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Multiple Roles of the Pyrimidyl Group in the Rhodium-Catalyzed Regioselective Synthesis and Functionalization of Indole-3-carboxylic Acid Esters

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Abstract: A regioselective synthesis of indole-3-carboxylic acid esters from anilines and diazo compounds has been realized by making use of the pyrimidyl group-assisted rhodium-catalyzed C–H activation and C–N bond formation. The reaction proceeds under mild conditions, exhibits good functional group tolerance and scalability. Reutilization of the pyrimidyl directing group in the resulting products provided an efficient strategy for further C-7 functionalization of indoles. Moreover, the pyrimidyl moiety could be readily removed as a leaving group to offer various free N–H indoles.

Keywords: C–H activation; diazo compounds; indole-3-carboxylic acid esters; pyrimidyl group; rhodium catalysis

Indole-3-carboxylic acid esters are one of the most important structural motifs widely present in numerous natural products, pharmaceuticals and bioactive compounds,[1] such as Arbidol,[2] Tropisetron,[3] PD 0298029[4] and Grandilodine A[5] (Figure 1). Consequently, tremendous efforts have been devoted to the synthesis and functionalization of indole-3-carboxylic acid esters.[6] During the past two decades, transition metal-catalyzed C–H functionalization has emerged as an economical and environmentally benign approach to achieve these structures. In 2008, Glorius[7] reported a Pd-catalyzed intramolecular oxidative cyclization to indole-3-carboxylic acid esters from *N*-arylenamines. Later, the Jiao and Cao groups achieved the skeletons *via* a Pd-catalyzed sequential Michael-type addition and cross-dehydrogenative coupling (CDC) reaction between anilines and electron-deficient alkynes.[8] However, the preparation of pre-activated substrates, the demand for excess oxidants, and limited substrate scopes still hampered their further applications to some extent. Therefore, the development of a promising strategy to access various indole-3-carboxylic acid esters from simple and readily available starting materials remains highly desirable in modern organic chemistry.

Recently, diazo compounds or related derivatives as carbene precursors have played an important role in C–H activation for direct C–C bond formation, in particular in the synthesis of heterocycles.[9] However, to the best of our knowledge, C–H activation involving diazo compounds is challenging. The diazo compounds could easily undergo a classic nucleophilic insertion reaction of metal carbenoids rather than insertion into the challenging aromatic C–H bond. Previously, Moody reported an indole-2-carboxylic acid ester synthesis from *N*-methylanilines and α-diazo-β-keto esters involving carbenoid insertion into the N–H bond followed by cyclization/condensation (Scheme 1).[10] In comparison, we wondered if we

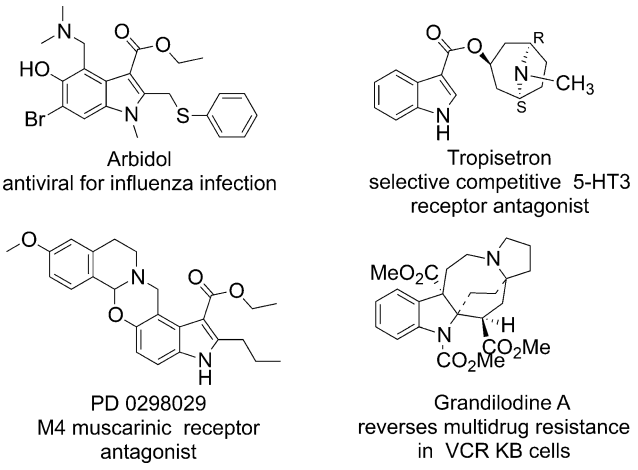

Figure 1. Examples of indole-3-carboxylic acid esters in bioactive compounds.

