DOI: 10.1002/adsc.201700097

Advanced Synthesis & Catalysis

Mild Cobalt(III)-Catalyzed C–H Hydroarylation of Conjugated C=C/C=O Bonds

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Received: January 24, 2017; Revised: March 7, 2017; Published online: ■■ ■■, 0000

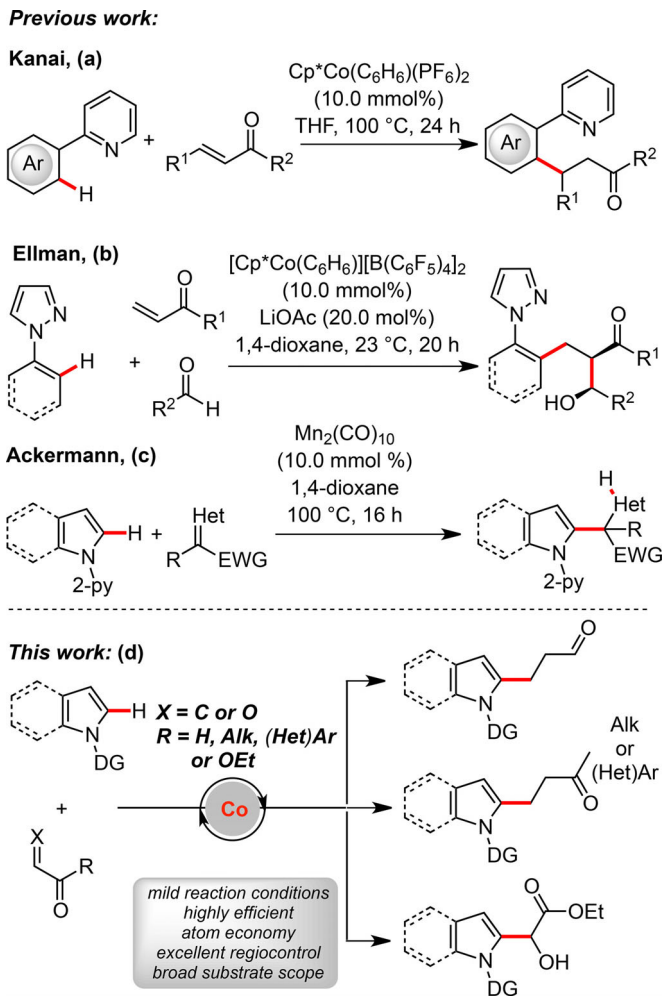
Supporting information for this article is available under http://dx.doi.org/10.1002/adsc.201700097.

Abstract: An efficient cobalt(III)-catalyzed C-2-selective indole C–H hydroarylation of acrolein, enones, and glyoxylates was achieved under mild reaction conditions. The versatile cobalt(III) catalyst displayed excellent positional selectivity with the assistance of pyrimidinyl, pyridyl, and pyrazolyl directing groups, thus overcoming the inherent C-3 selectivity of an electrophilic indole derivatization. This approach provides an expedient route to indolyl-substituted aldehydes, ketones, and esters with wide functional group tolerance. In addition, it also features high step- and atom-economy.

Keywords: C–H functionalization; cobalt(III) catalysis; hydroarylation; indoles; positional selectivity

Introduction

Indoles are among the most pharmaceutically useful heterocycles, as found in diverse biologically active compounds. Therefore, the synthesis of indole derivatives has attracted considerable recent attention.[1] Generally, the C-3 position of indole is the favored site for electrophilic substitution, while various C-3 decorated indoles can be successfully constructed by simple applications of the Friedel–Crafts reaction.[2] Hence, the C-2 C–H functionalized product was delivered only when the C-3 position is unavailable, except for sporadic examples.[3] Since transition metal-catalyzed C–H functionalization has become a powerful tool for organic synthesis in recent decades, site selectivity is predictable by the introduction of heteroatom-containing directing groups.[4] In this process, many research efforts have led to remarkable progress for transition metal-catalyzed C-2 selective C–H functionalization on indoles with the assistance of N-directing groups.[5] Remarkably, regioselective C–H functionalization at the C-7 position of indoles was first proved to be feasible by Hartwig.[6] Further advances were recently achieved by Ma,[7] Shi[8] and Chang[9] with the introduction of appropriate directing groups. Various functionalizations on the *ortho*- and *meta*-positions around the N-atom of the indole core were realized through C–H activation. Despite these major advances, transition metal-catalyzed selective C-2 C–H hydroarylation of electron-deficient olefins/aldehydes still remained challenging. The catalytic additions of inert C–H bonds to these α,β-unsaturated acceptors have recently experienced increasing attention.[10] While most of the achievements were restricted to the use of expensive 4d transition metal catalysts, a significant breakthrough was achieved using high-valent cobalt complexes as the appropriate catalysts, as reported by Kanai and co-workers,[11] and further major advances were accomplished in the recent past.[12] However, among a number of analogous Cp*Co(III) complexes, only [Cp*Co(benzene)]$(PF_6)_2$ displayed high efficacy for the addition of 2-arylpyridines onto multiple bonds in α,β-unsaturated enones and imines (Scheme 1a).[11a] Very recently, a remark-



