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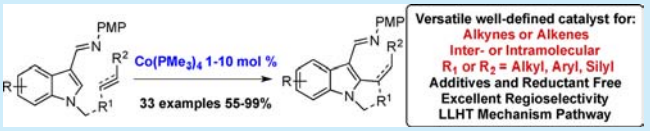
C2-Alkylation and Alkenylation of Indoles Catalyzed by a Low-Valent Cobalt Complex in the Absence of Reductant

Brendan J. Fallon, Etienne Derat, Muriel Amatore, Corinne Aubert, Fabrice Chemla, Franck Ferreira, Alejandro Perez-Luna, and Marc Petit*

UPMC UNIV Paris 06, Institut Parisien de Chimie Moléculaire, UMR CNRS 8232, Case 229, 4 Place Jussieu, 75252 Paris Cedex 05, France

Supporting Information

ABSTRACT: Herein an extremely versatile, well-defined, low-valent cobalt catalyst $[Co(PMe_3)_4]$ capable of intermolecular and intramolecular imine-directed C2-alkylation and alkenylation of indoles is reported. The reaction proceeds in the absence of reducing agents or additives, affording a range of substituted indoles and dihydropyrroloindoles in high yields and regioselectivities. With the aid of deuterium labeling studies and DFT (Density Functional Theory) calculations, a mechanism is proposed that is based on a Ligand-to-Ligand Hydrogen Transfer pathway.

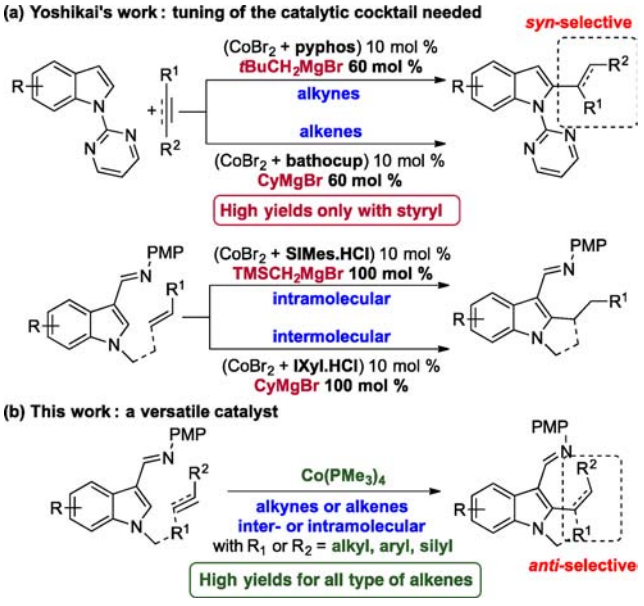


Transition-metal-catalyzed functionalization of aromatic C−H bonds has been the subject of intense research efforts over the past few decades due to the straightforward and step-economical nature of this approach.[1] Until recently, the majority of C−H functionalization was achieved using precious second and third row transition metal catalysts. In recent years, however, there has been a clear drive from the chemistry community to develop cheaper and more abundant catalysts based on first row transition metals.[2] Given the correlative reactivity of rhodium[3] with its group 9 analogue cobalt and the relative cost and abundancy of the latter, it is not surprising that cobalt catalysis has seen a surge of activity during the past decade.[4] Yoshikai and co-workers have been at the forefront of this development specifically in the area of low-valent bimetallic systems consisting of a cobalt salt, ligand, stoichiometric reductant, and in some cases additives such as pyridine.[5]

Despite these significant advancements made in low-valent cobalt-catalyzed C−H functionalization, the use of bimetallic combinations as catalytic systems suffers certain limitations: the omnipresent Grignard reagent whose exact role remains unclear, an ill-defined active catalytic species, and the need for screening of optimal reaction conditions (ligands, Grignard reagent, etc.) for a given reaction (Scheme 1a). In addition substrate scope and mechanistic studies are often hampered by the complex reaction mixture. To address some of these pertinent issues, and based on pioneering work,[6] our group recently reported a series of C−H functionalization reactions using a well-defined low-valent cobalt complex $[Co(PMe_3)_4]$ in the absence of a reductant.[7,8] We report herein on our development of a cobalt-catalyzed intermolecular and intramolecular C2-alkylation and alkenylation of indoles (Scheme 1b).