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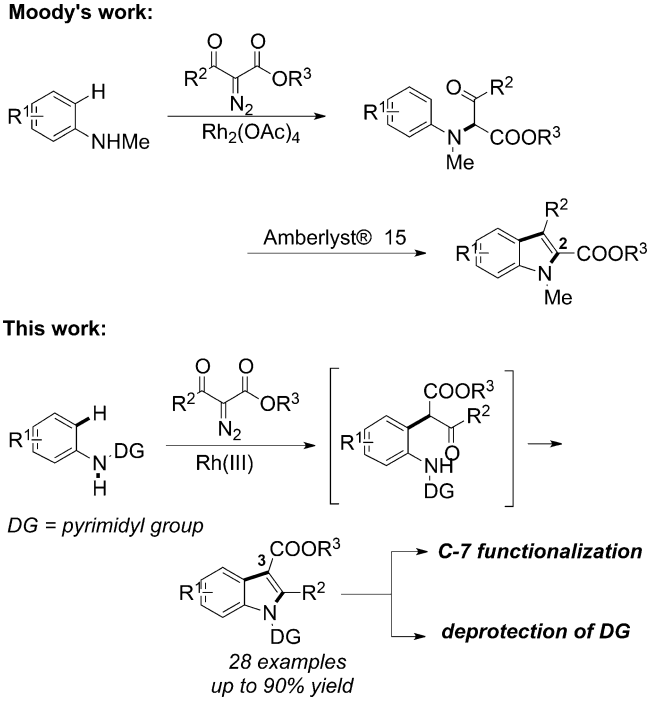
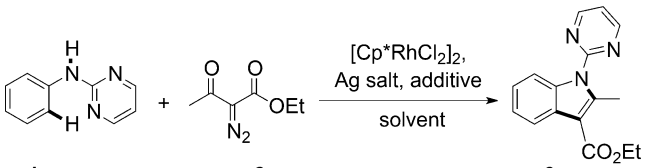


Scheme 1. Rhodium-catalyzed synthesis of indoles with anilines and diazo compounds.

could control the reaction pathway by introducing a directing group strategy,[11] thus leading to preferential aromatic C–H bond activation instead of the nucleophilic metal-carbene insertion to obtain different types of products. In continuation of our studies on the synthesis and applications of heterocycles *via* transition metal-mediated C–H functionalization,[12] herein, we report the rhodium(III)-catalyzed pyrimidyl-directed sequential aromatic C–H activation and C–N bond formation for the regioselective synthesis of indole-3-carboxylic acid esters from anilines and diazo compounds. Reutilization of the pyrimidyl as a directing group in the resulting products provided an efficient strategy for further C-7 functionalization of indoles. Moreover, the pyrimidyl group could be readily removed to offer various free N–H indoles in high efficiency.

We initiated our study with *N*-(2-pyrimidyl)aniline **1a** and ethyl 2-diazo-3-oxobutanoate **2a** as substrates. When the reaction was performed in the presence of $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10.0 mol%) in 1,2-dichloroethane (DCE, 2 mL) at 60 °C for 12 h, no desired product was observed. Then we examined different additives such as acids, bases and silver salts. With HOAc as additive, the desired ethyl 2-methyl-1-(pyrimidin-2-yl)-1*H*-indole-3-carboxylate **3aa** was obtained in 81% yield (Table 1, entry 4), and the structure was confirmed by ^1H and ^{13}C NMR spectroscopy, mass spectrometry, and single crystal X-ray analysis (see the Supporting Information for details).[13] We also at-

Table 1. Optimization of the reaction conditions.[a]



Entry	Ag Salt	Additive	Solvent	Time [h]	Yield [%]
1	$AgSbF_6$	–	DCE	12	N.R.
2	$AgSbF_6$	CsOAc	DCE	12	N.R.
3	$AgSbF_6$	Cs_2CO_3	DCE	12	N.R.
4	$AgSbF_6$	HOAc	DCE	12	81
5	–	HOAc	DCE	12	N.R.
6	$AgNTf_2$	HOAc	DCE	12	79
7	Ag_2CO_3	HOAc	DCE	12	5
8	$AgSbF_6$	PivOH	DCE	12	80
9	$AgSbF_6$	PhCOOH	DCE	12	73
10	$AgSbF_6$	HCOOH	DCE	12	11
11	$AgSbF_6$	HOAc	toluene	12	25
12	$AgSbF_6$	HOAc	CH_3CN	12	N.R.
13	$AgSbF_6$	HOAc	MeOH	12	74
14[b]	$AgSbF_6$	HOAc	DCE	6	86 (85[d])
15[c]	$AgSbF_6$	HOAc	DCE	6	43

