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α-Alkylation of Nitriles with Primary Alcohols by a Well-Defined Molecular Cobalt Catalyst

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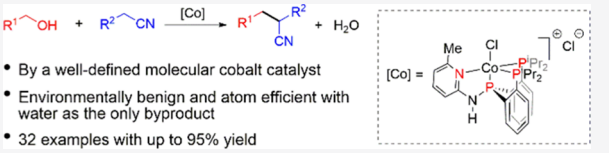
ABSTRACT: The α-alkylation of nitriles with primary alcohols to selectively synthesize nitriles by a well-defined molecular homogeneous cobalt catalyst is presented. Thirty-two examples with up to 95% yield are reported. Remarkably, this transformation is environmentally friendly and atom economical with water as the only byproduct.



INTRODUCTION

With the unique −C≡N functional group, nitriles are a class of organic compounds that have found ubiquitous applications in chemical and pharmaceutical industries.[1] α-Alkylated nitriles are key building blocks for the synthesis of various compounds such as carboxylic acids, amides, amines, ketones, etc.[1] Homogeneous transition-metal-mediated construction of the carbon−carbon bond belongs to one of the most imperative synthetic strategies for the products of added values.[2] Traditional alkylation requires toxic alkyl halides and stoichiometric amounts of bases, generating the copious amount of wastes.[3] An attractive alternative is to utilize alcohol as the alkylating agent via a borrowing hydrogen (BH) process.[4,5] In a typical BH process to α-alkylated nitriles, a primary alcohol is first dehydrogenated to an aldehyde with the catalyst "borrowing" a hydride and a proton. The aldehyde undergoes a nucleophilic attack by the nitrile in the presence of a base to generate an α,β-unsaturated nitrile, which is subsequently hydrogenated to the α-alkylated nitrile product by the catalyst "returning" the hydride and the proton. The BH strategy is more sustainable, environmentally friendly, and atom-efficient, with water as the only byproduct.[4,5]

In this regard, catalysts based on precious transition metals, such as Rh,[6a,b] Ir,[6c,d] Os,[6e] Ru,[6f] and Pd,[6g] have significantly promoted this field. With increasing concerns on sustainability and economy, base transition-metal surrogates like Fe, Co, Mn, Ni, and Cu are becoming more appealing.[7] It is just recently that such base transition-metal-catalyzed transformations are revealed.[8] A transition-metal-free method was recently reported using 80 mol % KO^{t}Bu under aerobic conditions.[9] As part of the study on methylation of C(sp^3)−H/C(sp^2)−H bonds, Liu and co-workers reported their seminal work on the nitrile alkylation by a cobalt salt $Co(BF_4)_2{\cdot}6H_2O$, P-$(CH_2CH_2PPh_2)_3$ (PP_3) ligand, and a stoichiometric amount of base, which is the only known cobalt example in literature.[8a] However, the reported substrates were very limited, and methanol was the only alcohol used.[8a] In addition, no mechanistic study on the α-alkylation of nitrile was disclosed.[8a] Herein, we present a systematic study on the selective nitrile alkylation with primary alcohols mediated by a well-defined molecular cobalt catalyst (Scheme 1).

We have recently developed a new tetradentate mixed P/N donor ligand ^{iPr}PPPN^{H}Py^{Me}.[10a] The air-stable cobalt complex **A** is an efficient precatalyst for dehydrogenation of secondary alcohols to ketones,[10a] dehydrogenative self-coupling of primary alcohols to esters,[10b] and β-alkylation of secondary alcohols with primary alcohols to ketones.[10c] We envision that the **A**-based catalytic system has a potential for the selective nitrile alkylation with primary alcohols to α-alkylated nitriles.

