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Cp*Co(III)-catalysed selective alkylation of C–H bonds of arenes and heteroarenes with α-diazocarbonyl compounds†

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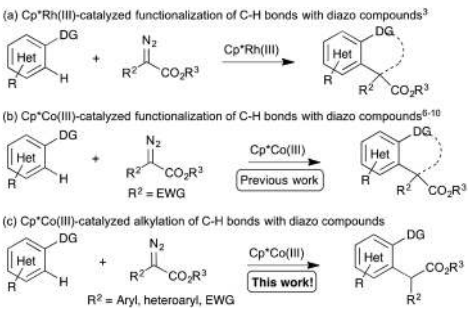
Cp*Co(III)-catalysed selective alkylation of directed C–H bonds of arenes and heteroarenes has been accomplished employing donor–acceptor carbenes, derived from α-diazocarbonyl compounds. The developed method allows ready access to various substituted α-(hetero)aryl-α-arylacetic acid derivatives in good to excellent yields. Synthetic utility was also shown through the synthesis of a substituted indole derivative, an anticancer agent.

Transition metal catalysed cross coupling of diazo compounds has emerged as a powerful tool in contemporary organic synthesis for the synthesis of complex structural frameworks with excellent atom and step economy.[1] Particularly, functionalization of widely abundant C–H bonds with diazo compounds *via* C–H bond metalation, metal–carbene formation and migratory insertion attracted much attention in recent years,[2] due to the possible construction of various functionalized arenes and heteroarenes. In this context, precious rhodium based Cp*Rh(III) catalysts have been well-explored, which demonstrated excellent reactivity in the directed C–H bond functionalization with various carbene precursors (Scheme 1a).[3] Recently these methods were replaced with highly abundant and less expensive cobalt based catalysts, Cp*Co(III) catalysts.

After the initial breakthrough by Matsunaga, Kanai and co-workers in 2013,[4] various research groups across the globe have demonstrated Cp*Co(III) catalysts as highly efficient alternatives to the Cp*Rh(III) catalyst in C–H bond functionalization.[5] Particularly, Glorius and co-workers demonstrated the first example of Cp*Co(III)-catalysed directed C–H coupling with both acceptor–acceptor and donor–acceptor carbenes derived from the corresponding diazo compounds for the synthesis of pyridoisoquinolinones[6] and subsequently extended to the synthesis of isoquinolin-3-ones (Scheme 1b).[7] On the other hand, the Cp*Co(III)-catalysed synthesis of 1-aminoisoquinoline through C–H/N–H bond functionalization of aryl amidines with diazo compounds was demonstrated by Ackermann and co-workers.[8] In 2015, Wang and co-workers reported Cp*Co(III)-catalysed selective alkylation of C–H bonds of (hetero)arenes with 2-diazomalonates.[9] Very recently, Shi and co-workers employed the Cp*Co(III)-catalyst for the alkylation of the C(sp^3)–H bond of 8-methylquinoline with diazo compounds.[10] However, most of these methods utilize the highly reactive acceptor–acceptor carbenes derived from 2-diazomalonates and their derivatives. Thus, the development of an efficient and general method for the Cp*Co(III)-catalysed directed C–H bond coupling with widely applied donor–acceptor carbenes[11] derived from α-diazocarbonyl compounds is highly desirable (Scheme 1c). Successful development of this method would offer ready access to α-(hetero)aryl-α-arylacetic acids, which are vital synthetic intermediates for the construction of various diarylmethine containing natural products and pharmaceuticals.[12] In continuation of our interest in C–H bond functionalization[13] with the Cp*Co(III)-catalyst,[14] we herein disclose an efficient Cp*Co(III)-catalysed selective alkylation of directed C–H bonds of arenes and heteroarenes for the synthesis of α-(hetero)aryl-α-arylacetic acid derivatives.

We started our investigation using 1-(pyridin-2-yl)-1*H*-indole **1a** and methyl 2-diazo-2-phenylacetate **2a** as model sub-



Scheme 1 Transition metal catalysed diazocoupling reactions.

