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C-Alkylation of Various Carbonucleophiles with Secondary Alcohols Under Co^{III}-Catalysis

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KEYWORDS C-Alkylation, Secondary Alcohol, Dehydrogenation, Cobalt, Borrowing Hydrogen Catalysis.

ABSTRACT: Oxindoles have been successfully α -alkylated under Cp*Co^{III} catalysis by a vast array of secondary alcohols, including cyclic, acyclic, symmetrical, and unsymmetrical, to produce C-alkylated oxindoles. This protocol was also extended to the α -alkylation of N,N-dimethyl barbituric acid and benzyl cyanides. The kinetic profile and other preliminary mechanistic investigations suggest a first order reaction rate in oxindole and catalyst. A plausible catalytic cycle is proposed on the basis of the kinetic profile, of other preliminary mechanistic investigations and of previous mechanistic studies on similar transformations, while DFT calculations provide insight into the nature of the active species.

Key chemical transformations by making use of fundamental feedstocks towards the expansion of new sustainable approaches is being highly explored in contemporary science.¹ Heterocyclic scaffolds are quite prevalent in natural products, pharmaceuticals, and other biologically active compounds.² Therefore, the development of protocols for their selective alkylation is of particular interest. For example, carbo-nucleophilic motifs such as oxindoles,³ benzyl cyanides⁴ and barbituric acids⁵ are prominent features in the core structure of various alkaloids or pharmaceutically relevant drugs (Figure 1a). Researchers across the World involved in drug discovery programs have started to validate the importance of these special scaffolds in numerous low-molecular-weight bioactive molecules and to identify and design novel chemical libraries against new biological targets.⁶ Conventional methods to access such rare secondary alkylated structures require the use of toxic reagents (alkyl or alkylaryl halides along with strong bases such as NaH, LiHMDS etc.) which obviously generates a considerable amount of waste.⁷ In addition, low-reactivity and poor selectivity of traditional approach, due to the competing N-alkylation reaction is a cause of concern.⁸ Of late, traditional alkylation using alkyl halides tend to be replaced by the metal-catalyzed borrowing hydrogen methodology,⁹ by directly employing biomass derived oxidized hydrocarbons such as alcohols as alkylating agent, thereby producing only water as the sole side product. In this process the alcohol undergoes a temporary dehydrogenation with the help of a transition metal catalyst to form a reactive carbonyl intermediate, which can then undergo a nucleophilic addition to an *in-situ* generated carbonucleophile to form an unsaturated intermediate. Finally, the hydrogen that was borrowed is returned by the metal to form the hydrogenated product. However, the currently known reactions catalyzed by transition-metals for such C-alkylation of carbonucleophiles are largely limited to primary alcohols as coupling partner, leaving room for further developments.¹⁰ Alkylation of various carbo-/heteronucleophiles with secondary alcohols is limited and mostly restricted to noble transition metals.^{11,12}

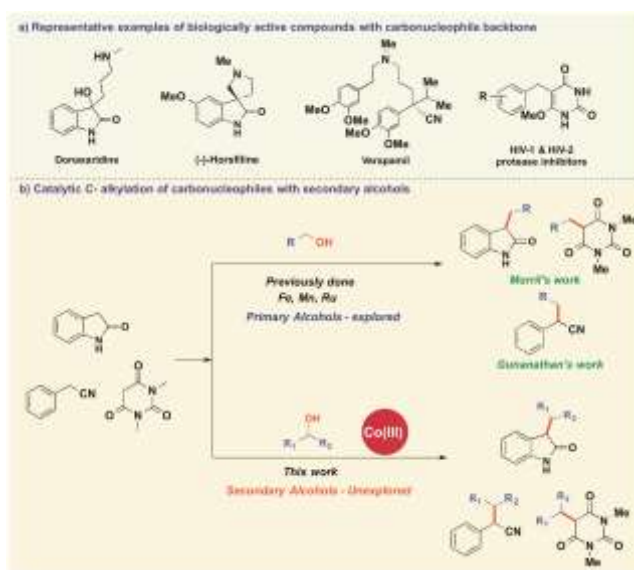
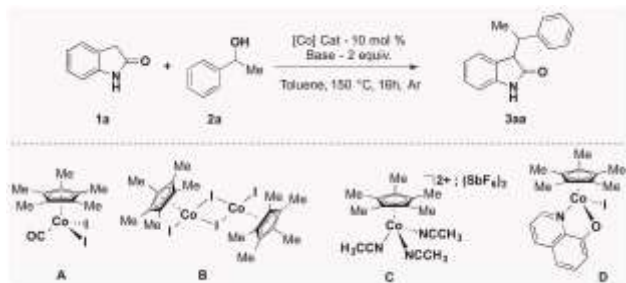


