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Selective Ketone Formations via Cobalt-Catalyzed β-Alkylation of Secondary Alcohols with Primary Alcohols

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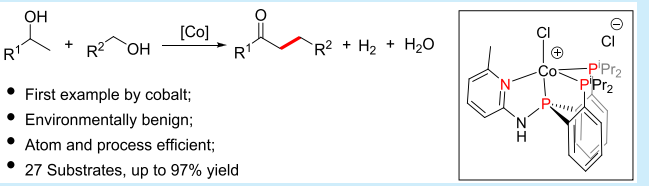
Supporting Information

ABSTRACT: A homogeneous cobalt-catalyzed β-alkylation of secondary alcohols with primary alcohols to selectively synthesize ketones via acceptorless dehydrogenative coupling is reported for the first time. Notably, this transformation is environmentally benign and atom economical with water and hydrogen gas as the only byproducts.



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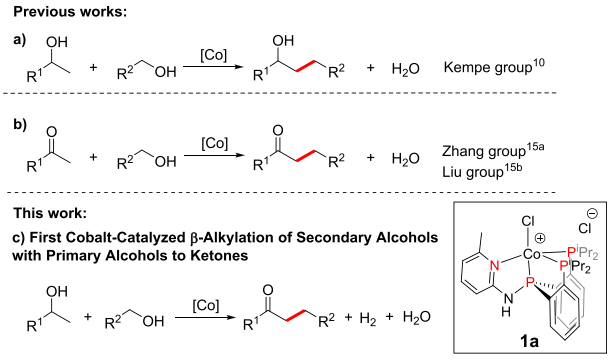
Homogeneous transition-metal-catalyzed carbon−carbon bond formations are among the paramount methods for value-added products.[1] In the conventional β-alkylation of secondary alcohols to synthesize ketones or alcohols, a multistep process is required, e.g., stoichiometric oxidation and alkylation with toxic and mutagenic alkyl halides, generating copious wastes.[2] Thus, it is highly desirable to develop alternative methods that are environmentally friendly and atom and process efficient, using readily available and less toxic substrates, e.g., alcohols. One such prominent synthetic strategy is acceptorless dehydrogenative coupling (ADC).[3,4] In a typical ADC pathway to ketones, primary and secondary alcohols are first dehydrogenated to aldehydes and ketones, respectively, with the catalyst taking the hydrogen atoms. The electrophilic aldehydes are attacked by the enolates formed via removal of the α-C−H of the ketones by a base, leading to the ketone products with loss of water. Finally, hydrogen gas is liberated from the hydrogenated catalyst. Alternatively, the hydrogenated catalyst can reduce the formed ketones, affording the alcohol products. This process is known as borrowing hydrogen (BH).[3,4] Offering great advantages over conventional methods, ADC and BH have recently attracted enormous interests.

Currently, precious metal catalysts based on Rh,[5] Ir,[6] Ru,[7] and Pd[8] dominate the β-alkylation of secondary alcohols with primary alcohols. With increasing concerns on sustainability and environment, less toxic and earth-abundant base metal analogues such as Fe,[9] Co,[10] Mn,[11] Ni,[12] and Cu[13] are becoming more appealing and have witnessed rapid recent developments. However, examples of homogeneous base metal catalyzed such transformations for ketone synthesis are rare.

In the Cu case, high catalyst and base loadings of 10% and 50% were mandatory, respectively.[13b] In the Mn version, unfortunately, very limited substrates were reported with moderate to good yields.[11c] Transition-metal-free examples are also available.[14] To the best of our knowledge, no homogeneous Co catalyst has been reported for β-alkylation of secondary alcohols with primary alcohols for selective ketone synthesis to date. Instead, there is just one example of alcohol formations via the BH process by a PNP−Co catalyst[10] (Scheme 1a). Methods for Co-catalyzed α-alkylation of ketones with primary alcohols to generate ketones are also known[15] (Scheme 1b). As the ketone reactants are normally obtained from stoichiometric oxidation of the secondary alcohols, it is more desirable to directly utilize secondary alcohols for the ketone formations (Scheme 1c). However, as H_2 is one of the byproducts, the formed ketones could be further hydrogenated to alcohols, imposing a challenge in product selectivity.[10] Herein, we report the first systematic study of homogeneous Co-catalyzed β-alkylation of secondary alcohols with primary alcohols to selectively synthesize ketones via ADC. Notably, this reaction is environmentally benign and atom efficient with water and hydrogen gas as the only byproducts.

