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CF_3-Carbenoid functionalization of *N*-(pyrimidin-2-yl)indole catalyzed by cobalt complexes: ligand control of selectivity

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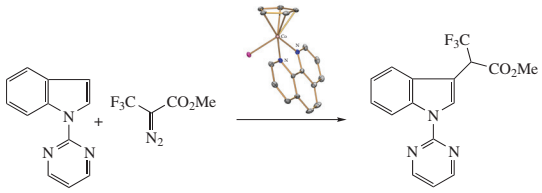
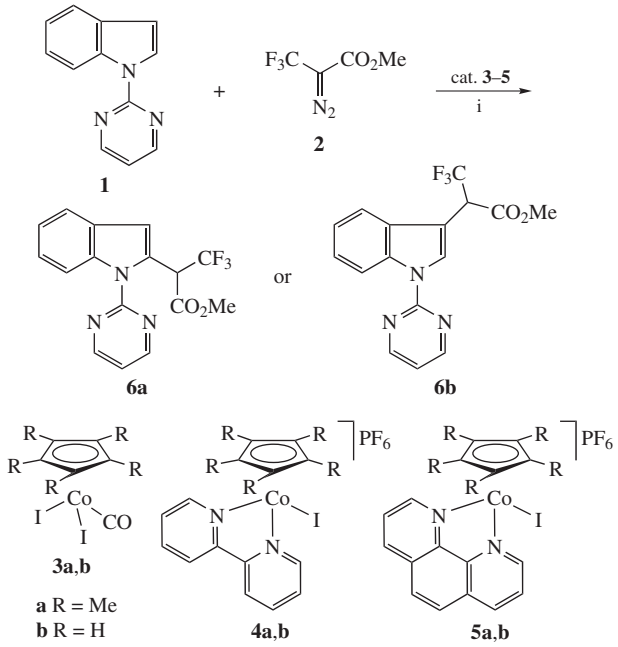
The carbonyl cobalt complex Cp*Co(CO)I_2 catalyzes carbenoid alkylation of *N*-(pyrimidin-2-yl)indole with methyl 3,3,3-trifluoro-2-diazopropionate regioselectively giving 2-substituted indole, while the N,N′-ligated cations [CpCo(L)I]$^+$ (L = bipy, phen) provide 3-substitution exclusively. The structure of [CpCo(phen)I]PF_6 was investigated by X-ray diffraction.



The direct catalytic approaches to C–H functionalization of indoles have attracted much attention of chemists due to their atom- and step-economy, which compares favourably to traditional organic synthesis.[1] In particular, diazo compounds (including methyl 3,3,3-trifluoro-2-diazopropionate) proved to be effective reagents for the carbenoid alkylation of indoles.[2] The selectivity strongly depends on the presence of directing group at the nitrogen atom as well as the type of catalytic system. For example, in the absence of directing group, copper, iron and rhodium salts catalyze electrophilic carbene insertion selectively giving 3-substituted indole derivatives in accordance with the highest C–H nucleophilic nature of this site.[3] At the same time, Yu with co-workers showed that the usage of the ruthenium complex [(*p*-cymene)$RuCl_2]_2$ as a catalyst leads to only 2-substituted indoles.[4] The factors to favor the 2-substitution in this case are unclear yet. In contrast, the presence of directing group (*e.g.* pyrimidinyl) at the nitrogen atom of indoles drives the reaction through the chelation-assistance mechanism[5] affording 2-substitution products. The cyclopentadienyl rhodium and iridium complexes [Cp*$MCl_2]_2$ proved to be most effective catalysts for this reaction pathway.[6] Recently, Wang with co-workers have developed alkylation of *N*-(pyrimidin-2-yl)indoles with methyl diazomalonate using the readily available cobalt complex Cp*Co(CO)I_2.[7] In continuation of our interest in the development of new practical methods for the selective incorporation of CF_3 groups into bioactive compounds,[8] we herein disclose novel catalytic systems based on the cobalt complexes for the 2- and 3-functionalization of *N*-(pyrimidin-2-yl)indole **1** using methyl 3,3,3-trifluoro-2-diazopropionate **2** as a cross-coupling partner (Scheme 1).



Scheme 1 *Reagents and conditions:* i, [Co] (5 mol%), $AgSbF_6$ (10 mol%), $ClCH_2CH_2Cl$, 100 °C.