Figure 1. Overview of C-Alkylation of carbonucleophiles

Only a handful of reports demonstrated the use of 3d transition metals.¹³ In this regard, Morris and co-workers reported iron-catalyzed C-alkylation of oxindoles with a broad scope of primary alcohols, except for two examples with linear aliphatic secondary alcohol.^{13a} In our quest to design inexpensive protocols under base metal catalysis, our group earlier reported C- and N-alkylation of ketones and amines with secondary alcohols under high-valent cobalt catalysis.^{13b-13c,14} Renaud and co-workers reported the iron-catalyzed direct α -alkylation of ketones using secondary alcohols.^{13d} Leitner and co-workers reported the α -alkylation of secondary alcohols with diol for the synthesis of cycloalkanes using manganese catalyst.^{13e} Based on the Gunanathan's pioneering work for the synthesis of α -olefinated benzylnitriles with secondary alcohol,^{12c} Balaraman and co-workers reported Mn-catalyzed C-alkylation of benzyl

nitrile to α -olefinated benzylnitriles without forming any alkylation products.^{13f} Although the α -alkylation of nitriles with primary alcohols catalyzed by 3d metals is known,¹⁵ no example of nitrile for α -alkylation by secondary alcohol is documented to date with any-metals as the rehydrogenation of tetra-substituted olefins is extremely difficult.^{12c} To the best of our knowledge, efficient catalytic system based on 3d metals for the C-alkylation of carbonucleophiles (e.g. oxindole, benzyl nitriles, etc) using secondary alcohols are hitherto unknown. Herein, we report the C-alkylation of oxindoles, N,N-dimethyl barbituric acid and benzyl cyanides with a broad scope of benzylic, linear and cyclic aliphatic secondary alcohols using air- and moisture stable Cp*Co^{III} precatalysts (Figure 1b).

Table 1. Optimization Studies and Control Experiments^a



| Entry | [Co] cat (mol %) | Base (equiv.) | Yield (%) ^b |
|-------|-------------------|------------------------------------|------------------------|
| 1 | A (10) | KOH (2) | 77 |
| 2 | B (10) | KOH (2) | 79 |
| 3 | C (10) | KOH (2) | 31 |
| 4 | D (10) | KOH (2) | 12 |
| 5 | A (10) | K ₂ CO ₃ (2) | 88 ^c |
| 6 | A (10) | KOH (2) | 43 ^c |
| 7 | A (10) | KOH (2) | 73 ^d |
| 8 | A (5) | KOH (2) | 52 ^c |
| 9 | A (10) | KOH (1.5) | 71 ^c |
| 10 | A (10) | KOH (2) | n.r. ^e |
| 11 | A (10) | - | n.r. |
| 12 | - | KOH (2) | n.r. |

^a Standard reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), [Co] (0.002 – 0.01 mmol), KOH (0.4 mmol) in toluene (0.2 M), at 150 °C for 16 h. ^b Isolated yield. ^c Conducted at 1M concentration. ^d TFT used as solvent. ^e PCy₃ (10 mol%) was used along with **A**. n.r. = no reaction.

We began our investigations with 2-oxindole (**1a**) and 1-phenylethanol (**2a**) as model reactants and by employing 10 mol% of [Cp*Co(CO)I₂] as precatalyst in the presence of KOH as the base in toluene (0.2 M) at 150 °C for 16 hours. Delightfully, the expected C-alkylated product was isolated in 77% yield (Table 1, entry 1). Intrigued by this, screening of other Cp*Co^{III} complexes led to marginal improvement in case of complex **B** (79%, Table 1, entry 2) whereas significant reduction in the yields of **3aa** was observed in case of complexes **C&D** (31% and 12%, Table 1, entries 3 and 4). However, increasing the reaction concentration to 1M led to remarkably better results