[a] *Reaction conditions:* **1a** (0.25 mmol, 1.0 equiv.), **2a** (0.50 mmol, 2.0 equiv.), $[Cp^*RhCl_2]_2$ (2.5 mol%), Ag salt (10.0 mol%) and additive (0.25 mmol, 1.0 equiv.) in solvent (2 mL), 60 °C, under air. Yields were determined by ^1H NMR using dibromomethane as the internal standard.
[b] HOAc (0.5 equiv.), 6 h.
[c] $[Cp^*RhCl_2]_2$ (1.25 mol%), HOAc (0.5 equiv.), 6 h.
[d] Isolated yield.

tempted the reaction with $[Cp^*RhCl_2]_2$ in the absence of $AgSbF_6$ (Table 1, entry 5), which was completely unreactive. Based on the above results, we found that a combination of an acid and a silver salt was indispensable in this cyclization reaction. Subsequently, the reaction conditions were further optimized by screening of different silver salts, acids and solvents (Table 1, entries 6–13). All of them failed to give a better yield. The isolated yield could be improved to 85% when the reaction time was shortened to 6 h. Reducing the amount of $[Cp^*RhCl_2]_2$ from 2.5 mol% to 1.25 mol% provided **3aa** in a lower yield (Table 1, entry 15).

With the optimized conditions in hand, we then examined the substrates scope of arylamines, and the results are shown in Table 2. Most of the substrates offered the corresponding ethyl 2-methyl-1-(pyrimidin-2-yl)-1*H*-indole-3-carboxylates in good to excellent yields. Methyl or *n*-butyl substitution at the *para*-position of the phenyl ring offered **3ba** and **3ca**, respectively in 84% yield. With a methoxy group as substituent the reaction gave **3da** in 67% yield. Halogen substituents led to **3ea**–**3ha** in 64–75% yield, which could be subjected to further synthetic transformations. It

