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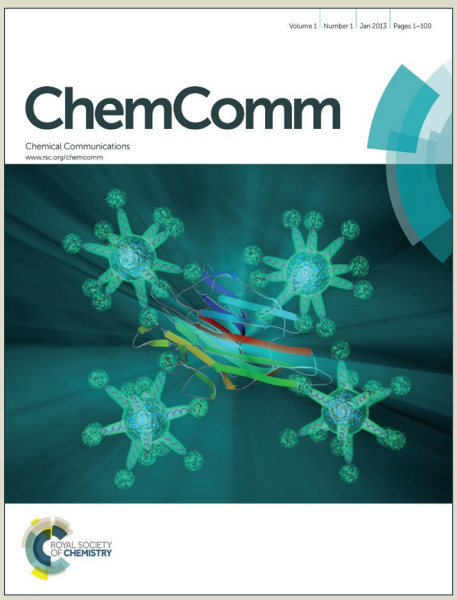

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ARTICLE TYPE

Direct C–H alkylation and indole formation of anilines with diazo compounds under rhodium catalysis

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The rhodium(III)-catalyzed direct functionalization of aniline C–H bonds with α-diazo compounds is described. These transformations provide the facile construction of *ortho*-alkylated anilines with diazo malonates or highly substituted indoles with diazo acetoacetates.

Transition-metal-catalyzed C–H bond functionalization has become an attractive alternative to traditional cross-coupling reactions, because such methods avoid a multistep preparation of preactivated starting materials and the production of stoichiometric amounts of metallic waste.[1] In this area, recent progress has been made on the catalytic carbenoid insertion reaction as a new approach toward C–H bond functionalization. For example, Yu et al. first described the Rh(III)-catalyzed carbene insertion of arene C–H bonds containing oxime and carboxylic acid directing groups using α-diazo esters to afford various *ortho*-functionalized arenes.[2] Also, this protocol has been successfully applied for the synthesis of isoquinolones through *ortho*-alkylation of benzylamines followed by intramolecular cyclization. In the meantime, Miura and coworkers reported the Co(II)-catalyzed C–H functionalization of 1,3-azoles with *N*-tosylhydrazones as carbene precursors.[3] Rovis, Glorius, and Cui respectively demonstrated the facile strategy for the formation of various heterocycles such as γ-lactams,[4] isoquinolines/pyridine *N*-oxides,[5] and azepinones[6] using electron-deficient diazo compounds under Rh(III) catalysis. Furthermore, the Rh(III)-catalyzed construction of 1-aminoindole derivatives using 2-acetyl-1-arylhydrazines and diazo compounds has been reported by Wang and coworkers.[7] Glorius et al. reported the Co(III)-catalyzed C–H functionalization of *N*-heteroarylarenes with diazo compounds to afford a new class of polycyclic hydrocarbons with tunable emission wavelengths.[8] Recently, Lee[9a] and Kim[9b] independently reported the efficient synthesis of cinnolines using azobenzenes and diazo compounds via C–H bond activation. Wang et al. disclosed the efficient formation of *ortho*-alkenyl phenol derivatives via the Rh(III)-catalyzed coupling reaction between *N*-phenoxyacetamides and *N*-tosylhydrazones and diazo esters.[10] Wang and coworkers also demonstrated the direct C–H alkylation of polyfluoroarenes with *N*-tosylhydrazones and diazo compounds under Cu(I) catalysis.[11] In addition, chelation-assisted sp^2 C–H functionalizations of a variety of (hetero)arenes using α-diazo esters were also described.[12]

The indole nucleus is a privileged structural motif in natural bioactive products, drugs, and other functional molecules.[13] The prevalence of indoles in bioactive molecules has led to lots of efforts for the development of many useful methods for their preparation. In particular, the Fischer indole synthesis[14] and the Larock's indole synthesis[15] represent valuable synthetic protocols. Recently, direct synthesis of indoles based on the catalytic C–H bond activation has attracted much attention owing to its remarkable potential for atom economy and environmental sustainability.[16]

In continuation of our recent studies on the rhodium-catalyzed C–H bond functionalization of aromatic compounds,[17] we herein present the Rh(III)-catalyzed *ortho*-C–H alkylation of anilines with α-diazo esters. Additionally, the synthesis of indoles derived from anilines and alkyl α-diazo acetoacetates is also described (Figure 1).[18]