The present study is notable for a number of reasons: (i) the catalytic system is compatible with internal alkynes, vinyl arenes, vinyl silanes, and for the first time simple alkenes which was not the case in previous reports under cobalt catalysis; (ii) no reductant or additives are necessary; (iii) both intermolecular and intramolecular variants are possible; and (iv) no optimization of catalyst or reaction conditions was necessary from our previous studies.

Scheme 1. C−H Functionalization of Indoles



Indoles and indeed fused tricyclic indoles represent a privileged framework present in many pharmaceutical and natural products.[9] Consequently having efficient and selective reactions to synthesize and modify these structures is desirable. Having previously demonstrated the ability of $[Co(PMe_3)_4]$ to carry out

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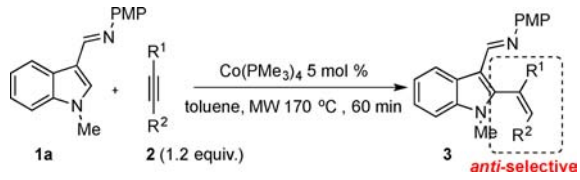
the hydroarylation of alkynes with aryl ketimines we began the present study with indole **1a** and diphenylacetylene **2a** (Table 1).

Table 1. C2-Alkenylation of Indole 1a with Alkynes[a]



entry	R^1	R^2	2	yield[b]	E/Z[c]
1	Ph	Ph	**2a**	**3aa** 99% (86%)[d]	1/99
2	Ph	TMS	**2b**	**3ab** 92%	10/90
3	Ph	n-C_4H_9	**2c**	**3ac** 65%[e]	12/88
4	3-Pyr	TMS	**2d**	**3ad** 99%	1/99
5	n-C_3H_7	n-C_3H_7	**2e**	**3ae** 99%	29/71
6	n-C_4H_9	n-C_4H_9	**2f**	**3af** 82%	28/72

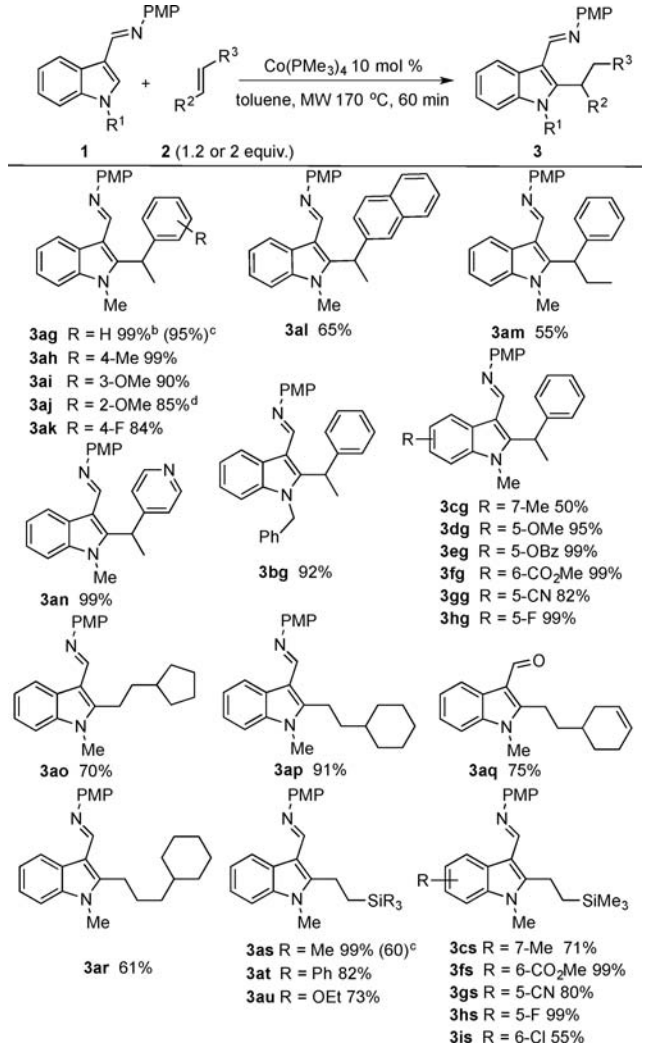
[a]Reaction performed on 0.5 mmol scale. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]yield using $HCo(PMe_3)_4$ as catalyst. [e]Product isolated as the corresponding aldehyde.