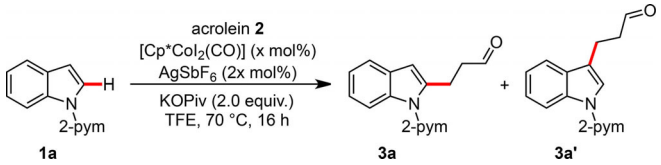
Scheme 1. Cobalt(III)/manganese(I)-catalyzed C–H hydroarylation of polar π-electrophiles (2-py = 2-pyridyl).

able two-step sequence consisting of cobalt(III)-catalyzed C–H hydroarylation of α,β-unsaturated enones and subsequent diastereoselective addition of the cobalt enolate to aldehydes was developed, as was reported by Ellman (Scheme 1b).[13] However, the substrate scope of the reaction needs to be further extended. For example, some important polar electrophiles, such as α,β-unsaturated aldehydes and glyoxylates, could not be employed in these processes; only rare examples of their hydroarylation have been accomplished by rhodium(III)[10a,14] and manganese(I)[15] catalysis *via* C–H functionalization (Scheme 1c). Based on our previous studies on direct C–H hydroarylation of polar π-electrophiles by ruthenium(II)[16] and rhodium(III)[17] catalysis, we herein report on a mild cobalt(III)-catalyzed C-2 selective C–H alkylation of indoles with C=C/C=O multiple bonds to deliver indole substituted aldehydes, ketones, and esters in an atom-economical mode (Scheme 1d).[18]

Results and Discussion

Our initial investigation focused on the cobalt(III)-catalyzed C-2 selective C–H hydroarylation of acrolein for the synthesis of β-indolylpropanal **3a** (Table 1). We were pleased to observe that the desired product **3a** was isolated in 84% yield when employing combinations of 5.0 mol% of $Cp^*CoI_2(CO)$, 10.0 mol% of $AgSbF_6$ and stoichiometric of KOPiv (Table 1, entry 1). Reducing the loading of KOPiv resulted in significantly reduced yield of the desired product **3a** (entry 2). In contrast, different catalyst loadings exerted a minor influence (entries 3 and 4). This allowed

Table 1. Optimization of the cobalt(III)-catalyzed C–H hydroarylation of acrolein **2**.[a]