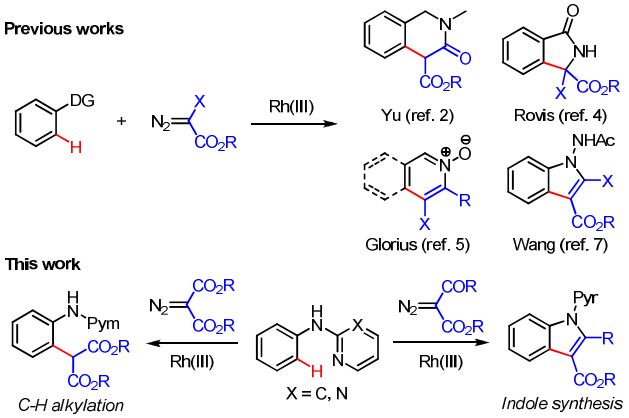
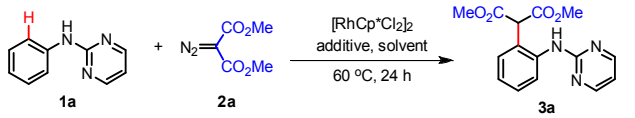


Figure 1 Rh(III)-catalyzed heterocycle synthesis using α-diazo esters.

In our initial study, *N*-phenylpyrimidin-2-amine (**1a**) and dimethyl 2-diazomalonate (**2a**) were chosen as model substrates for optimizing the reaction conditions, and the selected results are summarized in Table 1. To our delight, the rhodium complex, derived from $[Cp^*RhCl_2]_2$ and AgOAc, was found to promote the coupling of **1a** and **2a** in dichloroethane (DCE) at 60 °C for 24 h to give the *ortho*-alkylated product **3a** in 16% yield (entry 1). Screening of other solvents showed that MeOH was found to be

the most effective in this transformation (entries 2–6). Exchange of silver additive to $AgSbF_6$ and $AgNTf_2$ to generate cationic rhodium catalysts afforded the decreased reactivity (entries 7 and 8). Other additives such as Ag_2O and NaOAc were found to be less effective in this coupling reaction (entries 9 and 10). In addition, the use of both AgOAc and $AgSbF_6$ provided our desired product **3a** in low yield (entry 11). In addition, treatment of cobalt and iridium catalysts was found to display lower reactivity under otherwise identical conditions (entries 12 and 13). Furthermore, this reaction furnished almost comparable yield of the desired product **3a** under 2 equiv. loading of **2a** (entry 14).

Table 1 Selected optimization of the reaction conditions[a]

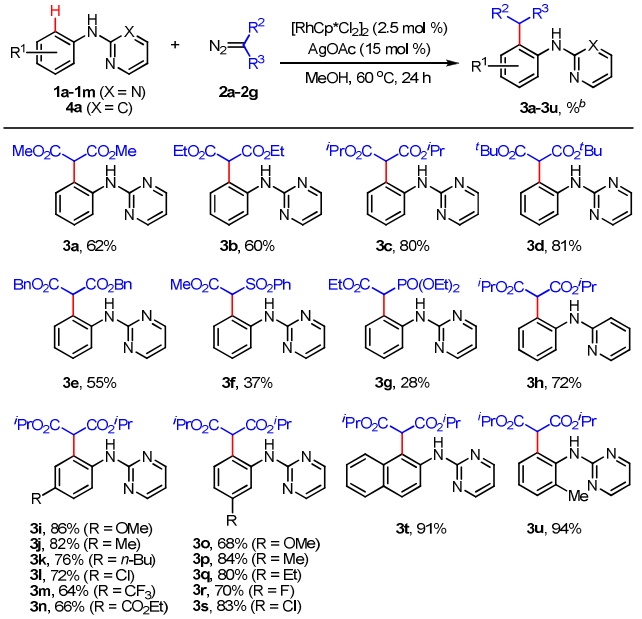


Entry	Additive (mol %)	Solvent	Yield (%)[b]
1	AgOAc (15)	DCE	16
2	AgOAc (15)	THF	trace
3	AgOAc (15)	toluene	48
4	AgOAc (15)	MeCN	10
5	AgOAc (15)	MeOH	62
6	AgOAc (15)	*t*-AmOH	5
7	$AgSbF_6$ (15)	MeOH	30
8	$AgNTf_2$ (15)	MeOH	26
9	Ag_2O (50)	MeOH	15
10	NaOAc (15)	MeOH	31
11	AgOAc (15) + $AgSbF_6$ (10)	MeOH	41
12[c]	AgOAc (15)	MeOH	N.R.
13[d]	AgOAc (15)	MeOH	25
14[e]	AgOAc (15)	MeOH	62

