efficient and simple approaches to access such compounds is still highly desirable. Motivated by this and our continuing interest in C–H functionalization of indoles,[19] we described herein a facile and mild Rh(III)-catalyzed one pot

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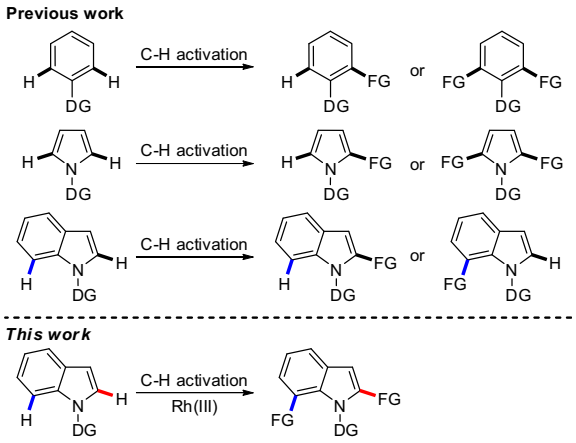
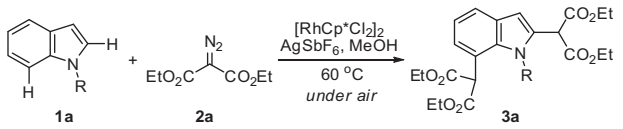


Scheme 1. Functionalization of (hetero)aromatic C–H bonds.

Table 1
Optimization of reaction conditions[a]



1a 2a 3a

Entry	R	Additive	Solvent	Yield[b]
1	Bn	AgOAc	EtOH	0
2	Boc	AgOAc	EtOH	0
3	Ph	AgOAc	EtOH	0
4	2-Py	AgOAc	EtOH	19
5	2-Pyrimidyl	AgOAc	EtOH	85
6	2-Pyrimidyl	AgO_2CCF_3	EtOH	18
7	2-Pyrimidyl	$AgSbF_6$	EtOH	95
8	2-Pyrimidyl	AgF	EtOH	45
9	2-Pyrimidyl	AgOTf	EtOH	15
10	2-Pyrimidyl	$AgSbF_6$	MeOH	92
11	2-Pyrimidyl	$AgSbF_6$	*i*-PrOH	74
12	2-Pyrimidyl	$AgSbF_6$	*t*-AmOH	90
13	2-Pyrimidyl	$AgSbF_6$	CH_3CN	58
14	2-Pyrimidyl	$AgSbF_6$	Toluene	0
15	2-Pyrimidyl	$AgSbF_6$	Dioxane	23

[a] Conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), $[RhCp^*Cl_2]_2$ (2.0 mol %), Ag(I) additive (8.0 mol %), solvent (2.0 mL), 60 °C.
[b] Isolated yields.

C2- and C7-alkylation of indoles through activation of two C–H bonds with different chemical status under the same catalytic system (Scheme 1).

At the outset of our study, the diazomelonate **2a** was chosen as a coupling partner of the sequential C–H alkylation. A variety of protecting groups on nitrogen atom of indoles had been tested in the presence of $[RhCp^*Cl_2]_2$ and AgOAc at 60 °C (Table 1, entries 1–5). It was found that the choice of the protecting group was very crucial for this transformation, and the pyrimidyl protected indole could afford the corresponding dialkylated product **3a** in 85% yield (Table 1, entry 5). It's probably because the pyrimidyl group contains two nitrogen atoms and is prone to form the six-membered metal complex for the second C–H bond activation. To our delight, the brief additives screening showed that $AgSbF_6$ was most effective, and the yield of reaction could be further improved to 95% (Table 1, entry 7). Next, the examination of other solvents showed that the protic solvents gave better results, while little or no product was observed with acetonitrile, toluene, and dioxane as reaction medium (Table 1, entries 10–15). Furthermore, the structure of the dialkylated indole derivatives **3ha** was confirmed by the single crystal X-ray analysis (Fig. 1).

With this efficient catalytic system in hand, the substrate scope was subsequently investigated. Gratifyingly, a wide range of indoles with substituents on C3, C4, C5, and even C6 positions are well suitable in this sequential C2- and C7–H activation process and the highest yield of 96% was achieved with a methyl group (Table 2). It should be noted that the present transformation was highly compatible with different C3-substituted indoles **1m** and **1n**. Nevertheless, substituent at C6-position of indoles is restricted to the fluoro group (**3la**). Other groups, such as chloro, methyl, and methoxyl, are ineffective, which demonstrated that the steric hindrance of C6-substituents had an influence on this reaction to some extent. Indoles containing both electron-donating and electron-withdrawing groups could smoothly couple with **2a** in this process and afford the C2- and C7-functionalized indoles in good to excellent yields. Halogen groups could also be incorporated into the indole ring at various positions, thus providing a useful functional handle for further transformation (**3ea**, **3ia**, **3ja**, **3la**, and **3na**). Interestingly, indole **1o** bearing polyaromatic rings was also applicable under current reaction conditions, furnishing the corresponding product in 90% yield. In addition, the reaction of substrates with a methyl or phenyl substituents on the pyrimidine ring also worked well (**3pa** and **3qa**).

To further explore the scope and limitation of this transformation, various diazo compounds were examined to couple with **1a**.

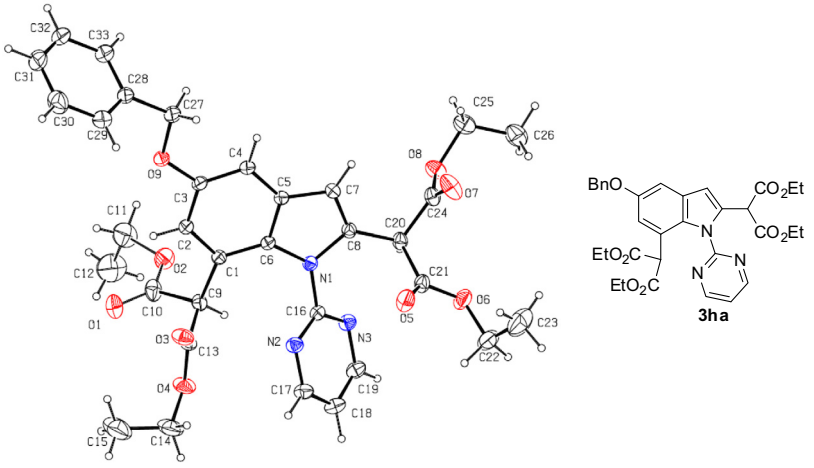


Figure 1. X-ray crystal structure of **3ha**.