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Cp*Co(III)-catalyzed direct functionalization of aromatic C–H bonds with α-diazomalonates

Xu-Ge Liu, Shang-Shi Zhang, Jia-Qiang Wu, Qingjiang Li, Honggen Wang *

School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China

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ABSTRACT

Cp*Co(III)-catalyzed intermolecular C(sp^2)–C(sp^3) assembly of (hetero)arenes with α-diazomalonates using a direct C–H functionalization logic was developed. A series of (hetero)arenes underwent alkylation efficiently under the assistance of pyrazolyl and pyrimidyl directing groups under relatively mild and operationally simple reaction conditions. Good functional group tolerance, satisfactory yields, and excellent regioselectivity were found.

The development of efficient and greener methods to the assembly of C–C bonds is the central topic in the discipline of organic chemistry.[1] In recent years, transition-metal catalyzed direct C–H functionalization offers a powerful and straightforward strategy for C–C bonds formation.[2] To this purpose, noble metal-based catalysts (such as Pd, Rh, Ru, and Ir) have been extensively investigated and therefore, have achieved significant advances.[2] Nevertheless, the exploration of cheap and earth-abundant first-row transition metals as catalysts is still of great interest. In this context, it has been demonstrated that iron[3], nickel[4], cobalt[5] and manganese[6] are effective in C–H activation reactions, though limitations such as low reactivity, drastic reaction conditions, and limited reaction types still exist. Pioneered by Kanai[7], and later advanced by the groups of Ackermann[8], Ellman[9], Glorius[10], and Chang[11], Cp*Co(III) was found to be an efficient catalyst for C–H functionalizations, which shows similar, and in certain cases complementary reactivity to its counterparts Cp*Rh(III) and Cp*Ir(III) species. Furthermore, the reactions initiated by Cp*Co(III) could take place under relatively mild reaction conditions compared to other first-row cheap metals.

The application of carbenoid in C–H bond functionalization under the catalysis of transition metals has been realized as a powerful approach for C–C bonds formation.[12] Classically, these reactions proceeded via a carbene formation and thereafter C–H insertion mechanism. Recently, it was demonstrated that an alternative mechanism involving C–H activation, metal-carbene formation, and migration insertion was operative in Cp*Rh(III)[13] and Cp*Ir(III)[14]-catalyzed C–H coupling reactions with diazo compounds. During the preparation of this manuscript, Glorius and Zhao realized the first example of Cp*Co(III)-catalyzed C–H alkylation with diazo compounds.[10b] An in situ cyclization enables the straightforward access toward several extended pi-systems. Herein, we report our development of an efficient Cp*Co(III)-catalyzed intermolecular C–H coupling with diazomalonates for the assembly of C(sp^2)–C(sp^3) bond. The reaction occurs under rather simple reaction conditions, and is operationally simple.

At the outset of our studies, *N*-phenylpyrazole (**1a**) was chosen as a model substrate (Table 1). The reaction of **1a** with 1.2 equiv of dimethyl diazomalonate **2a** in the presence of 5 mol % Cp*Co(CO)I_2 and 10 mol % AgSbF_6 in toluene at 100 °C delivered the desired alkylation product **3aa** in 5% yield (entry 1). A survey of different solvents led us to identify that reaction proceeded smoothly in DCE, effecting the alkylation in a good yield of 80% (entries 2–5). Control experiments showed that cobalt is essential for this transformation, as its omission gave no trace amount of **3aa** (entry 6). In addition, the employment of Ag salt to remove the iodide to generate cationic Cp*Co(III) species was also important (entries 7 and 8). Gratifyingly, the catalyst loading could be decreased to as low as 1 mol %, wherein a good yield of 70% could be maintained (entries 9 and 10). The attempt to lower the temperature failed (entries 11 and 12). Only 20% yield was obtained when the reaction was conducted at 50 °C.

With the optimized conditions in hand, the scope of the reaction was investigated. A variety of substituted *N*-phenylpyrazoles were synthesized and subjected to the reaction (Table 2). It was found that the commonly encountered functional groups such as

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* Corresponding author.
E-mail address: wanghg3@mail.sysu.edu.cn (H. Wang).

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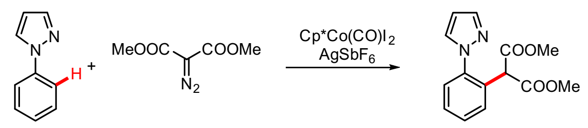
Table 1
Reaction optimization[a]