Product **3aa** was isolated in quantitative yield with complete *anti*-selectivity in line with our previous work and in contrast to the *syn*-selective system previously reported.[5a] The reaction of TMS-protected phenylacetylene also took place regioselectively, with the new C−C bond being formed at the position distal to the silyl group **3ab**.[10] The product **3ac** from 1-phenyl-1-hexyne addition was isolated in moderate yield and good stereoselectivity. The inclusion of alkynes bearing heteroatoms was also feasible with adduct **3ad** obtained in excellent yield and with complete regio- and stereoselectivity. To conclude the present scope on the alkenylation of internal alkynes, oct-4-yne and dec-5-yne were shown to participate smoothly albeit with lower stereoselectivity (Table 1, entries 5 and 6). Note that reaction with pyrimidylindole performed poorly using this catalytic system.

We then turned our attention to the C2-alkylation of indoles. To this end, we initially screened a variety of substituted styrenes (Scheme 2). The reaction showed good generality affording the desired products **3ag**−**3al** in excellent yields. In all cases the branched isomer was obtained exclusively with the exception of **3aj** presumably due to the steric impingement of the methoxy group in the 2-position.[11] The reaction could also be performed on gram scale without any noticeable decrease in yield for product **3ag**, while using $HCo(PMe_3)_4$ as catalyst the yield was marginally lower than that for $Co(PMe_3)_4$. *trans*-β-Methylstyrene was also converted to the desired product **3am** in moderate yield.[12] The present system showed excellent tolerance to the inclusion of *N*-heteroatoms with product **3an** isolated in quantitative yield. An indole substrate bearing a *N*-benzyl protecting group reacted smoothly to afford the adduct **3bg**. The addition of styrene to indoles substituted in the 5−7 positions yielded the desired alkylated products **3cg**−**3hg** in good to excellent yields. In addition a chemically susceptible ester group provided no issues with adduct **3fg** isolated in quantitative yields.

Next we explored the addition of simple vinyl and allyl alkenes that often have a very low or no reactivity in C−H alkylation reactions.[5e] Various C2-substituted indoles **3ao**−**3ar** were isolated in good to excellent yields with complete selectivity for the linear regioisomer. Finally for the present scope we explored a variety of vinyl silanes which proved to be amenable to the addition reaction with products **3as**−**3au** isolated in excellent yields and exclusively as the linear regioisomers. Of particular note

Scheme 2. Scope of C2-Alkylation with Various Olefins[a]



[a]Reaction was performed on a 0.5 mmol scale. [b]Reaction performed on gram scale without a decrease in isolated yield. [c]Yield using $HCo(PMe_3)_4$ as catalyst. [d]Product isolated as a mixture of branched vs linear in a ratio of 76/24.

is product **3au** because triethoxysilane is intrinsically prone to polymerization (via the sol−gel process) and not compatible with previously reported hydroarylation reactions in the presence of Grignard derivatives.[5e] As previously shown for styrene the reaction of various indole derivatives with vinyltrimethylsilane yielded the desired alkylated products **3cs**−**3is** in high yields.

As a natural extension of this work we became curious about the possibility of applying the current methodology to the synthesis of fused tricyclic indoles with dihydropyrroloindole skeletons. It seemed feasible that an indole bearing a *N*-homoallylic tether would cyclize to give the desired product through selective C−H activation at the C2-position.[5b] To this end indole **4a** was subjected to the reaction conditions described in Scheme 3 which afforded the five-membered cyclization product **5a** as the sole regioisomer in quantitative yield. Notably, the reaction temperature and catalytic loading could be significantly lowered compared to the intermolecular variant. Also worthy of mention is that no modulation of the catalyst $[Co(PMe_3)_4]$ was necessary, a feature not observed under the cobalt ternary catalytic system reported. The use of a ketimine directing group was also possible