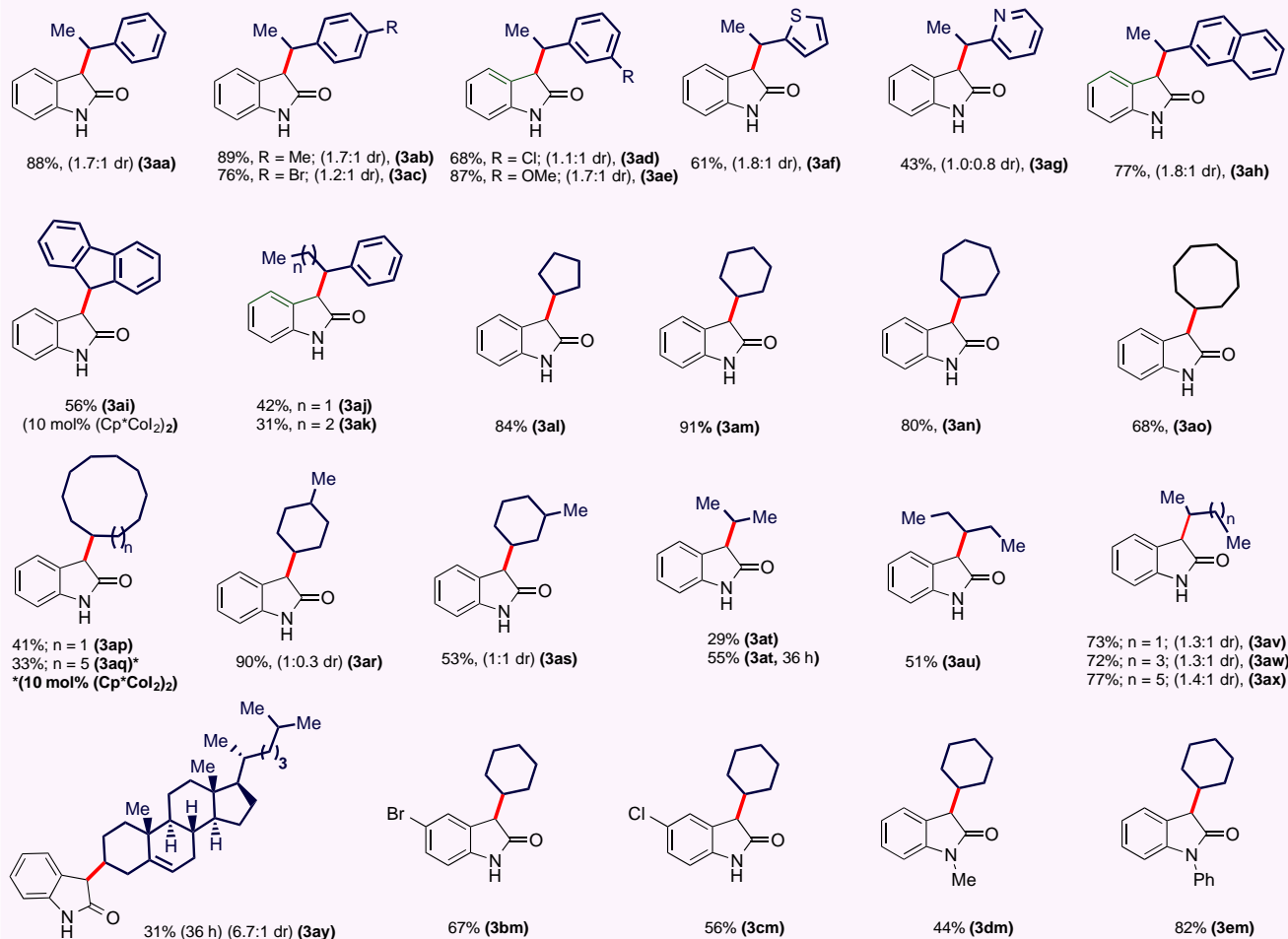
wherein product **3aa** formation improved to 88% (Table 1, entry 5). A brief screening of other bases, ligands and solvents did not improve the performance (entries 6-7, also see SI for comprehensive screening). The yield of **3aa** dropped to 52% when the catalyst loading was lowered from 10 mol% to 5 mol% (entry 8) and to 71% when the base loading was reduced to 1.5 equiv. (entry 9). Addition of a phosphine ligand (PCy₃) did not improve the yield further (entry 10). Finally, control experiments revealed that the reaction does not proceed in the absence of either the cobalt catalyst or the base (entry 11-12), indicating that both the catalyst and base are essential for the alkylation to occur.

With optimized conditions in hand, the scope of the reaction was explored as summarized in Scheme 1. A diverse range of aryl secondary alcohols with various substitutions were found to be compatible and afforded the desired C-alkylated products as diastereomer mixtures in good-to-excellent yields (Scheme 1a, **3aa-3ae**). The diastereomeric ratios were determined from ¹H NMR analyses. Heteroatom-containing aryl secondary alcohols were also effective in yielding the corresponding C-alkylated products in moderate-to-good yields (**3af-3ag**). Bulky aryl secondary alcohols such as naphthyl and fluorenyl formed the desired products in satisfactory yields (**3ah-3ai**). Next, 1-phenylpropanol and 1-phenylpentan-1-ol were employed and the expected products (**3aj-3ak**) were isolated in decent yields. Moving on, we then evaluated the tolerance of aliphatic secondary alcohols under our reaction conditions. To our extreme delight, various cyclic secondary alcohols were found to be reactive and afforded the corresponding C-alkylated products in good-to-excellent yields (**3al-3as**). Finally, the scope was further extended to unactivated linear aliphatic secondary alcohols. Gratifyingly, both symmetrical and unsymmetrical linear alcohols, including isopropyl, 3-pentyl, sec-butyl, 2-hexyl and 2-octyl, provided the desired product in good yields (**3at-3ax**). This protocol was employed in the late-stage functionalization of cholesterol and the corresponding alkylated derivative **3ay** was obtained as expected. To further verify the reaction scope, various substituted oxindoles, including N-substituted derivatives, along with cyclohexanol **2m** afforded the corresponding C-alkylated products under the optimized conditions (**3bm-3em**).