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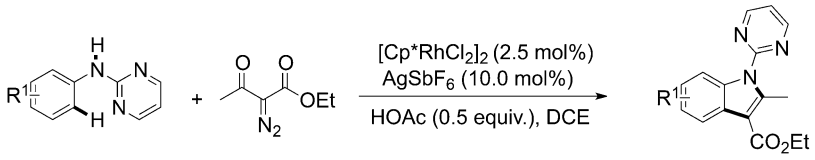
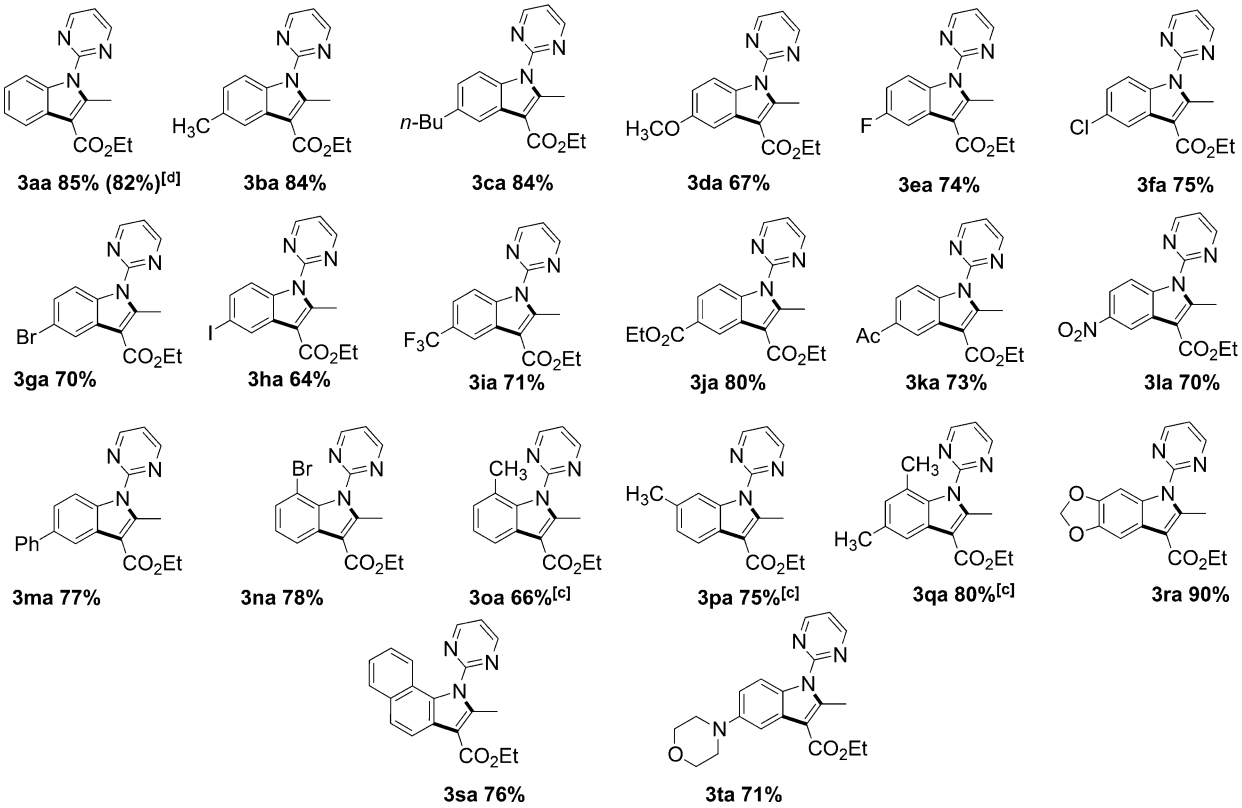
Table 2. Scope of arylamines.[a,b]





[a] *Reaction conditions:* **1** (0.25 mmol, 1.0 equiv.), **2a** (0.50 mmol, 2.0 equiv.), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10.0 mol%) and HOAc (0.5 equiv.) in DCE (2 mL) at 60 °C for 6 h under air atmosphere.
[b] Isolated yields.
[c] 80 °C.
[d] 5 mmol scale reaction.

was worth noting that the substrates with strong electron-withdrawing groups such as the CF_3, CO_2Et, Ac and NO_2 could also offer the desired products **3ia**–**3la** in 70–80% yield. *ortho*-Substituted arylamines **1n** and **1o** provided the corresponding products **3na** and **3oa** in 78% and 66% yields, respectively. *meta*-Methyl substituted **1p** reacted exclusively at the less sterically hindered position and afforded **3pa** in 75% yield. Poly-substituted **1q** and **1r** gave **3qa** in 80% yield and **3ra** in 90% yield. *N*-(Naphthalen-1-yl)pyrimidin-2-amine **1s** produced **3sa** in 76% yield. A morpholinyl group at the *para*-position of the phenyl ring led to **3ta** in 71% yield. In addition, the reaction could be conducted on a gram scale (5 mmol), and **3aa** was obtained in 82% yield (1.16 g).