To estimate the influence of catalyst structure on the catalytic activity and selectivity, we tested (cyclopentadienyl)cobalt complexes (both pentamethylated and unsubstituted) with weakly (*e.g.,* CO) and strongly (*e.g.,* 2,2′-bipyridyl and 1,10-phenanthroline) bonded auxiliary ligands. Complexes $(C_5R_5)Co(CO)I_2$ **3a**,**b**, $[(C_5R_5)Co(bipy)I]PF_6$ **4a**,**b** and [Cp*Co(phen)I]PF_6 **5a** were synthesized by known procedures.[9] Complex [CpCo(phen)I]PF_6 **5b** was prepared in good yield by King's method[9(a)] with the usage of the improved counterion-exchange operation.†

† *Synthesis of complex* **5b**. Benzene (5 ml) was added to a mixture of complex $CpCo(CO)I_2$ (114 mg, 0.28 mmol) and 1,10-phenanthroline (99 mg, 0.55 mmol), and the mixture was stirred overnight. The precipitate of [CpCo(phen)I]I was filtered off, washed with diethyl ether, and dried *in vacuo*. This substance was washed with small amount of water and extracted with methanol. Then an excess of an aqueous KPF_6 solution was added to the obtained solution. The dark violet precipitate that formed was filtered off, washed with water, and dried *in vacuo*. Reprecipitation from acetone with light petroleum gave complex [CpCo(phen)I]PF_6 **5b** (90 mg, 56%) as a dark violet solid. ^{1}H NMR (acetone-d_6) δ: 10.37 (d, 2H, H_{phen}, *J* 5.2 Hz), 8.92 (d, 2H, H_{phen}, *J* 8.4 Hz,), 8.27 (s, 2H, H_{phen}), 8.23 (dd, 2H, H_{phen}), 6.30 (s, 5H, H_{Cp}). Found (%): C, 38.10; H, 3.05; N, 4.84. Calc. for $C_{17}H_{13}N_2CoF_6IP \cdot 0.5\,C_6H_{14}$ (%): C, 38.79; H, 3.26; N, 4.53.

Table 1 Catalyst screening in the model carbenoid alkylation reaction[a] between compounds **1** and **2**.

Entry	Catalyst	*t*/h	Yield of **6a**[b] (%)	Yield of **6b**[b] (%)
1	Cp*Co(CO)I_2 (**3a**)	8	51	–
2	Cp*Co(CO)I_2 (**3a**)	24	66 (58)	–
3	CpCo(CO)I_2 (**3b**)	8	–	3
4	[Cp*Co(bipy)I]PF_6 (**4a**)	8	–	–
5	[Cp*Co(phen)I]PF_6 (**5a**)	8	–	–
6	[CpCo(bipy)I]PF_6 (**4b**)	8	–	49
7	[CpCo(bipy)I]PF_6 (**4b**)	24	–	85 (80)
8	[CpCo(phen)I]PF_6 (**5b**)	24	–	76 (69)

[a] *Reagents and conditions:* **1** (29 mg, 0.15 mmol), **2** (0.028 ml, 0.16 mmol), catalyst (5 mol%), $AgSbF_6$ (5 mg, 10 mol%), dichloroethane (2 ml), 100 °C. [b] Yield is calculated from ^{19}F NMR spectrum of the reaction mixture. Value in parentheses indicates yield after purification.

The structure of complex **5b** was determined by X-ray diffraction (Figure 1).‡ The symmetry-independent part of the unit cell contains two formula units. The unit cell contains solvate hexane molecule, which has been treated as a diffuse contribution to the overall scattering without specific atom positions by SQUEEZE/PLATON.[10] The structure of cation of salt **5b** is very close to that of the bipyridyl derivative **4b**.[9(c)] For example, the Co···Cp distances of 1.675 and 1.672 Å as well as the Co–N bonds of 1.948 and 1.955 Å for **4b** and **5b**, respectively, are very similar. At the same time, the angle N(1)–Co(1)–N(2) in **5b** (av. 83.5°) is somewhat larger than that in **4b** (82.5°), which is caused by longer distance N(1)···N(2) in **5b** (2.605 Å) *vs.* **4b** (2.567 Å) due to more restricted structural flexibility of phenanthroline as compared with bipyridyl ligand.