Scheme 1. Cobalt-Catalyzed Couplings of Secondary Alcohols or Ketones with Primary Alcohols



We have recently developed a new family of base transition-metal complexes supported by a ^{iPr}PPPN^{H}Py^{Me} tetradentate

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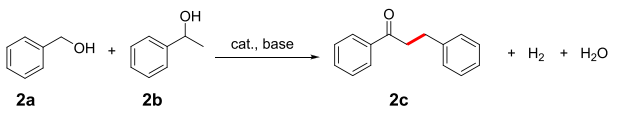
ligand.[16] The Co complex **1a** is an efficient catalyst for dehydrogenation of secondary alcohols to ketones[16] and dehydrogenative coupling of primary alcohols to esters.[17] We speculate that **1a** is a potentially efficient catalyst to mediate the β-alkylation of secondary alcohols with primary alcohols to synthesize ketones.

Initially, benzyl alcohol **2a** and 1-phenylethanol **2b** were chosen as the standard substrates. Different base additives were examined, and KO^{t}Bu turned out to be more suitable. Other reaction parameters were also optimized. Gratifyingly, the optimal results with 90% yield of 3-phenylpropiophenone **2c** were obtained using 2.5 mol % of **1a** and 7.5 mol % of KO^{t}Bu in toluene at 125 °C for 24 h under argon flow (Table 1, entry 2). It is noteworthy that the selectivity is excellent with a **2c**/1,3-diphenylpropanol **2d** ratio of 100:0, despite the fact that **2d** is known as the major side product of such transformation in the literature.[7e,12b,13b] Interestingly, when 5 mol % of KO^{t}Bu was utilized, which was exactly the amount of base used for activation of 2.5 mol % of **1a**, no **2c** product was observed, indicating the crucial role of base besides precatalyst activation (Table 1, entry 4). Further, control experiments showed both **1a** and base were essential for this reaction (Table 1, entries 5 and 6). Mercury tests demonstrated a homogeneous catalytic process. H_2 was confirmed by GC from the gas phase, suggesting an ADC pathway (see the SI).

Table 1. Optimization of Reaction Conditions[a]