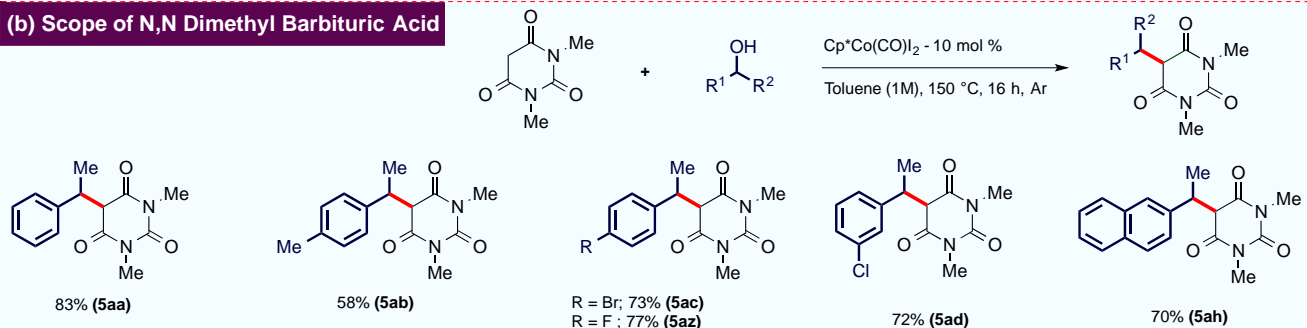
Barbituric acids comprise another class of heterocyclic compounds that exhibits a wide array of biological activities such as hypnotic, antimicrobial, antitumor and sedative properties.⁵ Since, they comprise an interesting class of carbonucleophiles, we examined the reactivity of N,N-dimethyl barbituric acid (**4**) under our standard conditions. Pleasingly, the expected products were obtained in good yields (Scheme 1b, **5aa-5ah**). This is the first report on alkylation of barbituric acids using secondary alcohols and the reaction does not require any base, unlike in the previous reaction. This is likely due to the greater acidity of barbituric acid (pK_a = 4.8) in comparison to other carbonucleophiles. We were also interested in employing benzyl cyanides as the carbonucleophile and a brief optimization (see SI) revealed that the C-alkylated product **6am** was formed in 77% yield from benzyl cyanide and cyclohexanol in the presence of 5 mol% of [Cp*Co(CO)I₂], 10 mol% of 2-(diphenylphosphino)benzoic acid as the ligand and 2 equiv. of ^tBuOK. The scope of the cyanides was extended to a few more cyclic secondary alcohols giving the products in good yields (Scheme 1c, **6am-6da**).

Scheme 1. Scope of Secondary Alcohols and Carbonucleophiles.