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), additive (quantity noted), solvent (1 mL) under air at 60 °C for 24 h in reaction tubes. [b] Isolated yield by flash column chromatography. [c] $[CoCp^*(CO)I_2]$ was used as a catalyst. [d] $[IrCp^*Cl_2]_2$ was used as a catalyst. [e] **2a** (0.6 mmol, 2 equiv.) was used.

With the optimized reaction conditions in hand, the substrate scope of *N*-phenylpyrimidin-2-amines and diazo compounds was examined, as shown in Table 2. The coupling of symmetrical α-diazo esters **2b–2e** and *N*-phenylpyrimidin-2-amine (**1a**) was found to be favoured in the alkylation reaction to afford our desired products **3b–3e** in good to high yields. However, in case of α-diazo esters **2f** and **2g** containing sulfonate and phosphonate groups, decreased yields of *ortho*-alkylation adducts **3f** and **3g** were obtained. This reaction was also found to be reactive with aniline compound **4a** containing a pyridinyl directing group to furnish **3h** in 72% yield. It should be noted that all reactions exclusively afforded the monoalkylated products, and a trace amount of dialkylated products was observed by ^1H NMR or GC-MS analysis. Furthermore, the reactions between *para*- and *meta*-substituted anilines **1b–1m** and **2c** were screened under standard reaction conditions. All reactions proceeded smoothly to afford the desired products **3i–3t** in satisfactory yields irrespective of the electronic property of substrates. Particularly noteworthy were the mono-selectivity and site-selectivity found at the more sterically accessible position as well as the tolerance of the reaction conditions to the chloro moiety, which provides a versatile synthetic handle for further reactions. Moreover, we were pleased to observe C–H alkylation of *ortho*-substituted aniline **1n**, which provided the corresponding product **3u** in 94% yield.

Table 2 Scope of *N*-phenylpyrimidin-2-amines and diazo compounds[a]

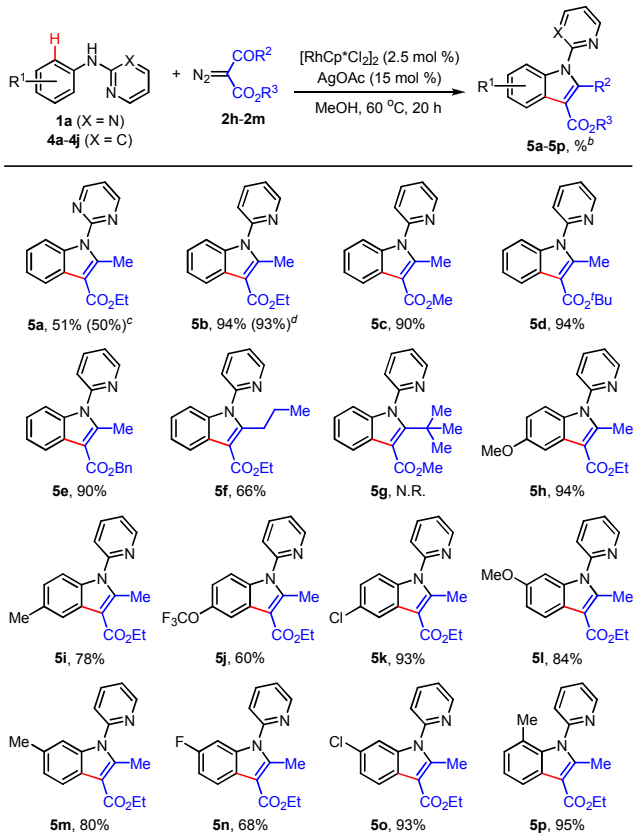


[a] Reaction conditions: **1a–1m** and **4a** (0.2 mmol), **2a–2g** (0.24 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), AgOAc (15 mol %), MeOH (1 mL) under air 60 °C for 24 h in sealed tubes. [b] Yield isolated by column chromatography.