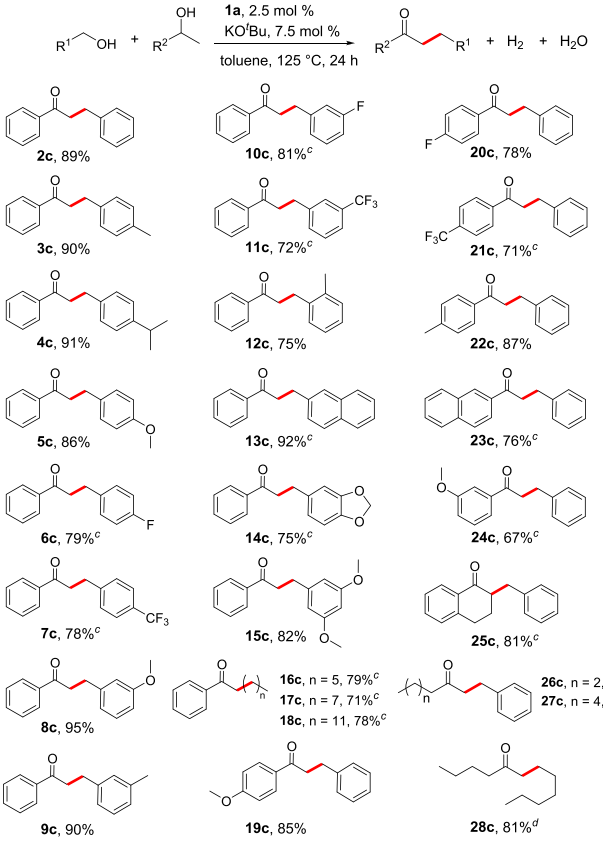
2a 2b 2c

entry	cat.	base	solvent	temp (°C)	yield[b] (%)
1	**1a**	KO^{t}Bu	toluene	105	31
2	**1a**	KO^{t}Bu	toluene	125	90 (86)[c]
3	**1a**	KO^{t}Bu	toluene	140	84
4[d]	**1a**	KO^{t}Bu	toluene	125	0
5		KO^{t}Bu	toluene	125	<1
6	**1a**		toluene	125	0
7	**1a**	KO^{t}Bu	1,4-dioxane	125	0
8	**1a**	NaO^{t}Bu	toluene	125	78
9	**1a**	KHMDS	toluene	125	59
10	**1a**	KOH	toluene	125	<1
11	**1a**	K_2CO_3	toluene	125	0

[a]General conditions: catalyst (2.5 mol %), base (7.5 mol %), **2a** (0.25 mmol), **2b** (0.3 mmol), and solvent (1.5 mL) for 24 h under an argon flow atmosphere. [b]Yields were determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard. [c]1 mmol scale, isolated yield. [d]KO^{t}Bu (5 mol %) was used.

Having established the optimized reactions, we next explored the substrate scope and efficiency of the reaction. We first investigated the scope of primary alcohols. Aromatic primary alcohols with electron-donating groups like −Me, −iPr, and −OMe at the *para* position furnished the corresponding ketones in excellent 90−93% yields (Table 2, **3c**−**5c**). Primary alcohols with electron-withdrawing groups at the *para* position also reacted smoothly (Table 2, **6c**, **7c**). Notably, *meta*-substituted substrates were transformed to the corresponding ketones as well (Table 2, **8c**−**11c**). Sterically hindered 2-methyl benzyl alcohol **12a** also proceeded in a good yield (Table 2, **12c**). Aliphatic primary alcohols afforded the desired ketones in 73−80% yields (Table 2, **16c**−**18c**).

Table 2. β-Alkylation of Secondary Alcohols with Primary Alcohols to Ketones[a,b]



[a]General conditions: **1a** (2.5 mol %), KO^{t}Bu (7.5 mol %), **2a** (0.25 mmol), **2b** (0.3 mmol), and toluene (1.5 mL) for 24 h under an argon flow atmosphere. [b]Isolated yield. [c]**1a** (5 mol %) and KO^{t}Bu (15 mol %) were used. [d]**1a** (5 mol %) and KO^{t}Bu (60 mol %) were used.

Next, we investigated the scope of secondary alcohols. *Para*-substituted aromatic secondary alcohols reacted with **2a** delivering the corresponding ketones in good to excellent yields (Table 2, **19c**−**22c**). *Meta*-substituted 1-(3-methoxyphenyl)ethanol **24b** showed a diminished activity (Table 2, **24c**). Aliphatic secondary alcohols were also amenable to this method, albeit under harsher conditions (Table 2, **26c**, **27c**). It is noteworthy that the reaction of *n*-hexanol **28a** and 2-hexanol **28b** proceeded smoothly, giving an 80% yield (Table 2, **28c**). To the best of our knowledge, β-alkylation of aliphatic secondary alcohols with primary alcohols to ketones mediated by homogeneous base transition-metal catalyst has not been disclosed before. Unfortunately, heterocyclic substrates were not tolerated. Couplings of different secondary alcohols, e.g., **2b** and cyclohexanol **29b**, were incompatible with this method.

We then sought a mechanistic understanding of this reaction. First, two derivatives of **1a** (**1b** and **1c**, Figure 1) were investigated. Compound **1b** bearing a dearomatized pyridine arm shows comparable activity to **1a** in an 81% yield, indicating **1b** is also a precatalyst. To test if metal ligand cooperativity (MLC) from the N−H linker plays a role, a ^{iPr}PPPN^{Me}Py^{Me} complex **1c** was tested as the precatalyst. A 66% yield of **2c** and 22% yield of **2d**, a further hydrogenated product from **2c**, were recorded, suggesting MLC may not have a crucial effect.