RESULTS AND DISCUSSION

We initiated the work to explore the reaction of the model substrates benzyl alcohol (0.5 mmol) and phenylacetonitrile (0.25 mmol) under various conditions. A temperature of 140 °C was required to obtain an optimized yield (Table 1, entries 1−3). After investigating various bases for the reaction, KOH turned out to be the most suitable base (Table 1, entries 3−6). It was shown that **A**, base, and $KHBEt_3$ were essential for this reaction (Table 1, entries 7−9). Twenty mole percent KOH was needed to optimize the yield (Table 1, entries 5 and 10). Interestingly, doubling **A** and $KHBEt_3$ loading gave a comparable yield (Table 1, entry 11). Solvents were also screened, and toluene was found to be the most suitable one (Table 1, entries 5, 12−14). Notably, a good 83% yield was observed in only 6 h, demonstrating the great reactivity of the catalytic system (Table 1, entry 16). Thus, the optimized conditions were obtained (Table 1 entry 5). Mercury test suggested a homogeneous catalytic process (Table 1, entry 17).

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Scheme 1. Well-Defined Molecular Cobalt Catalyst-Mediated α-Alkylation of Nitriles with Primary Alcohols

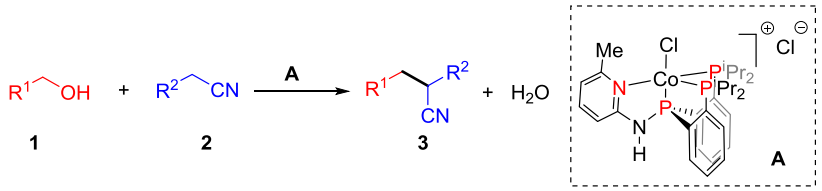
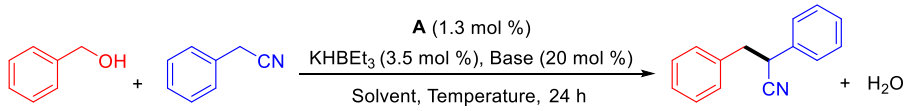


Table 1. Optimization of the Reaction Conditions[a]



entry	cat.	base	solvent	temp (°C)	yield[b] (%)
1	A	KO^{t}Bu	toluene	105	15
2	A	KO^{t}Bu	toluene	125	65
3	A	KO^{t}Bu	toluene	140	68
4	A	NaO^{t}Bu	toluene	140	74
5	A	KOH	toluene	140	88 (85)
6	A	K_2CO_3	toluene	140	13
7[c]	A	KOH	toluene	140	65
8	A		toluene	140	16
9		KOH	toluene	140	11
10[d]	A	KOH	toluene	140	68
11[e]	A	KOH	toluene	140	85
12	A	KOH	benzene	140	74
13	A	KOH	THF	140	66
14	A	KOH	*t*-AmOH	140	50
15[f]	A	KOH	toluene	140	82 (80)
16[g]	A	KOH	toluene	140	83
17[h]	A	KOH	toluene	140	83

[a]Reaction conditions: **A** (1.3 mol %), $KHBEt_3$ (3.5 mol %), base (20 mol %), **1a** (0.5 mmol), **2a** (0.25 mmol), and solvent (1.25 mL) were heated in a sealed 15 mL reaction tube for 24 h. [b]Yields were determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethoxybenzene as an internal standard. Isolated yield is in parenthesis. [c]Reaction was carried out in the absence of $KHBEt_3$. [d]KOH (10 mol %) was used. [e]**A** (2.6 mol %) and $KHBEt_3$ (7 mol %) were used. [f]**1a** (2.0 mmol) and **2a** (1.0 mmol) were used. [g]6 h. [h]Mercury (125 mg) was added to the reaction.