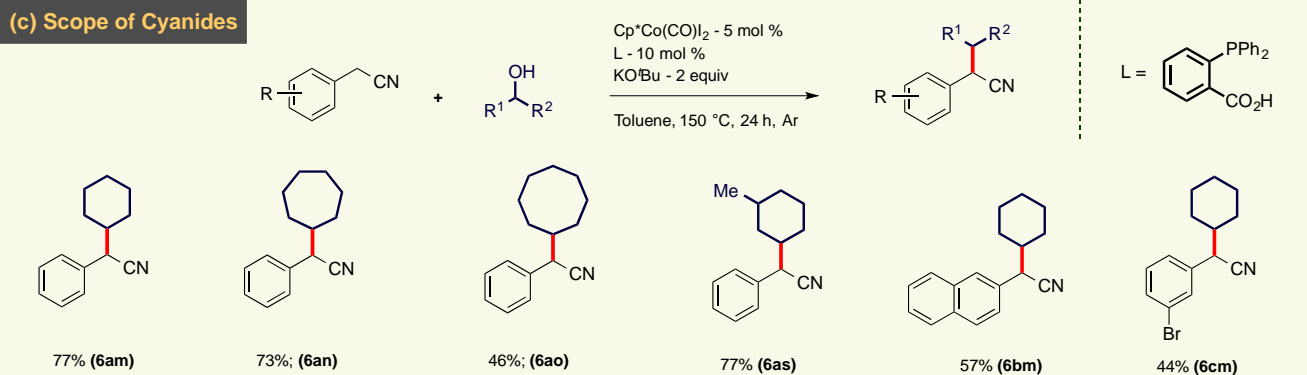
(a) Scope of Oxindoles



(b) Scope of N,N Dimethyl Barbituric Acid



(c) Scope of Cyanides



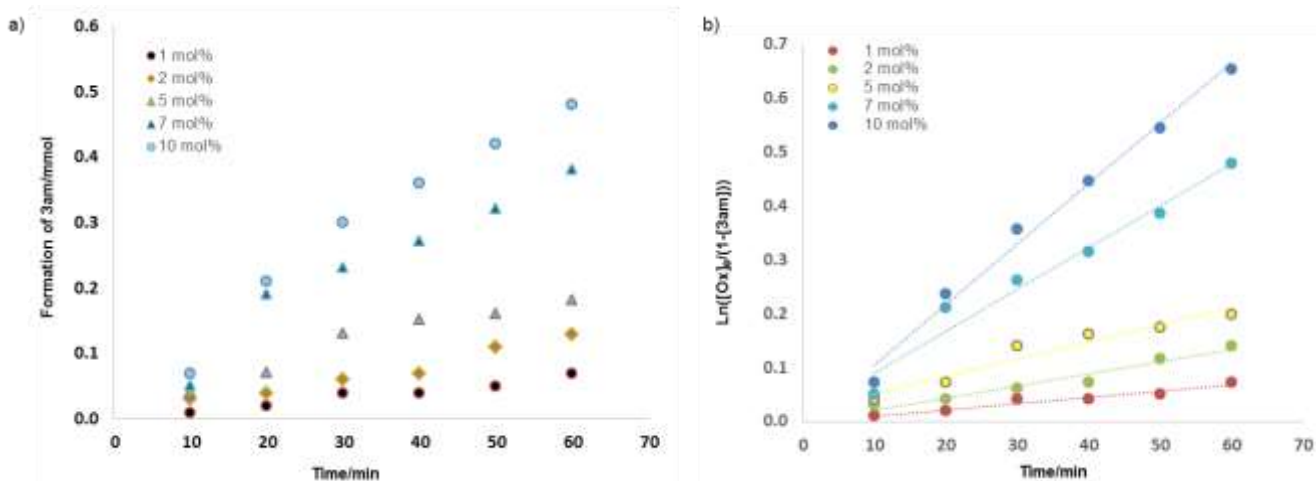
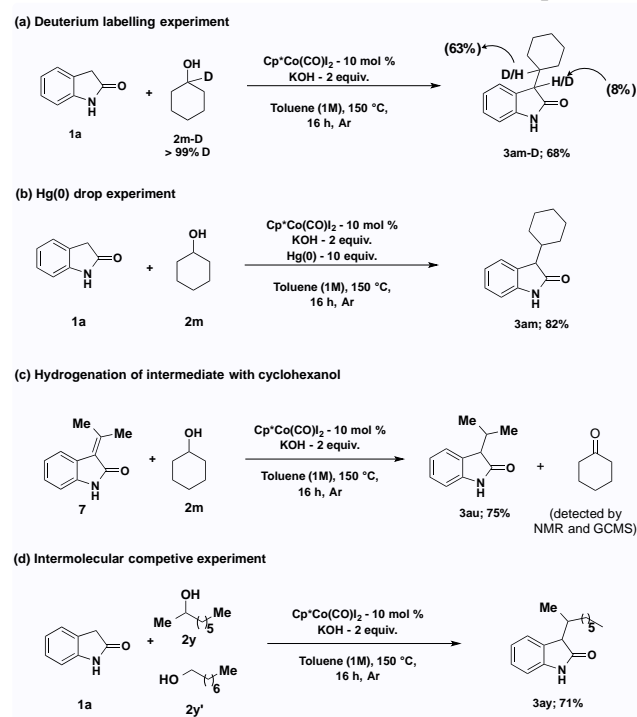


Figure 2: (a) Concentration vs. time plot for the **3am** formation in the C-alkylation of oxindole (**1a**) with cyclohexanol (**2m**) at various catalyst concentrations. (b) First-order plots of the **3am** formation at various concentrations.

However, linear and aryl secondary alcohols were found to be incompatible with our catalytic system. Although limited, this protocol is still attractive because it forms C-alkylated products directly from secondary alcohols, which are unexplored so far under any catalytic system.

To gain insights into the reaction mechanism, we monitored the reaction profile *via* ^1H NMR. The product formation data (Fig. 2a) gave a linear semilog plot, consistent with first-order dependence on the oxindole concentration (Fig. 2b, see SI for details), $v = k_{\text{obs}}[\mathbf{1a}]$. The pseudo-first order rate constant k_{obs} is obtained from the slope of this plot (0.0112 min^{-1}). The study was repeated at different catalyst concentrations, showing again linear semilog plots (Fig. 2b) and slopes that scaled linearly with the catalyst concentration (see SI for details), $k_{\text{obs}} = k[\mathbf{A}]$, indicating that the rate law also has a first-order dependence in catalyst. The rate constant (k) obtained from the best fit of the k_{obs} vs. $[\mathbf{A}]$ data is $0.111 \pm 0.001 \text{ L mol}^{-1} \text{ min}^{-1}$.