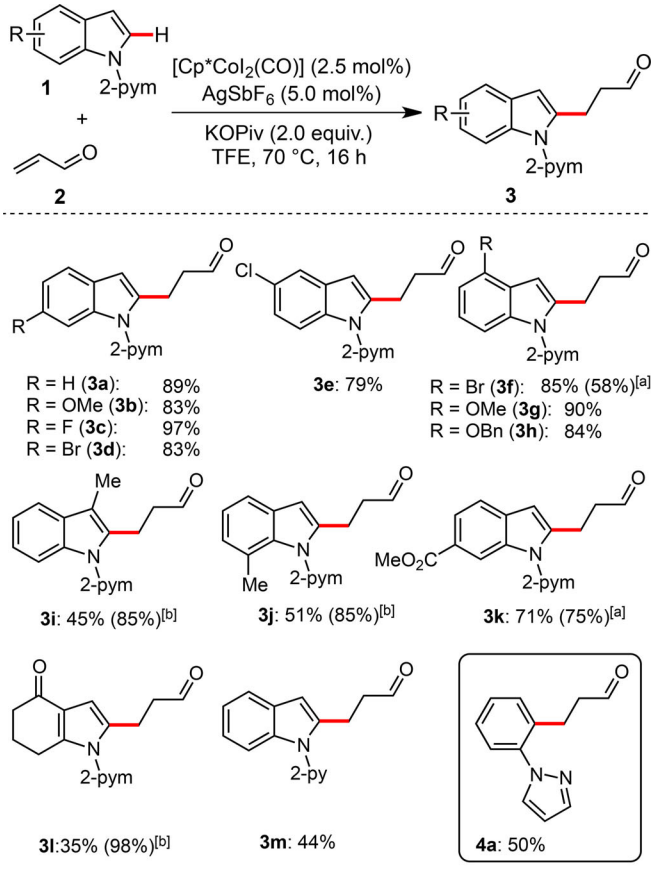
Entry	[Co] (mol%)	Additive	Base	Yield [%][b]
1	$Cp^*CoI_2(CO)$ (5.0)	$AgSbF_6$	KOPiv	84
2	$Cp^*CoI_2(CO)$ (5.0)	$AgSbF_6$	KOPiv	70[c]
3	**$Cp^*CoI_2(CO)$ (2.5)**	**$AgSbF_6$**	**KOPiv**	**89**
4	$Cp^*CoI_2(CO)$ (10.0)	$AgSbF_6$	KOPiv	91
5	$Cp^*CoI_2(CO)$ (1.0)	$AgSbF_6$	KOPiv	64
6	$Cp^*CoI_2(CO)$ (2.5)	–	KOPiv	81
7	–	$AgSbF_6$	KOPiv	0
8	$Cp^*CoI_2(CO)$ (2.5)	$AgSbF_6$	–	0 (40)[d]
9	–	$AgSbF_6$	–	0

[a] *General reaction conditions:* **1a** (0.25 mmol), **2** (0.45 mmol), $[Cp^*CoI_2(CO)]$ (2.5 mol%), $AgSbF_6$ (5.0 mol%), KOPiv (0.5 mmol, 2.0 equiv.), TFE (1.0 mL), under argon, 70 °C, 16 h.
[b] Isolated yield of **3a**.
[c] KOPiv (0.25 mmol, 1.0 equiv.).
[d] Isolated yield of **3a'** (TFE = trifluoroethanol; 2-pym = pyrimidin-2-yl).

for efficient catalysis to occur at a catalyst loading as low as 1.0 mol%, delivering **3a** in 64% yield, which highlighted again the outstanding efficacy of Cp*CoI_2(CO). To our surprise, the reaction occurred well in the absence of silver(I) sources (entry 6), while the opposite result was observed when the cobalt complex was omitted in the reaction (entry 7). Importantly, only C-3 substituted product **3a′** was obtained when the reaction was run without the assistance of carboxylate, which highlighted again the inherent property of indole and the importance of carboxylate assistance for the selective C–H functionalization (entries 8 and 9).[19]

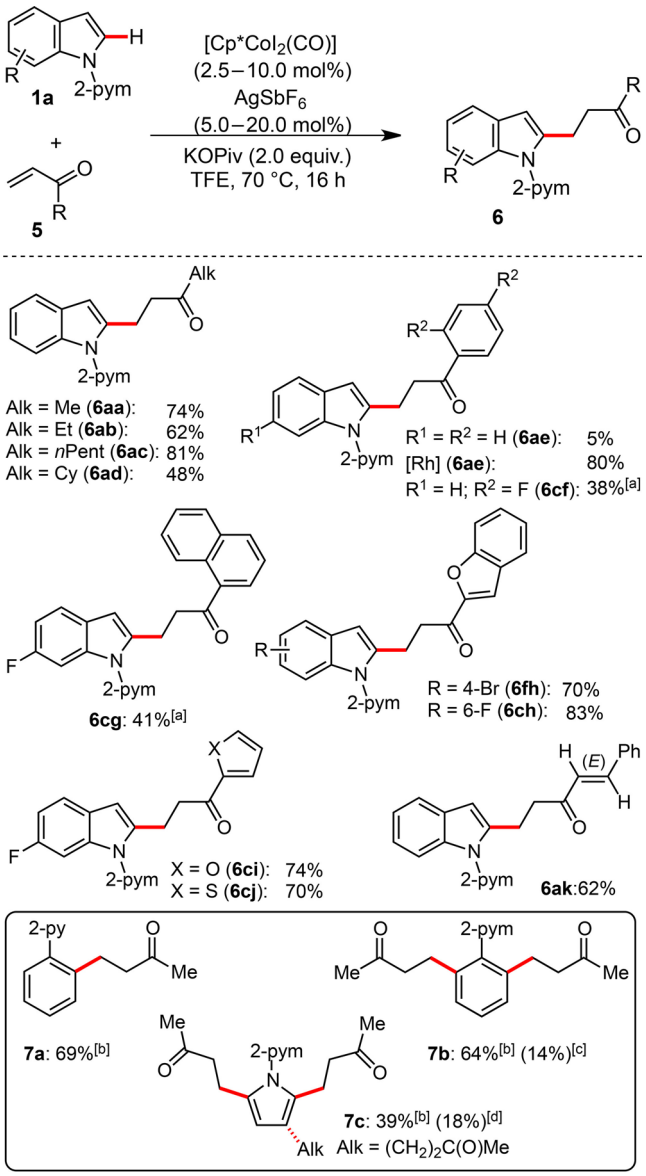
With the optimized reaction conditions in hand, a variety of indoles was investigated for direct C–H hydroarylation of acrolein **2** (Scheme 2). Different functional groups substituted on the C-3, C-4, C-5, C-6 or C-7 positions were well tolerated by our cobalt(III) catalysis, delivering the C-2 selective alkylated products in high yields (**3a**–**3l**). Beyond that, the electronic nature and steric hindrance of the substituent displayed a very minor influence on the reactivity. It is worth noting that the *N*-pyridylindole **1m** gave the decorated propanal **3m** in rather modest yield, as did the 1-phenyl-1*H*-pyrazole.