To test catalytic activity and selectivity of the cobalt complexes, we employed the model reaction of indole **1** with diazo compound **2** (see Scheme 1, Table 1). Silver hexafluoroantimonate was used as an additive necessary for abstraction of iodide-anions. It was found that pentamethylcyclopentadienyl complex **3a** expectedly catalyzes the reaction giving the 2-substituted indole **6a** in 51% yield (see Table 1, entry 1). The yield becomes somewhat higher with the increase of the reaction time from 8 to 24 h (entry 2).§ Probably, the reaction proceeds under chelation-assistance of pyrimidinyl group similar to carbenoid alkylation with methyl diazomalonate.[7] To the best of our knowledge, diazo compound **2** is the second example (after methyl diazomalonate) of a cross-coupling partner for the cobalt-assisted carbenoid alkylation. Previous attempts to use other diazo compounds (*e.g.,* keto ester diazo compounds) were unsuccessful. Surprisingly, the cobalt complex with the unsubstituted Cp ligand **3b** gives only trace amount of the 3-substituted indole **6b** under the same conditions (entry 3). The absence of product **6a** in this case can be due to the low stability of the CpCo species, which were proposed as the catalytic intermediates.[11,12]

Next, we found that introduction of N,N′-ligands (2,2′-bipyridyl and 1,10-phenanthroline) to the CpCo moiety leads to considerable increase in stability of catalytic intermediates and hence the yield of **6b** (see Table 1, entries 6–8). The best conversion of the starting materials was achieved using the bipyridyl derivative **4b** as a catalyst (entry 7).¶ The selectivity for the 3-substitution can be explained by only one accessible coordination site at the Co atom in these complexes because the Cp and N,N′-ligands are strongly bonded ligands. Therefore, we consider that the reaction catalyzed by complexes **4b** and **5b** proceeds *via* cobalt-assisted

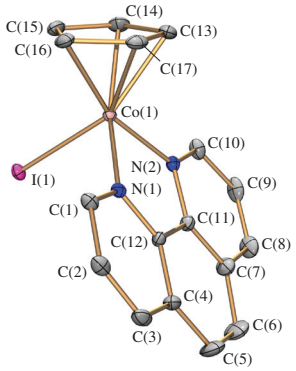
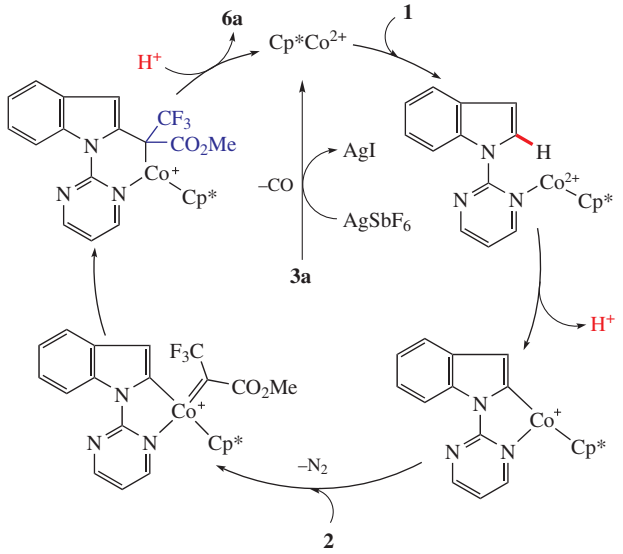


Figure 1 Cation of salt **5b** with atoms shown as thermal ellipsoids at 50% probability level (one of two independent molecules). Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) for the first/second symmetry-independent species: Co(1)–N(1) 1.957(2)/1.955(2), Co(1)–N(2) 1.959(2)/1.949(2), Co(1)–C(13) 2.054(2)/2.067(2), Co(1)–C(14) 2.062(2)/2.060(3), Co(1)–C(15) 2.083(2)/2.064(3), Co(1)–C(16) 2.057(2)/2.037(3), Co(1)–C(17) 2.059(2)/2.060(2), Co(1)–I(1) 2.5894(3)/2.5786(3); selected bond angles (°) N(1)–Co(1)–N(2) 83.31(8)/83.77(8).



Scheme 2 Chelate-assisted pathway (three vacant coordination sites).

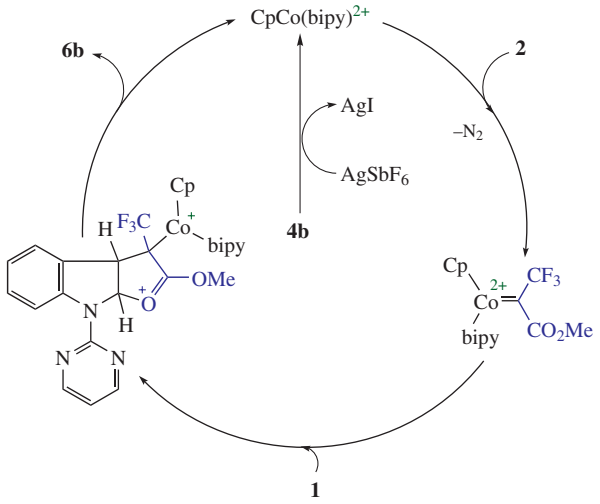
‡ Crystals of **5b** were grown up by slow diffusion in two-layer system, light petroleum and a solution of the complex in dichloromethane.