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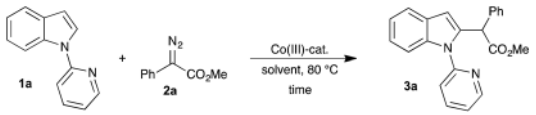
strates for Co(III)-catalysed C2-alkylation. The reaction of 1 equiv. of **1a** with 1.2 equiv. of **2a** in the presence of 5 mol% of $[Cp^*Co(MeCN)_3][SbF_6]_2$ in toluene at room temperature did not afford the expected product. To our delight the expected product **3a** was obtained in 77% yield after 12 h, when the temperature was raised to 60 °C (Table 1, entry 1). Further increasing the reaction temperature to 80 °C led to the formation of product **3a** in 86% after 9 h (Table 1, entry 2). Interestingly, changing the mode of reaction with slow addition of diazo compound **2a** also afforded **3a** in comparable yield. However, a subsequent increase in the temperature to 90 °C gave the product in a slightly less yield (Table 1, entry 3). Next, various solvents such as trifluorotoluene, DCE, THF, chlorobenzene and acetonitrile were examined. Unfortunately, none of them gave better yield than the reaction with toluene (Table 1, entries 4–8). On the other hand, using related Co(III)-catalysts such as Cp^*CoI_2CO, $[Cp^*CoI_2]_2$ and $Co(acac)_3$ resulted in the formation of the product in 61, 52 and 23% yield, respectively (Table 1, entries 9–11). Thus, 1 equiv. of **1** and 1.2 equiv. of **2** in the presence of 5 mol% of $[Cp^*Co(MeCN)_3][SbF_6]_2$ in toluene at 80 °C were chosen as optimized conditions.

Having the best-optimized conditions in hand, we next explored the generality of the method with various substituted diazoesters. Both methyl and ethyl 2-diazophenylacetate gave the corresponding C2-alkylated products **3a** and **3b** in 86 and 82% yield, under the optimized conditions (Scheme 2). Interestingly, an electron deficient diazoester derived from diethylmalonate showed similar reactivity to furnish the corresponding product **3c** in good yield. Additionally, 2-diazoarylacetate having various substitutions on the arene ring also provided the expected product in good yield. A *p-tert*-butyl substituted diazoester led to the formation of the product **3d** in 83% yield. The formation of readily amenable halo substituted derivatives **3e–3i** was achieved in excellent yields. Importantly, diazoesters having electron-withdrawing NO_2 groups at the *para* and *meta* position underwent a smooth reaction and resulted in the formation of products **3j** and **3k** in 89 and 87%, respectively. Similarly, OTs and CF_3 substituted diazoesters were also successfully converted to the C2-alkylated products **3l** and **3m** in ~82% yield. On the other hand, the *p*-methoxy substituted diazoester afforded the inseparable mixture of the C2-alkylated product and the C2,C3-cyclopropanated product in 76% yield with a 2.3 : 1 ratio. Most interestingly the pyridine based heterocyclic diazoester furnished the product **3n** in 83% yield.

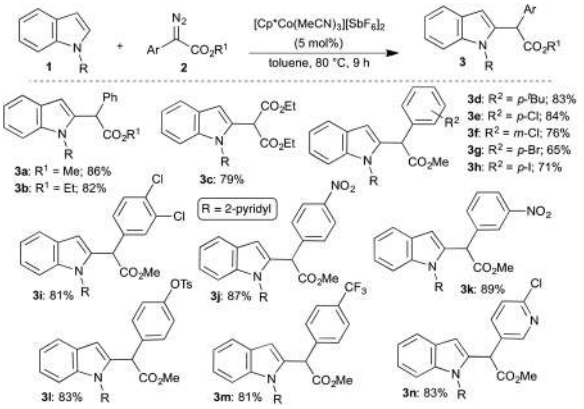
Next, the influence of substitutions on the indole moiety and on the directing group was investigated (Scheme 3). Electron donating methoxy and phenyl substitution at the 5-position of indole afforded the corresponding alkylated products **3o** and **3p** in 89 and 85% yield, respectively. The structure of **3o** was unambiguously confirmed by single crystal

Table 1 Co(III)-Catalysed alkylation with diazo compounds: optimization

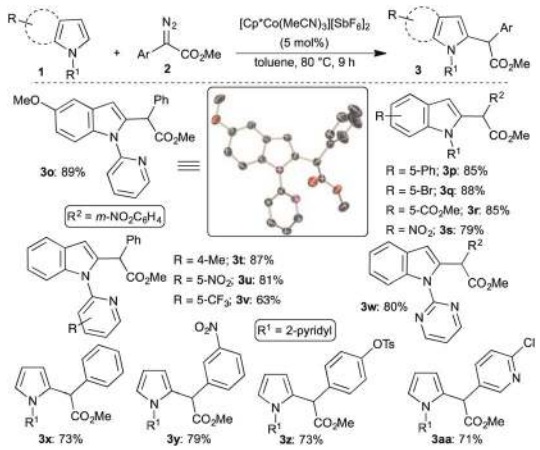


Entry	Co(III)-Cat.	Solvent	Time (h)	Conv.[a] (%)	Yield[b] (%)
1[c]	[Cp*Co]	Toluene	12	93	77
2	[Cp*Co]	Toluene	9	100	86 (85)[d]
3[e]	[Cp*Co]	Toluene	8	100	80
4	[Cp*Co]	$PhCF_3$	9	95	84
5	[Cp*Co]	DCE	9	100	59
6	[Cp*Co]	THF	9	91	73
7	[Cp*Co]	PhCl	9	85	69
8	[Cp*Co]	MeCN	9	91	59
9	$[Cp^*CoI_2CO]$	Toluene	12	79	61
10	$[Cp^*CoI_2]_2$	Toluene	12	67	52
11	$Co(acac)_3$	Toluene	14	41	23