Next, the scope of diazo acetoacetates was investigated, and the results are summarized in Table 3. Methyl, *tert*-butyl and benzyl α-diazoacetoacetates **2b**–**2d** afforded **3ab**–**3ad** in 57–76% yield. When we changed the group R^2 with ethyl and *n*-propyl, **3ae** and **3af** were obtained in 68% and 88% yield, respectively. Phenyl-substitued **2g** gave **3ag** in 22% yield. 1-Diazo-1-tosylpropan-2-one **2h** delivered C-3 sulfonylindole **3ah** in 49% yield. Moreover, ethyl 2-diazo-3-oxopropanoate **2i** was also suitable for this transformation, giving the desired **3ai** in 32% yield.

When α-diazo esters such as dimethyl malonic esters, methyl 2-diazo-2-(phenylsulfonyl)acetate and ethyl 2-diazo-2-(diethoxyphosphoryl)acetate were allowed to react with *N*-(2-pyrimidyl)aniline in the

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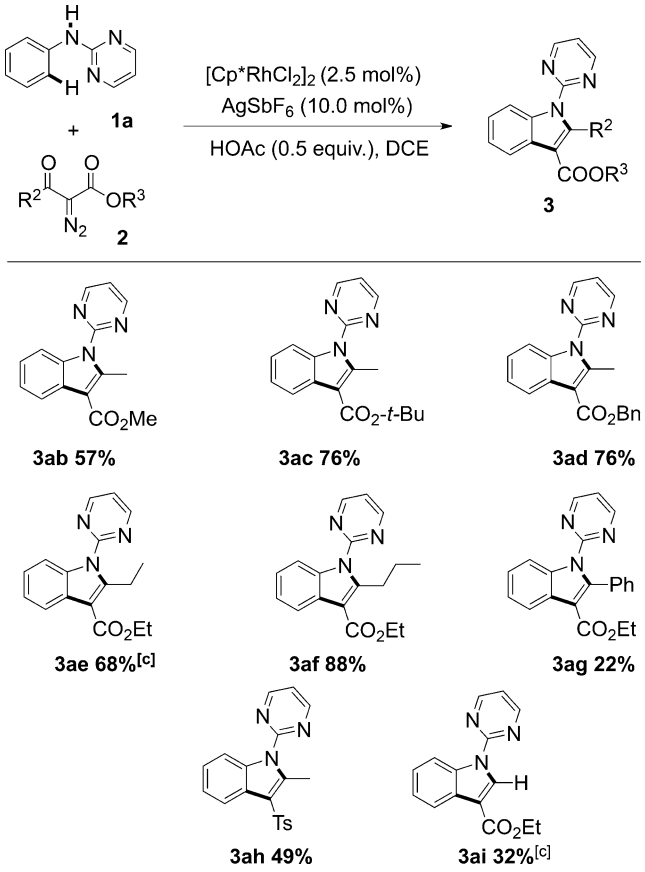
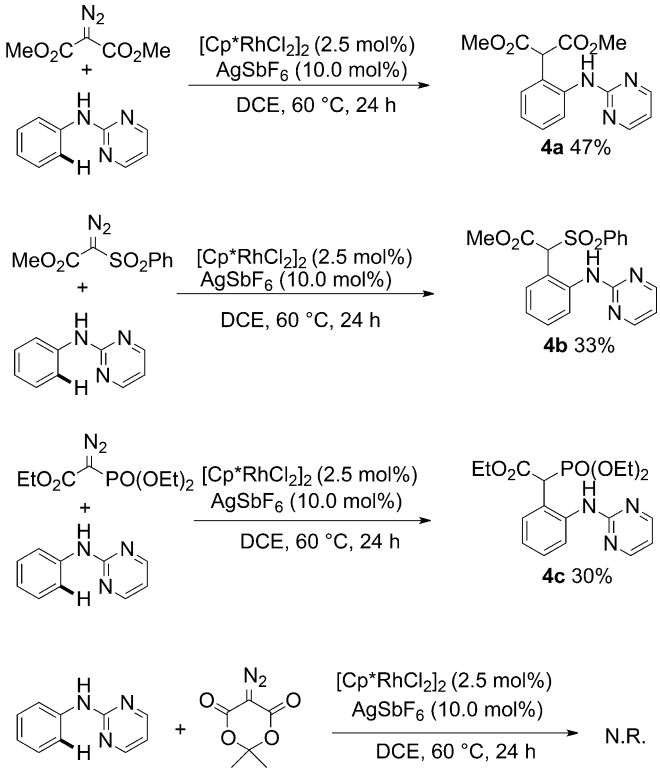
Table 3. Scope of diazo acetoacetates.[a,b]