The efficient cobalt(III) catalyst was subsequently tested in the C-2 selective hydroarylation of α,β-unsaturated ketones **5** (Scheme 3), aliphatic enones gave the β-indolyl ketones **6aa**–**6ad** in moderate to good yields under the standard reaction conditions. However, the reactivity of aryl vinyl ketones showed a significant deterioration under the optimized reaction conditions, thus delivering the oxa-Michael adducts with TFE as the main products. In contrast, a rhodium(III)



[a] Without $AgSbF_6$.
[b] [Cp*CoI_2(CO)] (10.0 mol%), AgSbF6 (20.0 mol%); (py = pyridine).

Scheme 2. Cobalt(III)-catalyzed C–H hydroarylation of acrolein **2**.

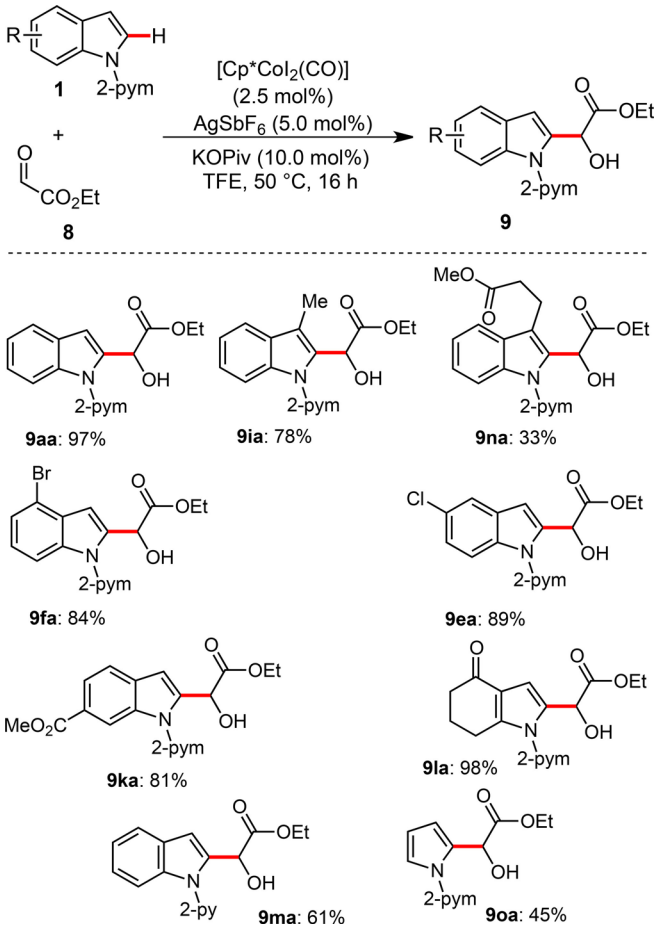


[a] 1.0 equiv. of $BF_3{\cdot}OEt_2$ was used.
[b] 2.0 equiv. of KOPiv were replaced by 10.0^^mol% of $Cu(OAc)_2$.
[c] Yield for mono-alkylated product.
[d] Yield for tri-alkylated product. (py = pyridine).