Scheme 2. Control Experiments

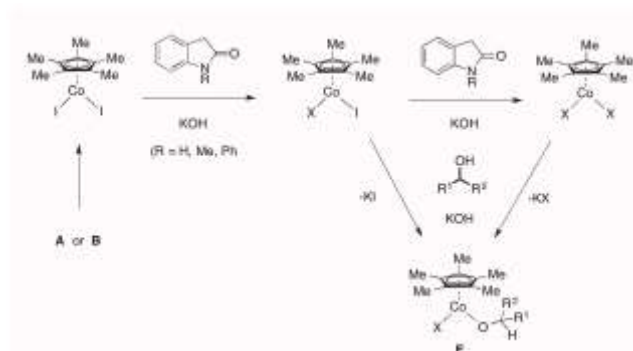


Next, we carried out various control experiments to further understand the reaction pathways as shown in Scheme 2. Deuterium labelling experiments were performed with **1a** and alcohol **2m-D** to validate the hydrogen-borrowing process. Under standard reaction conditions, the product **3am-D** formed in 68% yield and exhibited 8 and 63% deuterium incorporation at the α - and β -positions relative to the carbonyl group (Scheme 2a). Next, a mercury poisoning test where the reaction was carried out in the presence of 10 equiv. of Hg under standard conditions, which provided the alkylated product **3am** in 82% yield (91% without Hg) confirming that the system is indeed homogeneous (Scheme 2b). For further verification, intermediate **7** was prepared and a reaction was carried out under standard conditions using cyclohexanol as the hydride source. This yielded the product **3au** in 75% yield indicating that the final hydrogenation of the tetra substituted olefin is achieved with hydrogen originated from alcohol (Scheme 2c). We then performed an intramolecular competitive experiment by employing both 1-octanol (**2y'**) and 2-octanol (**2y**). Under standard reaction conditions selective alkylated product **3ay** was isolated, confirming that our catalytic system is selective for alkylation with secondary alcohols over primary alcohols (Scheme 2d). The reason for this selectivity appears to be associated to the decreased thermodynamic cost of the hydrogen borrowing step for secondary alcohol relative to primary ones.

In previous $\text{Cp}^*\text{Co}^{\text{III}}$ -catalyzed hydrogen borrowing chemistry,^{13b-13c} it was established that thermal CO loss from $[\text{Cp}^*\text{CoI}_2(\text{CO})] \mathbf{A}$, or bridge rupture from $[\text{Cp}^*\text{CoI}_2]_2 \mathbf{B}$, generate the 16-electron $[\text{Cp}^*\text{CoI}]$ complex (the two precatalysts have the same activity). Then, alcohol (ROH) deprotonation by the strong base and ligand exchange yields $[\text{Cp}^*\text{CoI}(\text{OR})]$, from which ketone is produced by β -H elimination. In the present case, however, the oxindole substrate is more acidic than the alcohol, raising questions about its possible implication as a ligand (Scheme 3), forming a new precatalyst $[\text{Cp}^*\text{CoIX}]$ or $[\text{Cp}^*\text{CoX}_2]$, where X is the deprotonated oxindole. When R = H, deprotonation may occur either at the N atom or at the C atom, whereas only the latter is possible for the N-substituted oxindoles, in which case the resulting anion is an enolate capable of bonding to the metal via either the C or the O atom. Subsequently, further exchange of the residual I ligand from $[\text{Cp}^*\text{CoIX}]$, or of an X ligand from $[\text{Cp}^*\text{CoX}_2]$, introduces the deprotonated alcohol to afford the alkoxide complex **E**, which may initiate the hydrogen borrowing chemistry. Preliminary

DFT calculations have explored the possible nature of these species. Since electron pairing energies may be considerable, particularly in high oxidation state complexes of the first row metals, the 16-electron Cp^*CoXI complex may adopt either a singlet or a triplet ground state.¹⁶ In addition, either a monodentate (κ^1) or a chelating ($\kappa^2:\text{N},\text{O}$) coordination mode is possible for both N- and O-bonded indolate, whereas the C-bonded ligand can only be monodentate. All these possibilities were probed for the two oxindoles **1a** ($\text{R} = \text{H}$) and **1d** ($\text{R} = \text{Me}$).

Scheme 3. Possible Interactions Between $[\text{Cp}^*\text{CoI}_2]$ and Deprotonated Oxindole



In order to save computational time, the calculations were carried on a simplified model system where the Cp^* ring was replaced with the unsubstituted Cp ligand. The results (see SI for details) are summarized in Fig. 3. For the $\text{CpCo}(\text{oxindolate-1-H})$ (derived from deprotonated **1a**), N- and C-coordination are much more favoured than O-coordination. For all three linkage isomers, the preferred binding is monodentate and the preferred spin state is triplet. Chelation to afford an electronically saturated configuration stabilizes the N-bonded complex in the singlet state, as expected from the formation of an additional bond,

but is insufficient to compensate the cost of pairing the two electrons in the more stable 16-electron spin triplet complex. Chelation is not favoured for the spin triplet because it would place one electron in a high-energy antibonding orbital (attempts to optimize 18-electron chelate structures in the triplet state led back to the corresponding monodentate minimum). For the O-bonded complex in the singlet state, although a minimum could be located, chelation destabilizes the system because the energy gain associated to the formation of the additional bond insufficiently compensates the loss of pyrrole ring aromaticity caused by the N lone pair involvement in the N-Co bond. It is interesting to note that the N-bonded isomer is actually more stable than the C-bonded one in terms of electronic energy (by 5.8 kcal/mol), but this advantage is compensated, according to the calculations, by the combined effect of a lower zero-point vibrational energy, higher entropy, and a greater solvation stabilization for the C-bonded isomer. For the $\text{CpCo}(\text{oxindolate-1-Me})$ (derived from deprotonated **1d**), no N binding is possible and the C-bonded 16-electron spin triplet complex is the most stable species. The relative energies obtained for the other possible binding modes and spin states are rather similar for the 1-H and 1-Me oxindolate systems. Thus, the calculation suggests that the key catalytically active species **E** most probably contains a monodentate C-bonded oxindolate ligand for both 1-H and 1-Me oxindoles. The calculation also confirms the greater oxindole stability in the 2-oxo form than in the tautomeric 2-hydroxy form (by 17.4 kcal/mol for **1a** and 16.6 kcal/mol for **1d**). These collective results, together with those previously obtained for other $\text{Cp}^*\text{Co}^{\text{III}}$ -catalyzed alkylations by the “hydrogen borrowing” strategy (e.g. of amines^{13b} and ketones^{13c}), allow us to propose the mechanism shown in Scheme 4. The cycle can proceed, similarly to the amine alkylation cycle,^{13b} by β -H elimination from intermediate **E** to produce intermediate **F** with the coordinated ketone.