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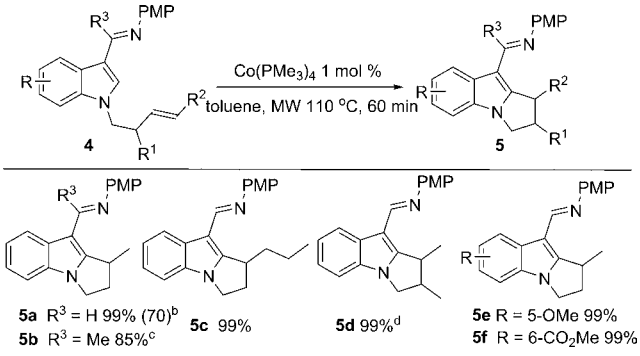
Scheme 3. Cyclization of Indoles Bearing Tethered Alkenes[a]



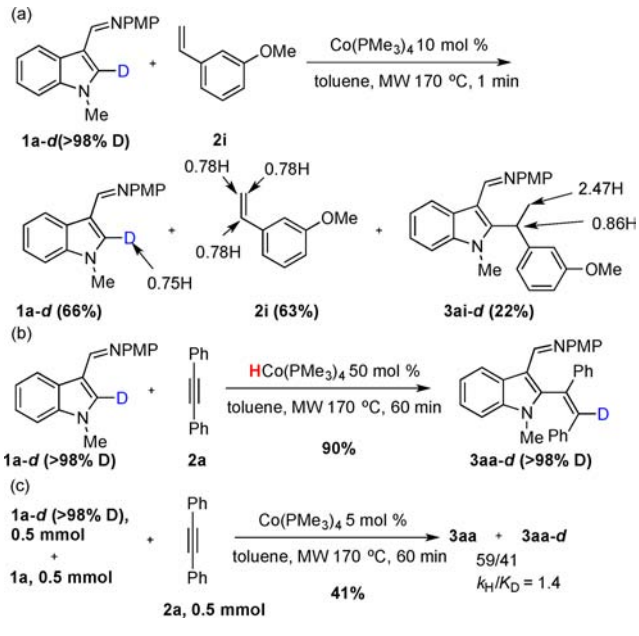
[a]Reaction was performed on 0.5 mmol scale. [b]Yield using HCo(PMe$_3$)$_4$ as catalyst. [c]Product isolated as the corresponding ketone. [d]Product isolated as 86/14 mixture of *trans*/*cis* diastereoisomers.

allowing the formation of product **5b** in good yield. Indole **4c**, bearing a substituted homoallylic terminal position, cyclized to give the five-membered tricycle **5c** as the sole product. Interestingly under our reaction conditions, substrate **4d** bearing a methyl substituent in the allylic position gave the dihydropyrroloindole **5d** in high diasteroselectivity while the same substrate gave exclusively the six-membered ring using Yoshikai's conditions.[5b]

This result strongly confirms the important role of the ligand in the regioselectivity of the final product. Indoles presenting electron-donating (OMe) and electron-withdrawing (CO_2Me) groups **4e** and **4f** respectively were also amenable with the current cyclization reaction. In line with earlier reports with cobalt and in contrast to rhodium catalysis *N*-allylindole derivatives did not cyclize to the corresponding five-membered ring products. This result suggests that ring formation takes places directly through a 5-*exo*-type cyclization.

To probe the reaction mechanism, we initially carried out a series of experiments using deuterium-labeled imine **1a-*d***. The reaction of **1a-*d*** with 3-methoxystyrene **2i** (Scheme 4a) was quenched after 1 min, affording the hydroarylation product **3ai-*d*** in 22% yield along with recovery of both starting materials **1a-*d*** 66% and **2i** 63%. The deuterium content at the C2-position of **1a-*d*** was significantly reduced (by 75%), and a similar degree of deuterium incorporation was observed in the recovered alkene **2i** (≈ 66%). Consistent with these observations we observed deuterium incorporation into both the methyl group and the methine moiety of **3ai-*d***. These results suggest the initial steps are reversible through a putative β-H elimination.[5d] To gain further insight into the mechanism, **1a-*d*** was reacted with diphenylacetylene **2a** in the presence of 50 mol % HCo(PMe$_3$)$_4$ to afford **3aa-*d*** with a deuterium transfer up to 99% (Scheme 4b). This observation was consistent with our previous study on the hydroarylation of aryl ketimines with alkynes and was strongly suggestive that the C−H bond activation proceeded in a concerted manner also termed Ligand-to-Ligand Hydrogen Transfer (LLHT).[7,13] Finally, a competition experiment between **1a-*d*** and **1a** in the presence of **2a** was ran to determine the KIE (Scheme 4c), and a value of 1.4 was obtained. This value suggests that cleavage of the C−H bond is not turnover-limiting.[14] Rather, this value is consistent with reversible cleavage of the C−H bond before an irreversible step.