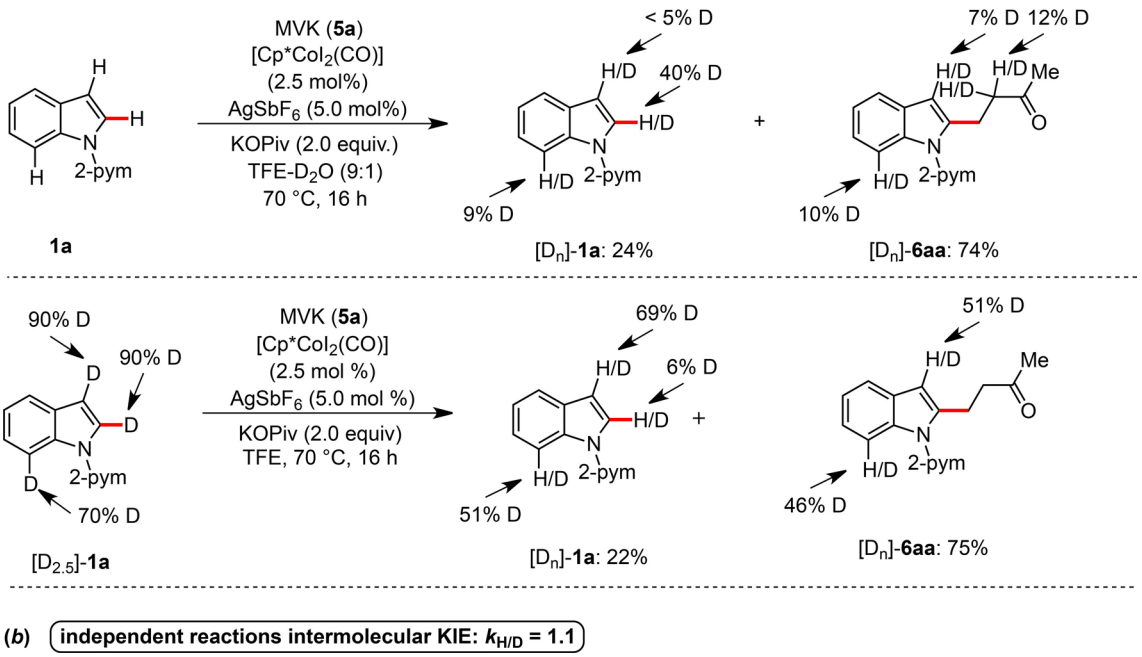
Scheme 3. Cobalt(III)-catalyzed C–H hydroarylation of α,β-unsaturated ketones **5**.

catalyst furnished the corresponding hydroarylated product **6ae** with high efficacy. The aryl vinyl ketones of **5f** and **5g** yielded the desired products in moderate yields when a stoichimetric amount of $BF_3{\cdot}OEt_2$ was used as the additive. To our delight, various heteroaryl vinyl ketones, such as benzofuran, furan and thiophene, demonstrated favorable reactivities for C–H hydroarylation. It is worth noting that the conjugated alkene **5k** was also successfully employed as the Michael acceptor, exclusively generating the *E*-olefin **6ak** as the product. In addition, the cobalt(III) catalyst was further proved to be appropriate to arenes **7a**–**7c**. Interestingly, the dialkylated product was mainly obtained with the assistance of pyrimidine, as compared to pyridine. Intriguingly, pyrrole also delivered a trialkylated product **7c′**, which was not expected, albeit the yield was as low as 18%.

Moreover, we next explored the cobalt(III) catalyst for the C–H hydroarylation of C=O bonds. Very recently, Ackermann and co-workers developed a manganese(I)-catalyzed C–H hydroarylation of C=Het bonds, thus highlighting its unique position selectivity on indoles.[15] Our studies demonstrated that 2.5 mol% of $Cp^*CoI_2(CO)$, along with catalytic amounts of $AgSbF_6$ and KOPiv enabled the efficient C-2 selective C–H addition to glyoxylate **8** under mild reaction conditions (Scheme 4). Various functional groups, such as bromo, chloro, ester, and ketone substituents, were well tolerated by our cobalt(III) catalyst. Notably, a more sterically hindered methyl or propionate group at the C-3 position of indole also



Scheme 4. Cobalt(III)-catalyzed C–H hydroarylation of glyoxylate **8**.