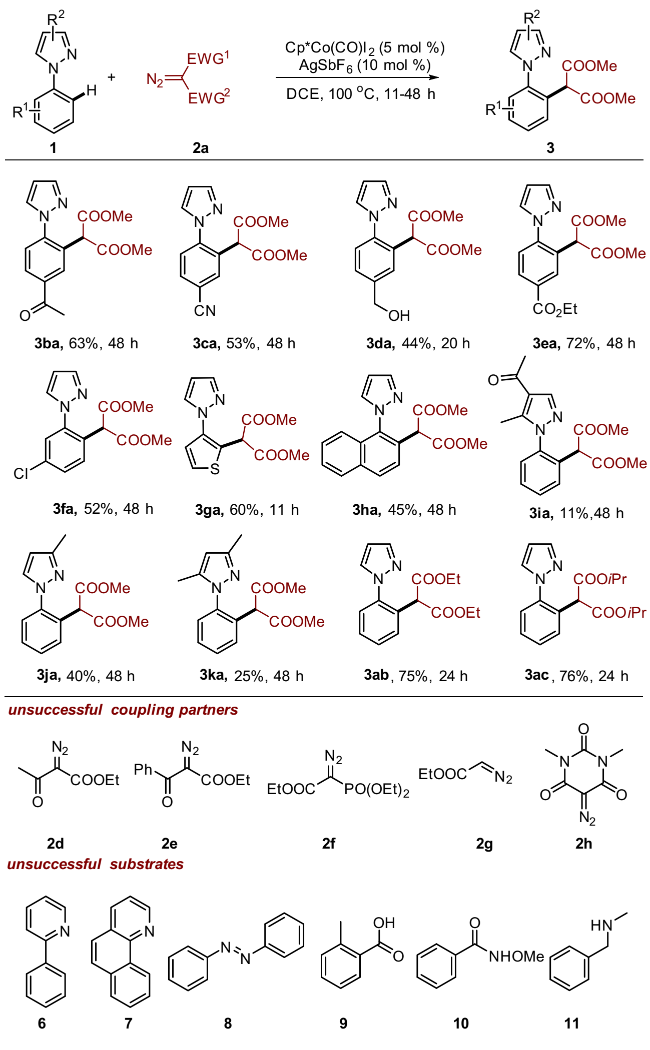


1a **2a** **3aa**

Entry	Cp*Co(III) (mol %)	$AgSbF_6$ (mol %)	Solvent	T (°C)	Yield[b] (%)
1	5	10	Toluene	100	5
2	5	10	DMF	100	Trace
3	5	10	EtOH	100	Trace
4	5	10	CH_3CN	100	0
5	5	10	DCE	100	80
6	0	10	DCE	100	0
7	5	0	DCE	100	0
8	0	0	DCE	100	0
9	2.5	5	DCE	100	74
10	1	2	DCE	100	72
11	5	10	DCE	25	0
12	5	10	DCE	50	20

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), $Cp^*Co(CO)I_2$, $AgSbF_6$, solvent (2.0 mL), 12 h.
[b] Isolated yield.

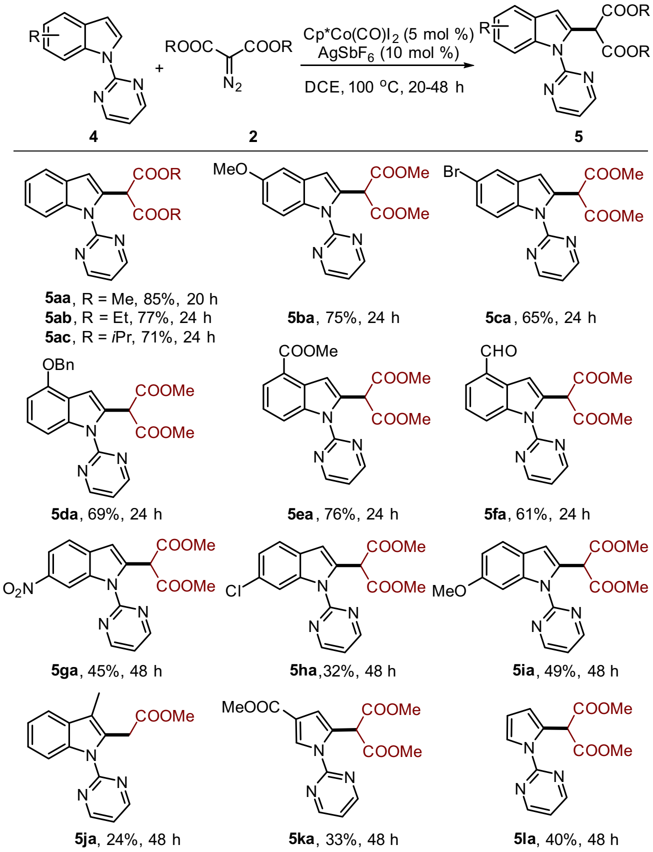
Table 2
Cp*Co(III)-catalyzed coupling of *N*-arylpyrazoles with diazo compounds[a]



3ba, 63%, 48 h
3ca, 53%, 48 h
3da, 44%, 20 h
3ea, 72%, 48 h
3fa, 52%, 48 h
3ga, 60%, 11 h
3ha, 45%, 48 h
3ia, 11%,48 h
3ja, 40%, 48 h
3ka, 25%, 48 h
3ab, 75%, 24 h
3ac, 76%, 24 h

[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.36 mmol), $Cp^*Co(CO)I_2$ (5 mol %), $AgSbF_6$ (10 mol %), DCE (2.0 mL), 100 °C. Yields of isolated products.