[a] *Reaction conditions:* **1a** (0.25 mmol, 1.0 equiv.), **2** (0.50 mmol, 2.0 equiv.), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10.0 mol%) and HOAc (0.5 equiv.) in DCE (2 mL) at 60 °C for 6 h under air atmosphere.

[b] Isolated yields.

[c] 24 h.



Scheme 2. Alkylation of *N*-(2-pyrimidyl)aniline with α-diazo esters.

presence of $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10.0 mol%) in 1,2-dichloroethane (DCE, 2 mL) at 60 °C for 24 h, all reactions afforded the monoalkylated products **4a–4c** in 30–47% yield. The diazo derivative of Meldrum's acid could not give any alkylated or annular product (Scheme 2).

To date, only few efficient protocols for direct C-7 functionalization of indoles *via* C–H activation have been reported.[14] In our reaction, the pyrimidyl group in the resulting product **3aa** could be reutilized as a directing group for further C-7 functionalization *via* C–H activation. For instance, transition metal-catalyzed direct alkenylation,[15] amination,[16] acyloxylation,[17] cyanation,[18] alkylation,[9m] amidation[19] and acylation[20] all proceeded smoothly and offered the corresponding products **5–11** in moderate to excellent yields (Scheme 3).

Removing the directing groups under mild conditions is a common challenge in C–H activation, because the directing group was unnecessary in the final target structures. The pyrimidyl group in the resulting product **3aa** could be readily removed by treatment with NaOEt in DMSO at 100 °C for 24 h,[21] providing the unprotected ethyl 2-methyl-1*H*-indole-3-carboxylate **12** in 85% yield. Moreover, in our reaction, the C-3 ester group could be removed, and the corresponding product **13** was obtained in 82% yield, which could be further hydrolyzed to afford 2-methyl-1*H*-indole **14** in a yield of 80%. With regard to the C-7 functionalized indole **5**, it could also be successfully hydrolyzed to afford 2,3,7-trisubstituted indole **15** in 71% isolated yield (Scheme 4).

Finally, a kinetic isotope effect experiment was carried out. It gave a K_H/K_D ratio of 1.6, thus indicating that C–H cleavage might be involved in the rate-determining step (Scheme 5, see the Supporting Information for details).

Based on the previous studies,[9i–m,19] we propose a plausible reaction mechanism as illustrated in Scheme 6. First, the rhodium complex would be activated by $AgSbF_6$ to generate electrophilic cationic complex Cp*Rh(III), which then participated in the directed C–H cleavage to offer intermediate **A**. Subsequently, intermediate **A** reacted with diazo compound **2aa** to generate rhodium(III)-carbene intermediate **B**. Migratory insertion into the rhodium-