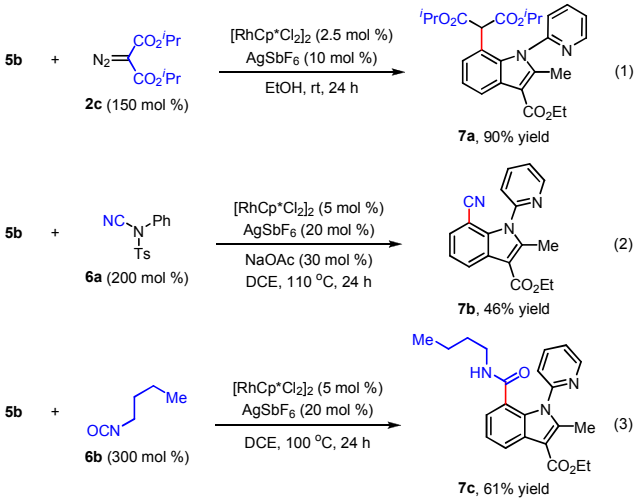
During the screening of substrate scope of diazo compounds, we found that ethyl α-diazo acetoacetate (**2h**) was coupled with **1a** to give C2- and C3-substituted indole **5a** in 51% yield, which might be formed via *ortho*-alkylation of **1a** and subsequent intramolecular condensation (Table 3). Thus, we investigated the further optimization for the synthesis of indole from **1a** and **2h**. Interestingly, we found that a pyridinyl directing group is unique in its ability to facilitate high levels of indole formation under the standard reaction conditions. Thus disubstituted indole **5b** at C2- and C3-positions was obtained in 94% yield. Further study revealed that alkyl α-diazo acetoacetates **2i–2l** were found to be favored in indole formation reaction, affording the corresponding products **5c–5f** in good to high yields, whereas sterically congested methyl 2-diazo-4,4-dimethyl-3-oxopentanoate (**2m**) was unreactive under the current reaction conditions. In addition, *para*-substituted aniline derivatives **4b–4e** participated in the alkylation and tandem cyclization to provide indole adducts **5h–5k** with good reactivity. Notably, the reaction of *meta*-substituted *N*-phenylpyridin-2-amines **4f–4i** preferentially occurred at the less sterically hindered position to afford the corresponding product **5l–5o** as single regioisomers. To our pleasure, this transformation could be applied to *ortho*-substituted aniline **4j** under the present conditions to furnish C7-substituted indole **5p** in 95% yield. To demonstrate the practicable synthesis of substituted indoles, we scaled up the reactions to 4 mmol of *N*-

phenylpyridin-2-amine (**4a**), and obtained 1.04 g of **5b** in 93% isolated yield.

Table 3 Scope of indole synthesis[a]

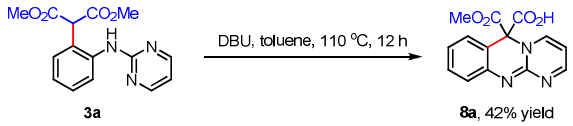


[a] Reaction conditions: **1a** and **4a**–**4j** (0.2 mmol), **2h**–**2m** (0.24 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), AgOAc (15 mol %), MeOH (1 mL) under air 60 °C for 24 h in sealed tubes. [b] Yield isolated by column chromatography. [c] **2h** (0.6 mmol, 2 equiv.) was used. [d] Scale-up experiment of **4a** (4 mmol scale).



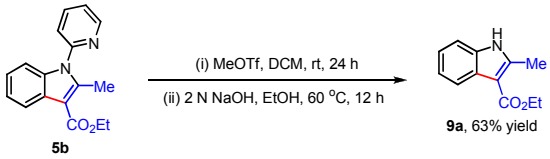
Scheme 1 Catalytic functionalization of indole C-7 position.