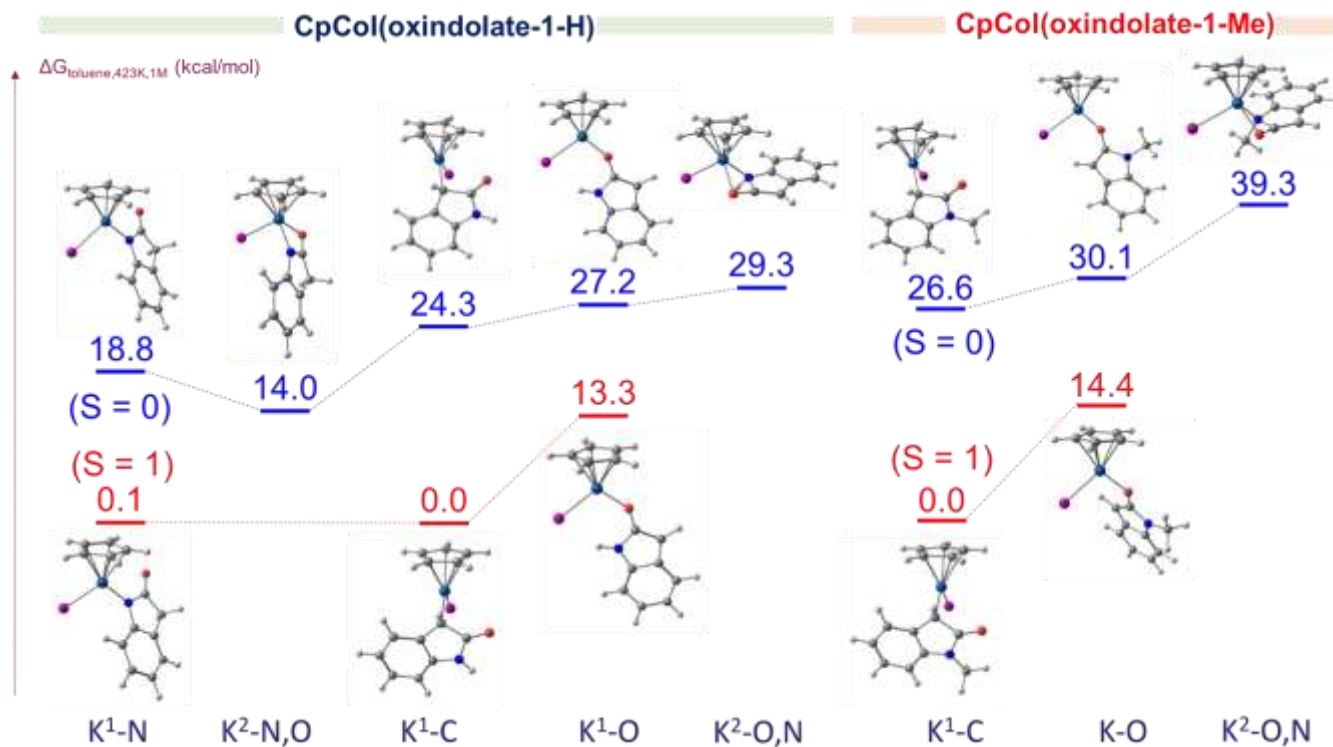
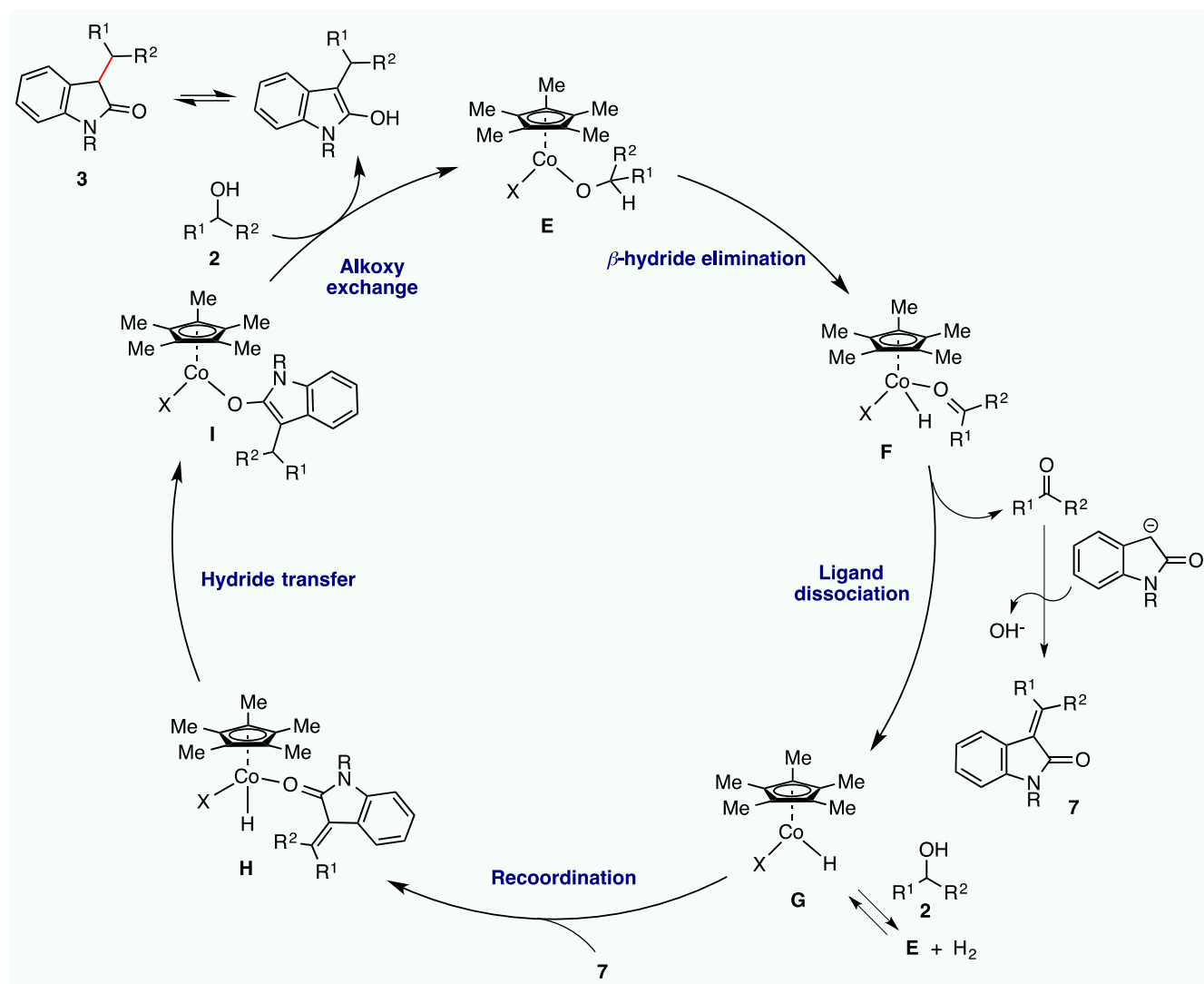