Scheme 5. Mechanistic studies.

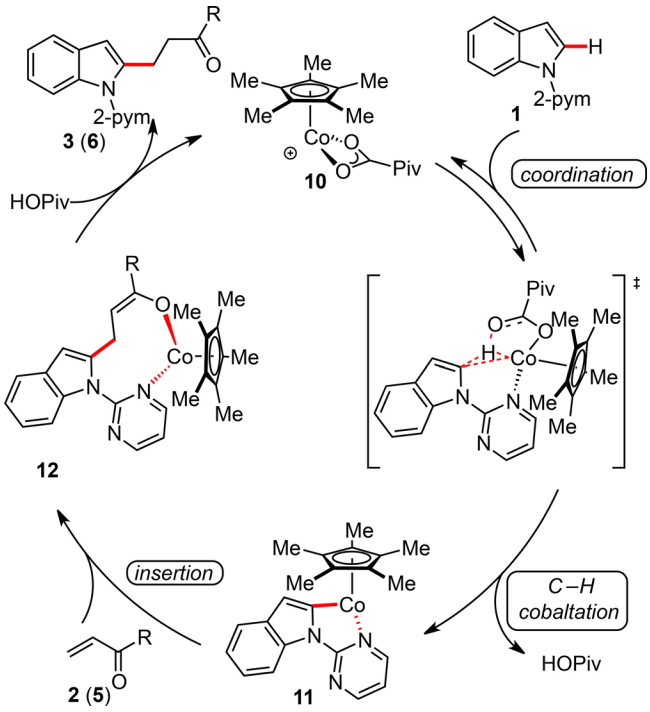
underwent the C–H hydroarylation process, albeit the product **9na** was delivered in a rather modest yield, as was also observed when employing pyrrole as the substrate. However, the C–H additions with trifluoroacetaldehyde and trifluoropyruvate exclusively occurred on the C-3 position of indole in low yields (see the Supporting Information).

In order to unravel the mode of action of the reaction, we performed the cobalt(III)-catalyzed C–H bond functionalization with **2a** in the presence of D_2O as the co-solvent. Obvious evidence of H/D scrambling on both the reisolated starting material [D_n]-**1a** and desired product [D_n]-**6aa** was observed, which illustrates that the cobalt(III)-catalyzed C–H cobaltation step is reversible, as was proved again when employing [$D_{2.5}$]-**1a** as the starting material (Scheme 5a). Furthermore, a minor kinetic isotope effects of $k_{H/D}$ = 1.1 was found, which demonstrates that the C–H bond cobaltation is not the rate-determining step (Scheme 5b).

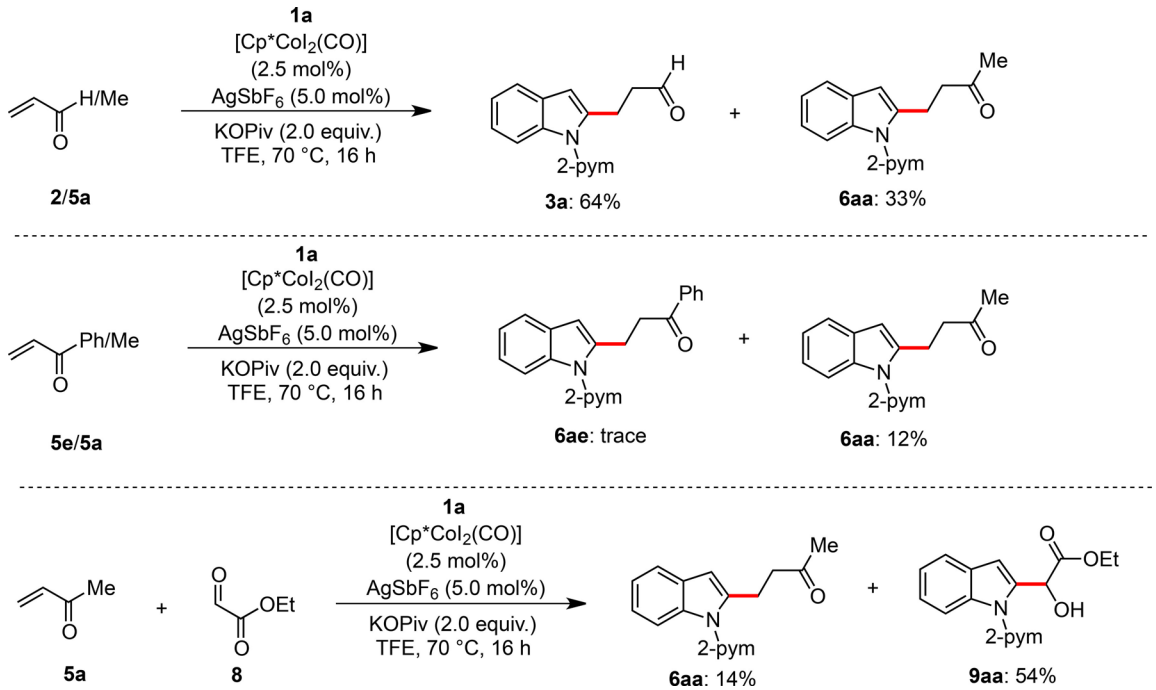
Thereafter, we became interested in disclosing the reactivity of different α,β-unsaturated carbonyl compounds and glyoxylate for their direct C–H alkylation with **1a** (Scheme 6). The results of a set of intermolecular competition experiments revealed that acrolein **2** and glyoxylate **8** are more reactive than aliphatic enones, while the aryl vinyl ketones are inherently less reactive.