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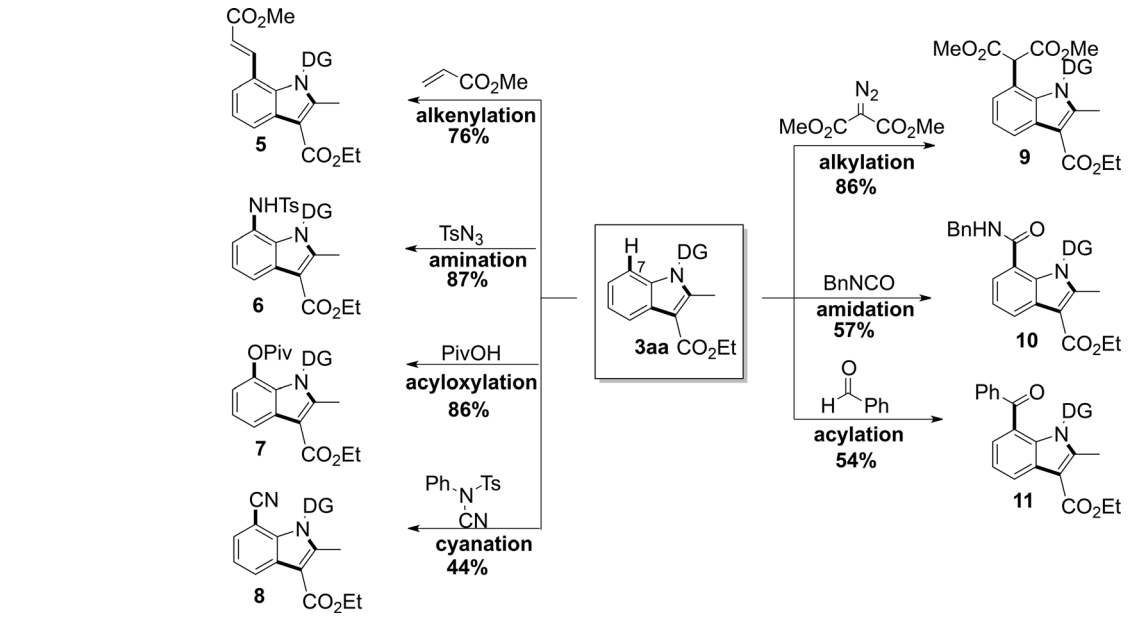
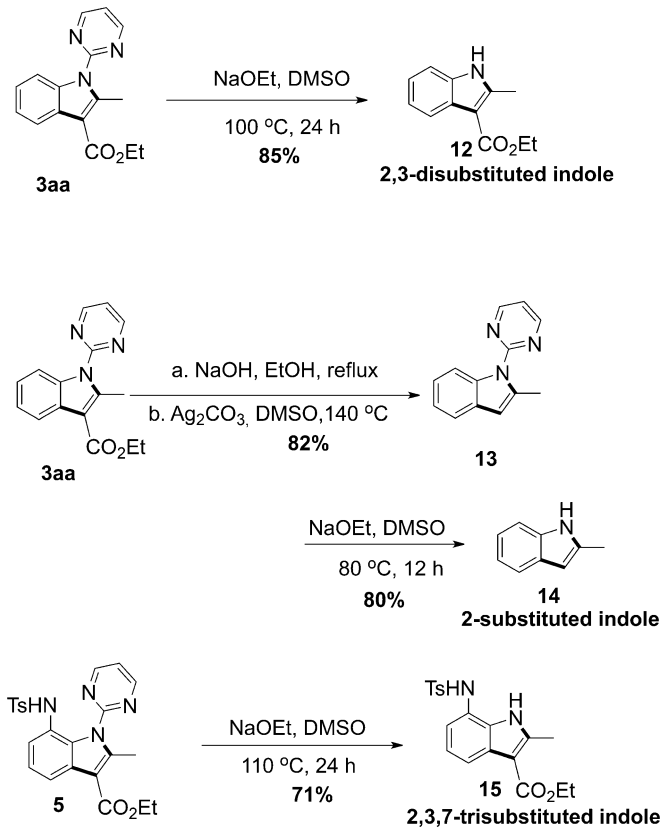


Scheme 3. Reutilization of the pyrimidyl as directing group for further C-7 functionalization of indoles.



Scheme 4. Deprotection of pyrimidyl group to synthesize free N–H functionalized indoles.

carbon bond produced the seven-membered rhodacycle **C**. Upon protonation by acetic acid, the intermediate **D** was achieved along with the regeneration of the active rhodium(III) catalyst for the next catalytic cycle. Enol intermediate **E** was formed through keto-enol tautomerization, and the final product **3aa** was obtained by a dehydration process.