Scheme 4. Deuterium Labelling Experiments



To complete the mechanistic study, (Density Functional Theory) calculations at the B3LYP-D3/def2-SV(P) level were undertaken. Results are summarized in Figure 1. The barriers for C−H activation of indole **1a** with diphenylacetylene and styrene were found to be respectively 12.46 and 8.02 kcal/mol. These values are consistent with a C−H activation which is not the rate-determining step. Analyzing the electronic structure of the transition state reveals that the unpaired electron remains on cobalt and that the activation occurs through an LLHT mechanism, similar to that previously found.[7,8,13]

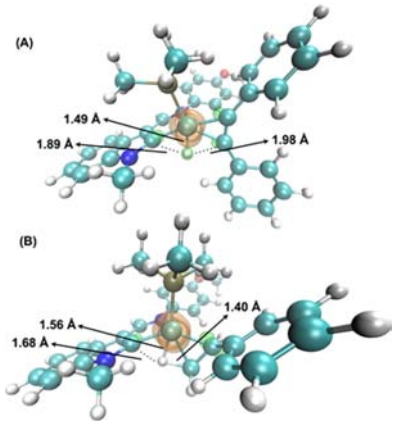


Figure 1. DFT-calculated TS structures for the C−H activation, respectively with (A) diphenylacetylene and (B) styrene. The spin density isosurface is also shown (orange: alpha spin density; green: beta spin density).

Based on the results from the deuterium-labeling experiments and DFT calculations, we can propose a common catalytic cycle for both alkenylation and alkylation (Scheme 5). This cycle consists of a concerted C−H activation/hydrogen transfer to generate an intermediate (**II**). The H/D scrambling observed during the reaction of **1a-*d*** with **2i** suggests that this initial step is reversible. Intermediate **II** would then undergo a reductive elimination resulting in the formation of intermediate **III**. The *anti*-selectivity observed in the hydroarylation of alkynes can be explained by isomerization of the double bond.

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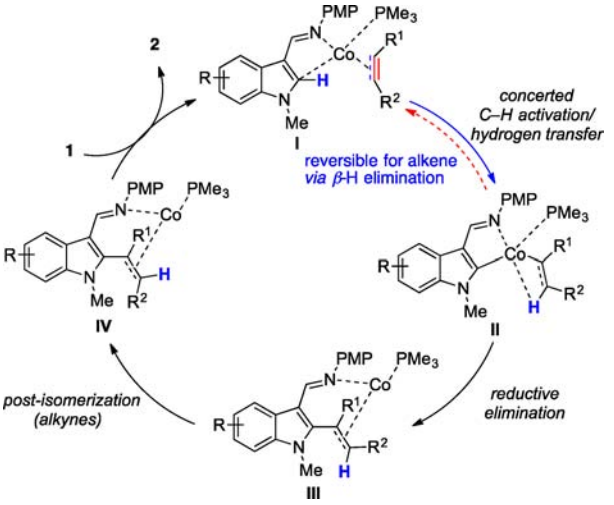
Scheme 5. Proposed Catalytic Cycle



In summary, we disclose the use of a well-defined low-valent cobalt complex for the functionalization of indoles in the absence of an external reductant or additives. The versatility of this catalyst allows performance of the imine-directed C2-alkenylation and alkylation of indoles with a large family of alkenes (bearing styryl, silyl, and alkyl groups) without any tuning of the catalytic system for the first time. Deuterium labeling studies and DFT calculations confirm that $[Co(PMe_3)_4]$ operates through an LLHT mechanism for the hydroarylation of both alkenes and alkynes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00939.

Experimental procedures and physical properties of compounds. (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: marc.petit@upmc.fr.

Notes

The authors declare no competing financial interest.

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