Crystal data: $C_{17}H_{13}CoF_6IN_2P$, triclinic, space group $P\bar{1}$, a = 6.7192(4), b = 13.7893(7) and c = 22.2064(12) Å, α = 74.7660(10)°, β = 82.8470(10)°, γ = 86.9130(10)°, V = 1969.26(19) Å^3, Z = 4, d_{calc} = 1.943 g cm^{-3}, μ = = 2.580 mm^{-1}, $F(000)$ = 1112, R_1 = 0.0290 [from 11129 unique reflections with $I > 2\sigma(I)$] and wR_2 = 0.0787 (from all 12302 unique reflections).

CCDC 1819723 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

§ *Methyl 3,3,3-trifluoro-2-[1-(pyrimidin-2-yl)indol-2-yl]propionate* **6a**. Dichloroethane (2 ml) was added to a mixture of **1** (29 mg, 0.15 mmol), **2** (0.028 ml, 0.16 mmol), **3a** (3.6 mg, 0.0075 mmol), and $AgSbF_6$ (5 mg, 0.015 mmol). The reaction mixture was stirred under heating (100 °C, in oil bath) for 24 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (light petroleum–ethyl acetate, 7 : 1) to afford product **6a** in 58% yield (29 mg). ^1H NMR ($CDCl_3$) δ: 8.77 (d, 2H, H_{Ar}, J 4.8 Hz), 8.43 (d, 1H, H_{Ar}, J 8.4 Hz), 7.62 (d, 1H, H_{Ar}, J 7.6 Hz), 7.33 (t, 1H, H_{Ar}, J 7.4 Hz), 7.25 (t, 1H, H_{Ar}, J 7.4 Hz), 7.17 (t, 1H, H_{Ar}, J 4.8 Hz), 6.99 (s, 1H, H_{Ar}), 6.14 (q, 1H, CH, J 8.4 Hz), 3.76 (s, 3H, OMe) [*cf.* ref 6(*b*)]. ^{19}F NMR ($CDCl_3$) δ: –66.16.

¶ *Methyl 3,3,3-trifluoro-2-[1-(pyrimidin-2-yl)indol-3-yl]propionate* **6b**. The procedure analogous to that described for synthesis of **6a** was used with **4b** (4.7 mg, 0.0075 mmol) as a catalyst and light petroleum–ethyl acetate (20 : 1) as an eluent for chromatography to give **6b** (40 mg, 80%). ^1H NMR ($CDCl_3$) δ: 8.83 (d, 1H, H_{Ar}, J 8.4 Hz), 8.68 (d, 2H, H_{Ar}, J 4.8 Hz), 8.51 (s, 1H, H_{Ar}), 7.65 (d, 1H, H_{Ar}, J 8.0 Hz), 7.39 (t, 1H, H_{Ar}, J 7.6 Hz), 7.31 (t, 1H, H_{Ar}, J 7.6 Hz), 7.05 (t, 1H, H_{Ar}, J 4.8 Hz), 4.71 (q, 1H, CH, J 8.0 Hz), 3.80 (s, 3H, OMe) [*cf.* ref. 6(*b*)]. ^{19}F NMR ($CDCl_3$) δ: –67.54.



Scheme 3 Cobalt-assisted carbenoid pathway (one vacant coordination site).

carbenoid mechanism similar to the copper catalysis.[3] Interestingly, nothing of products **6a** or **6b** was obtained when the pentamethylated derivatives **4a** and **5a** were used (entries 4 and 5), which can be caused by sterically hindered methyl groups hampering the formation of cobalt-carbenoid intermediates.

In summary, we have developed catalytic systems based on the cobalt complexes for the regioselective CF_3-carbenoid functionalization of *N*-(pyrimidin-2-yl)indole at the 2- or 3-position. Introduction of strongly bonded N,N′-ligands to the cobalt atom leads to switch of the reaction mechanism from chelation-assisted to the simple cobalt-assisted carbenoid insertion as a result of blocking vacant coordination sites at the cobalt atom (Schemes 2 and 3). The cobalt complexes with N,N′-ligands **4b** and **5b** were used for the C–H activation for the first time.

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