In summary, the pyrimidyl as a directing group played a pivotal role in our rhodium(III)-catalyzed regioselective synthesis of indole-3-carboxylic acid esters from anilines and diazo compounds. The procedure involved C–H activation, carbene migration insertion and C–N bond formation, exhibited good functional group tolerance and scalability. Reutilization of the pyrimidyl as directing group in the resulting products provided an efficient strategy for further C-7 functionalization of indoles. Moreover, the pyrimidyl as leaving group could be readily removed to offer free N–H indoles under mild reaction conditions. Further investigations on the construction of complex functionalized heterocycles are in progress in our laboratory.

Experimental Section

General Procedure

A sealed tube was charged with pyrimidylarylamines **1** (0.25 mmol, 1.0 equiv.), $[Cp^*RhCl_2]_2$ (3.9 mg, 2.5 mol%), $AgSbF_6$ (8.6 mg, 10.0 mol%), HOAc (8 μL, 0.5 equiv.), diazo compounds **2** (0.5 mmol, 2.0 equiv.) and DCE (2 mL). The reaction mixture was vigorously stirred at 60 °C (oil bath temperature) for 6 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (20 mL) and filtered through a plug of celite. The solvent was evaporated, and the residue was purified by flash chromatography on

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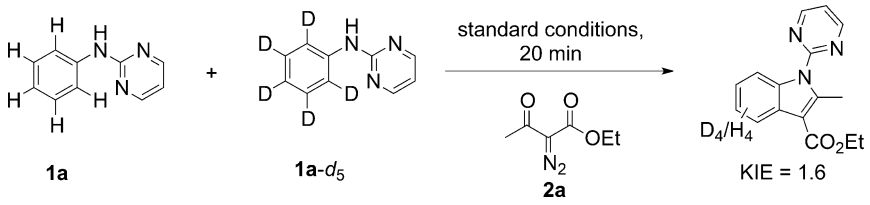
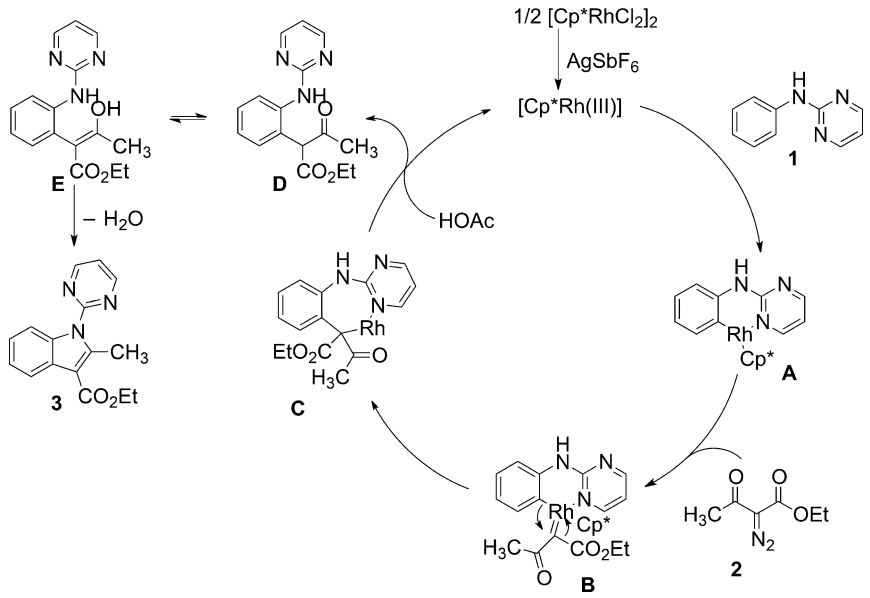


Scheme 5. Intermolecular kinetic isotope study.



Scheme 6. Proposed mechanism.

silica gel (petroleum ether/ethyl acetate) to afford the corresponding products **3**.

Acknowledgements

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