With the optimized conditions in hand, we then probed the scope of the reaction by examining a wide range of primary alcohols and nitriles. First, we explored the scope of primary alcohols. Aromatic primary alcohols bearing electron-donating groups such as −OMe, −^{i}Pr, and −Me at the para position afforded the desired nitriles in good 70−80% yields (Table 2, entries **3b**, **3c**, and **3q**). Aromatic primary alcohols with electron-withdrawing groups like −Cl and $-CF_3$ at the para position also transformed smoothly (Table 2, entries **3d** and **3w**). 2-Methyl benzyl alcohol showed a diminished activity in a 57% yield probably due to the steric hindrance (Table 2, entry **3r**). Notably, 2-naphthyl methanol proceeds successfully in a very good 88% yield (Table 2, entry **3v**). Heteroaryl alcohols, such as piperonyl alcohol and 2-furfurylmethanol, furnished the corresponding nitriles in moderate yields (Table 2, entries **3e**, **3f**, **3p**, and **3t**). Moreover, aliphatic primary alcohols could also be applied to give the desired nitrile products in good to excellent yields (80−95%) using 2.6 mol % **A** and 15 mol % KO^{t}Bu (Table 2, entries **3x**−**3ae**). It is worth noting that the alkene functional group is intact (Table 2, entries **3x**). A methanol/4-methoxybenzonitrile ratio of 10 was required to reach an 80% yield of 2-(4-methoxyphenyl)propanenitrile (Table 2, entry **3ae**). Next, we investigated the scope of nitriles. Similarly, a variety of aromatic nitriles with electron-donating or -withdrawing groups at different positions could be utilized for the alkylation reactions with 50−90% yields (Table 2, entries **3g**−**3ae**). Importantly, nitriles bearing pyridyl and naphthyl ring delivered the corresponding products in 60 and 71% yields, respectively (Table 2, entries **3n** and **3o**). Unfortunately, benzenepropanenitrile and aliphatic nitriles did not work under these conditions (Table 2, entry **3af**).

Next, we performed a mechanistic study to understand the nitrile alkylation reaction. We first explored the reactivity of **A** derivatives **B** and **C** using the model substrates[10a] (Figure 1). **B** is air-sensitive, but **C** is air-stable. **B**, with a dearomatized pyridine arm, demonstrated a slightly diminished activity compared to **A** (73% yield), indicating **B** is also a precatalyst. **C** that bears a N−Me linker on the pyridine arm efficiently mediated the reaction leading to an 82% yield, suggesting metal−ligand cooperativity (MLC) that might originate from the N−H linker on **A** did not play an essential role.

We have shown that **A** can mediate the self-coupling of primary alcohols to esters.[10b] Mechanistic study suggests a pathway that involves dehydrogenation of primary alcohols to aldehydes followed by the Tishchenko reaction to esters. We also reported dehydrogenation of secondary alcohols to ketones catalyzed by **A**.[10a] Thus, aldehyde is likely an intermediate in the α-alkylation of nitriles with primary