Based on our experimental findings and previous mechanistic explorations,[20] we propose that the formation of key intermediate **11** through cobalt(III)-catalyzed C–H activation can be rationalized in terms of a concerted metalation deprotonation (CMD), migratory insertion of conjugated alkenes, and subsequent proto-demetalation sequence to generate the alkylated products (Scheme 7).

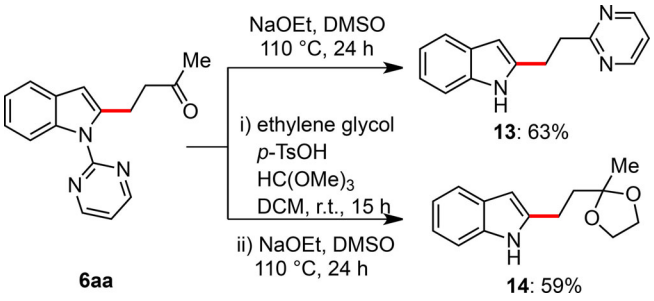
Finally, we tried to illustrate the synthetic potential of the protocol by removing the *N*-pyrimidyl substitu-



Scheme 7. Catalytic cycle for the C–H hydroarylation.



Scheme 6. Competition experiments between **2**, **5** and **8**.



Scheme 8. Removal of the directing group.

ent (Scheme 8). According to the previous protocol,[21] only the product **13** was obtained when **6aa** was treated with NaOEt (4.0 equiv.) in DMSO, Li proposed a formal 1,4-shift mechanism for this process.[18a] Thereafter, we devised a two-step reaction sequence, which led to the β-indolyl ketal **14** in good yield.[10l]

Conclusions

In conclusion, we have developed a highly C-2 selective C–H alkylation of indoles with conjugated alkenes and aldehydes under cobalt(III) catalysis. Since acrolein and enones have been recognized as effective electrophiles and widely utilized in Diels–Alder reactions, as well as Michael addition reactions, this present work highlights their reactivities for catalytic C(sp^2)–H addition, thus providing an expedient route to β-indolyl aldehydes and ketones. Beyond that, the mild cobalt(III)-catalyzed C–H hydroarylation of glyoxylate could deliver indolyl acetates with high efficacy. Detailed mechanistic studies revealed the priority of different conjugated C=C/C=O bonds and suggested that the C–H cobaltation is not the rate-determining step.