Table 3
Cp*Co(III)-catalyzed coupling of *N*-pyrimidinylindoles with 2-diazomalonates[a]

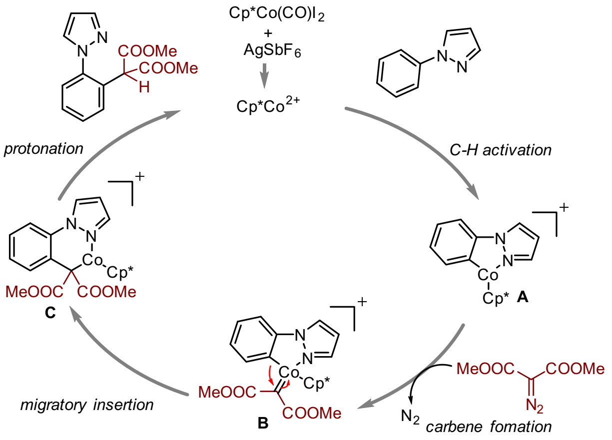


5aa, R = Me, 85%, 20 h
5ab, R = Et, 77%, 24 h
5ac, R = *i*Pr, 71%, 24 h
5ba, 75%, 24 h
5ca, 65%, 24 h
5da, 69%, 24 h
5ea, 76%, 24 h
5fa, 61%, 24 h
5ga, 45%, 48 h
5ha,32%, 48 h
5ia, 49%, 48 h
5ja, 24%, 48 h
5ka, 33%, 48 h
5la, 40%, 48 h

[a] Reaction conditions: **4** (0.3 mmol), **2** (0.36 mmol), $Cp^*Co(CO)I_2$ (5 mol %), $AgSbF_6$ (10 mol %), DCE (2.0 mL), 100 °C. Yields of isolated products.

acetyl (**3ba**), cyano (**3ca**), hydroxymethyl (**3da**), ester (**3ea**), and chloro (**3fa**) were tolerated in this transformation, giving the desired products in moderate-to-good yields. These functionalities offer ample opportunities for further functionalizations. With meta-chloro substituted *N*-phenylpyrazole, only reaction taking place at the less hindered position was found (**3fa**). Of note, thiophene **1g** underwent efficiently, with alkylation occurring selectively at the α position (**3ga**). 1-(Naphthalen-1-yl)-1*H*-pyrazole was also a suitable substrate, giving **3ha** in 45% yield. The substituent effect on the pyrazole ring was also examined. When an electron-withdrawing acetyl group was introduced, a low yield of only 11% was obtained (**3ia**), probably due to an attenuated coordination ability of the resulting pyrazole ring. With electron-releasing methyl group substituted, the yields were also decreased, indicative of a bad compatibility of steric hindrance on the directing group (**3ja** and **3ka**). Of note, no dialkylation was observed in these reactions. It was found that diethyl diazomalonate **2b** and diisopropyldiazomelonate **2c** were also efficient coupling partners for this transformation (**3ab** and **3ac**). To our disappointment, however, the use of diazo compounds **2d**–**2h**, gave no corresponding products. And attempt to expand the scope to other substrates failed (substrates 6–11), with none of which giving any desired products.

To further expand the scope, we explored the direct alkylation reaction of indoles. Indoles are important skeletons in numerous functional molecules. As shown in Table 3, it was found that using the same protocol described above, the indoles underwent functionalization efficiently under the assistance of a pyrimidyl directing group.[15] Thus, different functional groups, such as methoxyl



Scheme 1. Proposed mechanism.

(**5ba**, **5ia**), halogen (**5ca**, **5ha**), benzyloxyl (**5da**), ester (**5ea**), nitro (**5ga**), and even formyl (**5fa**), substituted at different positions were well tolerated in this reaction. Interestingly, when β-methyl indole was employed, the anticipated product was not detected. Instead, the monoester **5ja**, assumably derived from a subsequent decarbalkoxylation, was isolated in 24% yield. Importantly, the direct alkylation of pyroles was also feasible under the identical reaction conditions (**5ka** and **5la**).

A reaction mechanism was proposed and is outlined in Scheme 1. The active catalyst Cp^*Co^{2+} is generated by the ligand abstraction with $AgSbF_6$. C–H activation takes place under the assistance of the corresponding directing group, forming a cyclometallated intermediate **A**. **A** reacts with α-diazomalonates to diliver a metal carbene species **B**. Subsequently, a migratory insertion furnishes intermediate **C**. Upon protonation, the final product is produced and the catalyst is regenerated.

In conclusion, we developed a $Cp^*Co(III)$-catalyzed C–H coupling reaction with α-diazomalonates for the direct alkylation of (hetero)arenes under the assistance of pyrazoyl or pyrimidyl directing group. The reaction proceeded under relatively mild and operationally simple reaction conditions. Good functional group tolerance, satisfactory yields, and excellent regioselectivity were found.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.05.025.

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