Reaction conditions: **1a** (0.25 mmol, 1 equiv.), **2a** (0.31 mmol, 1.2 equiv.), [Cp*Co] = $[Cp^*Co(MeCN)_3][SbF_6]_2$ (5 mol%), solvent (1.5 mL), temp, time. [a] Based on the recovered starting material. [b] All are isolated yields. [c] 60 °C. [d] Diazoester was added slowly over a period of 30 minutes. [e] 90 °C.



Scheme 2 Cobalt catalysed selective C2-alkylation. Scope of diazo compounds.



Scheme 3 Co-Catalysed selective C2-alkylation. Scope of indole derivatives.

X-ray analysis.[15] Similarly, electron withdrawing substituents such as methoxycarbonyl and nitro at the 5-position of indole underwent a smooth reaction to give **3q** and **3r** in 85% and 79% yield, respectively. A substrate derived from 5-bromo indole also resulted in the formation of the corresponding alkylated product **3s** in 88% yield. In addition to the screening of different substituted indole derivatives, the effect of substitution on the directing group was also examined. Electronically different methyl and nitro substituted pyridine containing indoles furnished the products **3t** and **3u** in 87 and 81% yield, respectively. Importantly, the indole derivative carrying a trifluoromethyl substituent on the pyridine ring also led to the product **3v** in 69% yield. Instead of pyridine, pyrimidine was also found to be a highly efficient directing group, which was illustrated with the formation of product **3w** in 80% yield under the present conditions. Subsequently, C2-selective alkylation of pyrrole derivatives was investigated and found that the pyrrole derivatives were also well acceptable under the optimized conditions. For instance, 2-(1*H*-pyrrol-1-yl)pyridine reacted smoothly with various diazoesters under the developed reaction conditions to furnish the products **3x**, **3y**, **3z** and **3aa** in 73, 73, 79 and 71% yield, respectively.

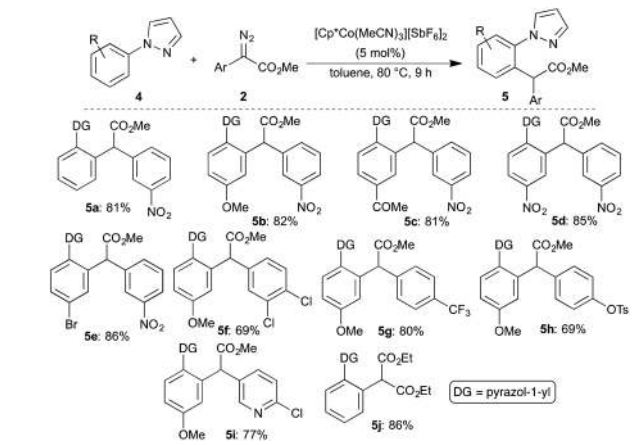
After successful demonstration of selective C2-alkylation of indole and pyrrole derivatives, extension of the method to the selective alkylation of C–H bonds of arenes was envisaged. To achieve the selective alkylation of C–H bonds of arenes, pyrazole was employed as the directing group. To our delight, the reaction of 1-phenyl-1*H*-pyrazole **4a** with methyl 2-diazo-2-(3-nitrophenyl)acetate under the developed conditions afforded **5a** in 81% yield (Scheme 4).

Encouraged by the efficiency of the developed method, various 1-aryl-1*H*-pyrazoles were subjected to afford the corresponding alkylated products. For example, both electron rich (4-methoxyphenyl) and electron deficient (4-acetylphenyl and 4-nitrophenyl)arylpyrazoles underwent a smooth reaction with diazoesters in the presence of Cp*Co(III) and furnished the products **5b**, **5c** and **5d** in 82, 81 and 85% yield, respectively. A 4-bromophenyl substituted pyrazole derivative led to the product **5e** in 86% yield. Consequently, substitution on the diazo compound was also tested. The chloro substituted diazoester resulted in the formation of product **5f** in 69% yield. Similarly, CF_3 and OTs substituted diazoesters also furnished the corresponding products **5g** and **5h** in 80 and 69% yield, respectively. Importantly, the heteroaryl substituted, pyridine based diazoester gave the product **5i** in 77% yield. Furthermore, the electron deficient diazoester derived from diethylmalonate was also found to be a suitable coupling partner to give the product **5j** in 86% yield.