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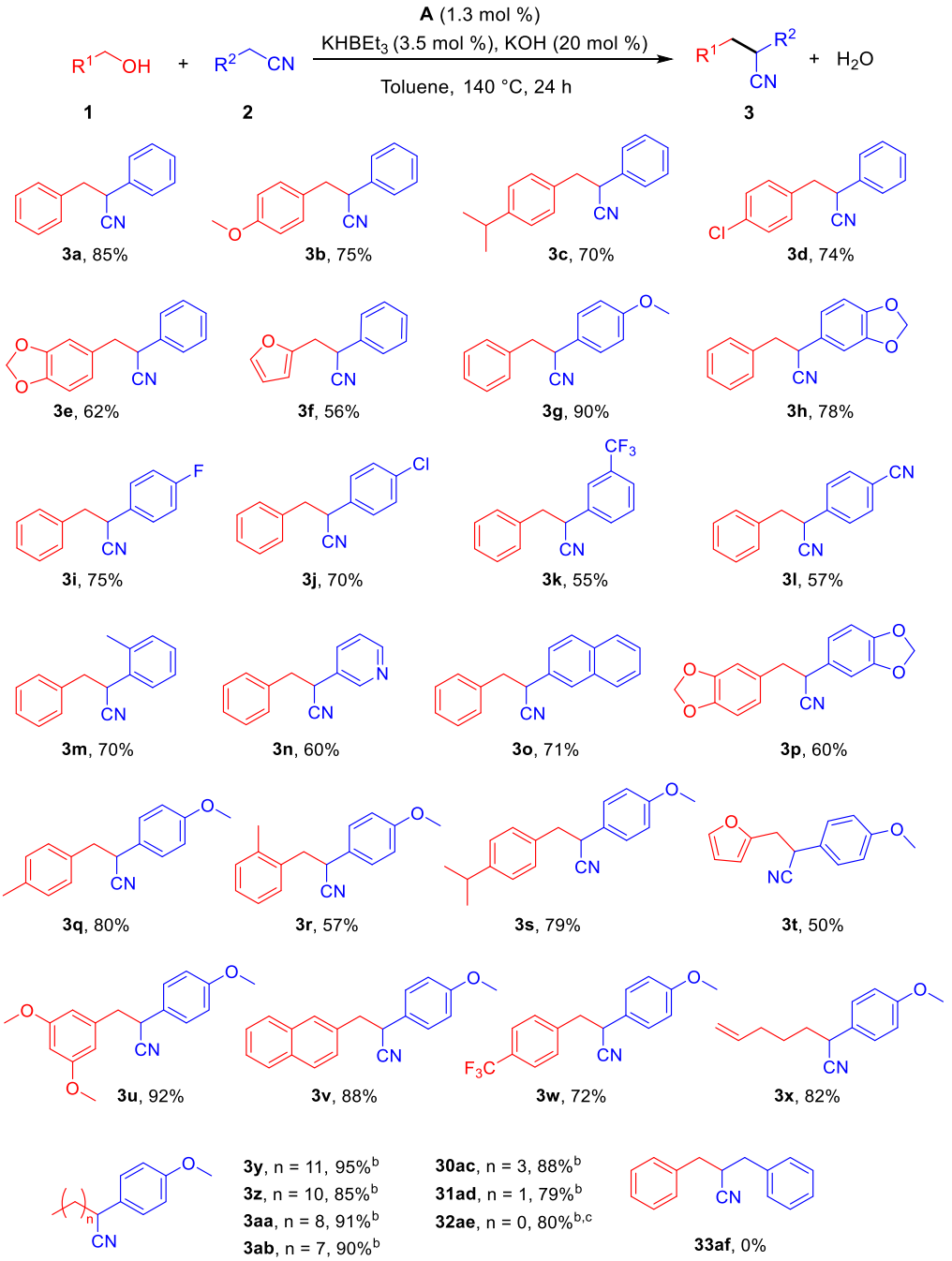
Table 2. α-Alkylation of Nitriles with Primary Alcohols[a,b,c]



[a]Reaction conditions: **A** (1.3 mol %), $KHBEt_3$ (3.5 mol %), KOH (20 mol %), alcohol (0.5 mmol), nitrile (0.25 mmol), and toluene (1.25 mL) were heated in a 15 mL reaction tube for 24 h. Isolated yields are given. [b]Reaction was carried out using **A** (2.6 mol %) and KO^{t}Bu (15 mol %). [c]Reaction was carried out using MeOH (2.5 mmol) for 60 h.

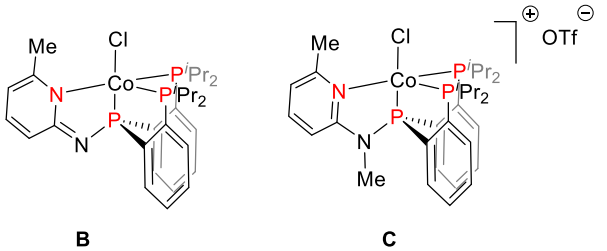


Figure 1. **A** derivatives **B** and **C** examined.

alcohols. The condensation of benzaldehyde and phenylacetonitrile under the optimal conditions afforded 2,3-diphenylacrylonitrile in an 86% yield (Scheme 2A).