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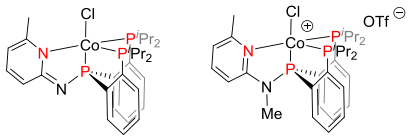
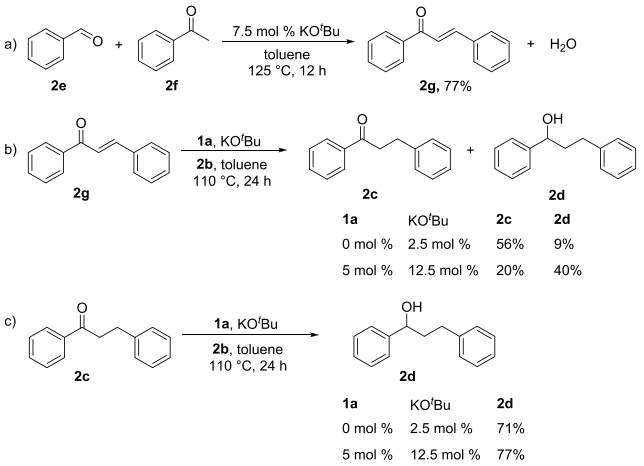


1b 1c

Figure 1. Derivatives **1b** and **1c** of compound **1a** examined.

Our prior work showed that **1a** was capable of mediating dehydrogenation of primary and secondary alcohols to esters (via aldehydes)[17] and ketones,[16] respectively. In the current study, when benzaldehyde **2e** reacted with acetophenone **2f** in the presence of 7.5 mol % of KO^{t}Bu (Scheme 2a), a 77% yield

Scheme 2. Control Experiments



of chalcone **2g** was observed, which suggested that the α,β-unsaturated ketone is likely one of the intermediates in the alkylation of secondary alcohols with primary alcohols. Interestingly, in a transfer hydrogenation experiment employing **2b** as the hydrogen source in a sealed reaction vessel, **2g** can be hydrogenated to **2c** (56% yield) and **2d** (9% yield) by 2.5 mol % of KO^{t}Bu alone (Scheme 2b). This suggests a base-mediated Meerwein–Ponndorf–Verley (MPV) type reduction pathway.[14,18] Alternatively, with 5 mol % of **1a** and 12.5 mol % of KO^{t}Bu,[19] a 20% yield of **2c** and a 40% yield of **2d** were observed, suggesting that **1a** may favor alcohol formations under these conditions. To further testify this proposal, we explored the transfer hydrogenation of **2c** with **2b** in a seal reaction vessel (Scheme 2c). Using 2.5 mol % of KO^{t}Bu alone, a 71% yield of **2d** was obtained, advocating an operational MPV reduction. Notably, in the presence of 12.5 mol % of KO^{t}Bu and 5 mol % of **1a**,[19] a slight increase in **2d** yield (77%) was observed. In addition, when the standard reaction (Table 1, entry 2) was carried out in a sealed reaction vessel, only a 34% yield of **2c** resulted together with a 26% yield of **2d**, suggesting the essential role of utilizing open systems for the selective ketone synthesis, in which extrusion of hydrogen gas could efficiently suppress the formation of the alcohol side-products.

In summary, we reported the first homogeneous cobalt-catalyzed β-alkylation of secondary alcohols with primary alcohols to form ketones. Remarkably, this is an environmentally benign and atom-efficient process, which contributes to sustainable synthesis by base transition-metal catalysts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02727.

Experimental details, additional figures, and other results (PDF)

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Notes

The authors declare no competing financial interest.

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(19) As 1 equiv of **1a** depletes 2 equiv of KO^{t}Bu in the activation process, 5 mol % of **1a**/12.5 mol % of KO^{t}Bu were employed to make the net KO^{t}Bu amount 2.5 mol %.

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