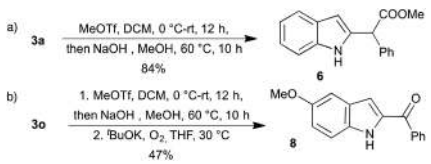
Subsequently, the synthetic utility of the developed method was demonstrated through the conversion to vital synthetic intermediates. Removal of the directing group from the compound **3a** *via* the treatment of **3a** with MeOTf in DCM followed by the reaction with aqueous NaOH in methanol at 60 °C afforded methyl α-(indol-2-yl)-α-phenylacetate **6** in 84% yield (Scheme 5). Similarly, the formation of methyl 2-(5-methoxy-1*H*-indol-2-yl)-2-phenylacetate **7** was achieved through the deprotection of the pyridine group in **3o**, which on further oxidative decarboxylation with ^{t}BuOK in THF under an oxygen atmosphere furnished the 2-aroylindole derivative **8**, which was a potent anticancer agent,[16] in 47% overall yield.

In order to understand the insight of the reaction mechanism, a control experiment with a non-directing protecting group and a deuterium exchange experiment were performed. Thus, the reaction of *N*-methyl and *N*-phenylindole under the optimized conditions gave the selective C3-alkylated products **9a** and **9b** in 69 and 63% yield and no C2-alkylation product was observed. On the other hand, *N*-tosylindole did not afford any alkylated product. Next, the reaction was carried out in the presence of one equivalent of CD_3OD under the standard reaction conditions and the reaction mixture was analysed after 2.5 h. From the reaction mixture 45% of the starting material **1a** was recovered along with 42% of product **3j** (Scheme 6).

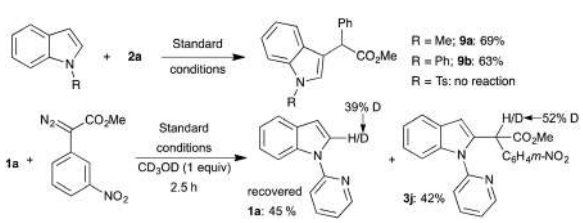
Interestingly, a significant amount of D incorporation at α to ester moiety was observed in the product **3j** as well as at the C2-position of recovered **1a**. These observations indicate



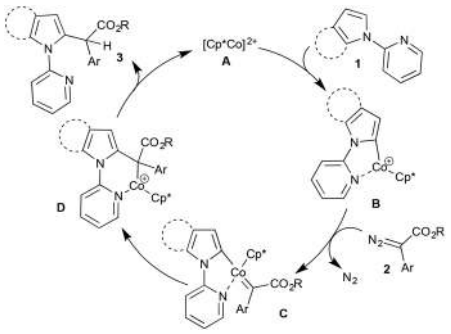
Scheme 4 Co-Catalysed selective alkylation of arenes.



Scheme 5 Synthetic applications of the developed method.



Scheme 6 Preliminary mechanistic investigation.



Scheme 7 Plausible mechanism.

that (1) the developed reaction involves initial Co–C bond formation at the C2-position of indole through directed C–H bond cleavage, which is reversible, (2) the incorporation of carbene occurs after Co–C bond formation and (3) alkylation at the C2-position of indole does not occur *via* a concerted manner.

Based on this preliminary investigation and earlier reports on the Cp*Co(III)-catalysed C–H bond functionalization, a plausible mechanism for the developed reaction was proposed (Scheme 7). At first, active cobalt catalyst **A** coordinates with the substrate **1** followed by C–H bond cleavage generating the cobaltacycle intermediate **B**. The reaction of diazoester **2** with cobaltacycle **B** would form metal carbene intermediate **C** *via* extrusion of nitrogen. Subsequent 1,1-migratory insertion of carbene to the Co–C bond would give the 6-membered cobaltacycle, which on protodemetalation would afford the expected alkylated product **3** and regenerate the active metal species **A** to continue the catalytic cycle.

In conclusion, we have successfully developed Cp*Co(III)-catalysed directed selective C2-alkylation of arenes and heteroarenes with donor–acceptor carbenes derived from diazocarbonyl compounds. The developed method is quite simple and showed excellent compatibility to various functional groups as well as directing groups and allowed the synthesis of α-(hetero) aryl-α-arylacetic acid derivatives in excellent yield. Ready removal of the directing group and synthesis of indole based anticancer agents were demonstrated to show the synthetic utility of the developed method. Furthermore, a plausible mechanism was also proposed based on the preliminary mechanistic investigation.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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