Experimental Section

Typical Procedure A for Direct C–H Hydroarylation of Acrolein

A suspension of indole **1** (0.50 mmol, 1.00 equiv.), acrolein **2** (1.0 mmol, 2.00 equiv.), [Cp*CoI_2(CO)] (6.0 mg, 2.5 mol%), $AgSbF_6$ (8.6 mg, 5.0 mol%), and KOPiv (70.0 mg, 2.0 equiv.) in anhydrous TFE (2.0 mL) was stirred at 70 °C for 16 h under an atmosphere of argon. At ambient temperature, the solvent was evaporated under vacuum and the remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) to afford product **3a** as a slightly yellow solid; yield: 112 mg (89%); mp 86–87 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.84 (t, J = 1.3 Hz, 1H), 8.77 (d, J = 4.8 Hz, 2H), 8.32 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 7.2 Hz, 1H), 7.27–7.16 (m, 2H), 7.14 (t, J = 4.8 Hz, 1H), 6.47–6.46 (m, 1H), 3.50 (t, J = 7.3 Hz, 2H), 2.90 (td, J = 7.6, 1.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 201.7, 158.2, 139.9, 137.0, 129.2, 123.0, 122.1, 119.9, 117.1, 114.3, 106.5, 43.6, 22.5; IR (ATR): ν = 2716, 1709, 1558, 1435, 744 cm^{-1}; HR-MS (ESI): m/z = 252.1131 [M+H$^+$], calcd. for $C_{15}H_{14}N_3O$ [M+H$^+$]: 252.1131

Typical Procedure B for Direct C–H Hydroarylation of α,β-Unsaturated Ketones

A suspension of indole **1** (0.50 mmol, 1.00 equiv.), methyl vinyl ketone **5a** (1.0 mmol, 2.00 equiv.), [Cp*CoI_2(CO)] (6.0 mg, 2.5 mol%), $AgSbF_6$ (8.6 mg, 5.0 mol%), and KOPiv (70.0 mg, 2.0 equiv.) in anhydrous TFE (2.0 mL) was stirred at 70 °C for 16 h under an atmosphere of argon. At ambient temperature, the solvent was evaporated under vacuum and the remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) to afford product **6aa** as a colorless solid; yield: 98 mg (74%); mp 66–68 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.78 (d, J = 4.8 Hz, 2H), 8.29 (d, J = 8.1 Hz, 1H), 7.52 (d, J = 7.2 Hz, 1H), 7.25–7.20 (m, 1H), 7.20–7.16 (m, 1H), 7.14 (t, J = 4.8 Hz, 1H), 6.45 (s, 1H), 3.47–3.39 (m, 2H), 2.95–2.84 (m, 2H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 207.9, 158.2, 158.2, 140.6, 137.0, 129.2, 122.8, 122.0, 119.8, 117.1, 114.2, 106.1, 43.5, 30.0, 23.8; IR (ATR): ν = 2919, 1716, 1559, 1419, 1247, 744 cm^{-1}; HR-MS (ESI): m/z = 266.1284 [M+H$^+$], calcd. for $C_{16}H_{16}N_3O$ [M+H$^+$]: 266.1288.

Typical Procedure C for Direct C–H Hydroarylation of Glyoxylate

A suspension of indole **1** (0.50 mmol, 1.00 equiv,), glyoxylate **8** (1.0 mmol, 2.00 equiv,), [Cp*CoI_2(CO)] (6.0 mg, 2.5 mol%), $AgSbF_6$ (8.6 mg, 5.0 mol%), and KOPiv (7.0 mg, 10.0 mol%) in anhydrous TFE (2.0 mL) was stirred at 50 °C for 16 h under an atmosphere of argon. At ambient temperature, the solvent was evaporated under vacuum and the remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 3:2) to afford product **9aa** as a yellow solid; yield: 144 mg (97%); mp 113–115 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.71 (d, J = 4.9 Hz, 2H), 8.59 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.38–7.30 (m, 1H), 7.29–7.20 (m, 1H), 7.11 (t, J = 4.9 Hz, 1H), 6.80 (s, 1H), 5.86 (d, J = 10.3 Hz, 1H), 5.51 (d, J = 10.3 Hz, 1H), 4.12–3.93 (m, 2H), 0.97 (t, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.7, 158.1, 157.4, 137.1, 137.0, 128.9, 124.6, 122.7, 121.0, 116.7, 115.7, 111.9, 69.2, 61.4, 14.0; IR (ATR): ν = 2995, 1740, 1578, 1429, 1247, 1063, 670 cm^{-1}; HR-MS (ESI): m/z = 347.1119 [M+H$^+$], calcd. for $C_{16}H_{16}N_3O_3$ [M+H$^+$]: 347.1121.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Grant No. 21602083), National Natural Science Foundation of Jiangsu Province (Grant No. BK20160160), and the Fundamental Research Funds for the Central Universities (JUSRP51703A).

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Mild Cobalt(III)-Catalyzed C–H Hydroarylation of Conjugated C=C/C=O Bonds

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