Next, we investigated the catalytic C7-functionalization of indole **5b**, generated from our indole formation protocol, with various coupling partners. First, we were delighted to find that alkylation reaction using diisopropyl 2-diazomalonate (**2c**) can be performed under slightly modified reaction conditions to provide C7-alkylated product **7a** in 90% yield (Scheme 1, eq. 1).[12b] Furthermore, cyanation[19] and amidation[20] reactions were achieved at indolic C7-position to give the corresponding products **7b** and **7c**, respectively (Scheme 1, eqs. 2 and 3). While performing the intramolecular cyclization between ester and amine groups of **3a** to afford indolin-2-one under basic conditions, a tricyclic 6*H*-pyrimido[2,1-b]quinazoline **8a** was unexpectedly obtained in 42% yield (Scheme 2).



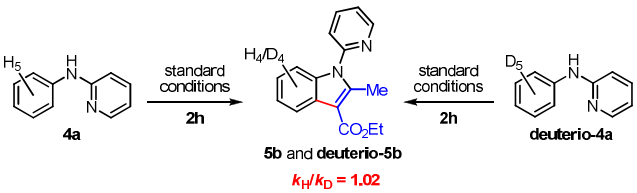
Scheme 2 Transformation of alkylated aniline.

Finally, we successfully removed the pyridinyl directing group of indole **5b** by treating with MeOTf and subsequent base-mediated hydrolysis to result in the free (NH)-indole **9a** in 63% yield (Scheme 3).[21]

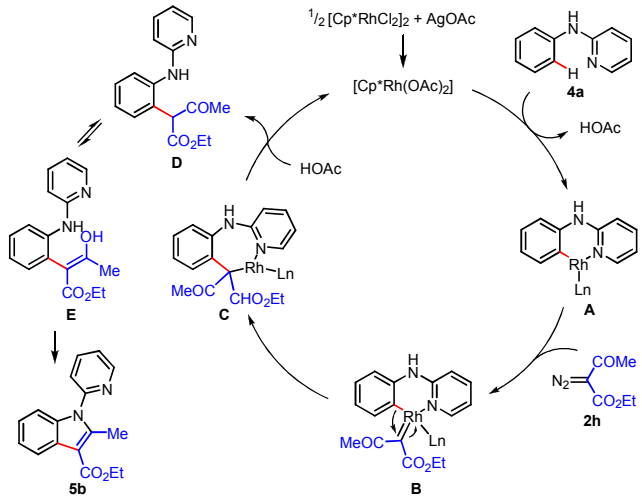


Scheme 3 Removal of a pyridinyl directing group.

To gain a mechanistic insight, the kinetic isotope effect experiments of **4a** and **deuterio-4a** were carried out (Scheme 4). The KIE value of 1.02 was observed, thus indicating that C–H cleavage might not be involved in the rate-determining step (see Supplementary Information for details).[22]



Scheme 4 KIE experiments.



Scheme 5 Proposed reaction pathway.

Based on the precedent literatures on C–H functionalization of aromatic compounds using α-diazo esters,[2,5,12c] a plausible reaction pathway for *ortho*-alkylation anilines and subsequent indole formation is depicted in Scheme 5. First, coordination of a pyridinyl directing group on **4a** to a Rh(III) catalyst and subsequent C–H cleavage generates a six-membered rhodacycle **A**. Then coordination of α-diazo compound **2h** to **A** and subsequent release of N_2 affords a metal-carbenoid intermediate **B**. Migratory insertion delivers a 7-membered rhodacycle species **C**, which undergoes protonation to yield the *ortho*-alkylated product **D** and an active Rh(III) catalyst. Enol intermediate **E**, formed through keto-enol tautomerization, can undergo dehydration process to afford indole product **5b**.

In conclusion, we disclosed the rhodium(III)-catalyzed C–H alkylation reaction of *N*-phenylpyrimidin-2-amines with α-diazo compounds. Notably, anilines containing a pyridine directing group were easily transformed with α-diazo acetoacetates into highly substituted indoles, which are known to be crucial scaffolds of biologically active molecules. Furthermore, the formed indole adducts were subsequently used in the sequential C–H functionalization process to give C7-alkylated, cyanated, and amidated indoles. Our ongoing studies seek to expand the scope to the alkylation of sp^3 C–H bonds and the synthesis of complex heterocycles.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and spectroscopic data for all compounds. See DOI: 10.1039/b000000x/

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