Figure 3: Energetic profile for the Cp*CoIX system with X = deprotonated oxindole **1a** (R = H) and **1d** (R = Me).

Scheme 4: Proposed Catalytic Cycle



After dissociation to generate the 16-electron hydride complex **G**, the ketone is attacked by the deprotonated oxindole to yield the unsaturated intermediate **7**, which coordinates to yield intermediate **H**. The latter then receives the hydride ligand by insertion selectively at the γ -position to afford **I**. Proton exchange with a new alcohol molecule regenerates **E** and releases the product as the 2-hydroxyindole tautomer, which finally rearranges to the alkylated oxindole. The small amount of deuterium incorporation at the β -position, observed for the experiment carried out with **2m-D**, may be rationalized by the competition of a reversible dehydrogenation process via intermediate **G**, producing HD. The reverse of this step would place the deuterium atom in the alcohol at the protic hydroxide position. Then, this deuterium atom can get involved in the final proton transfer step (**I** to **E**), ending up at the β -position of the alkylated product by tautomerization. The same process also rationalizes the reduced deuterium fraction at the product γ -position from the control experiments. A full DFT investigation of the catalytic cycle is ongoing and will be reported in due course.

In conclusion, we herein report the use of a bench-stable, high-valence Cp*Co^{III} catalyst for the C-alkylation of various carbon nucleophiles with secondary alcohols. A diverse array of aryl, cyclic and acyclic aliphatic secondary alcohols are tolerant with the developed method for the selective C-alkylation of oxindoles. Preliminary investigations reveal that the reaction follows first order kinetics and is indeed a homogenous hydrogen autotransfer process. Based on inferences from DFT calculations, a mechanistic pathway has been proposed. We have also demonstrated the selective C-alkylation of N,N-dimethyl barbituric acid and benzyl cyanides with secondary alcohols under high valent Co(III) catalysis. This developed protocol forms an entire library of new scaffolds, thereby opening the gateway for many other applications.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: .

Experimental methods, optimization of reaction conditions, and other supplementary data (PDF)

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Notes

The author declares no competing financial interest.

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