Without **A** and $KHBEt_3$, a comparable yield of 88% was also obtained (Scheme 2B). These results suggest that α,β-unsaturated nitrile is a possible intermediate,[11] and its formation can be mediated by base alone. Interestingly, the transfer hydrogenation of 2,3-diphenylacrylonitrile with benzyl alcohol (2 equiv) proceeded to completion by 20 mol % KOH in the standard conditions, with or without **A**/$KHBEt_3$ (Scheme 2C,D). This unexpected result supports a base-

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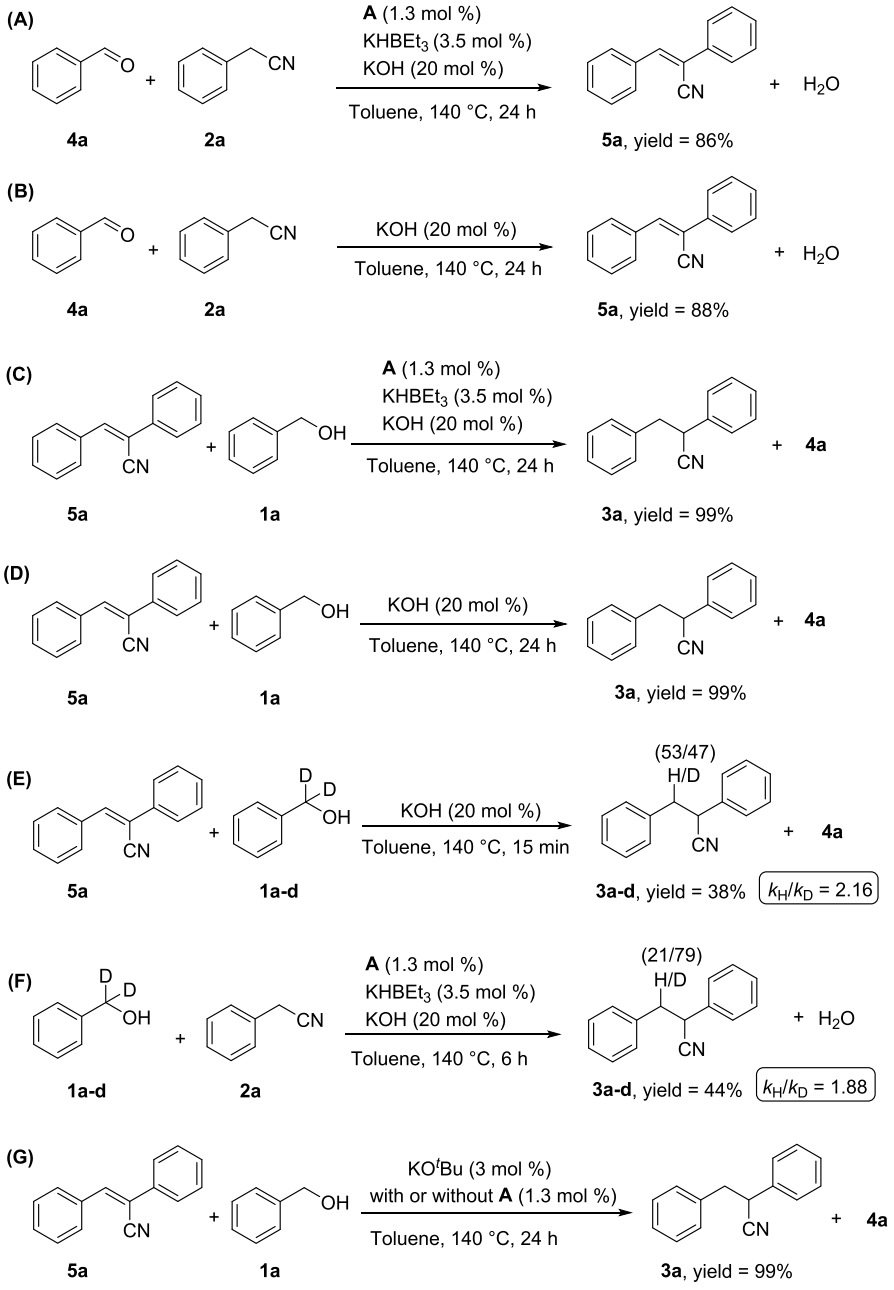
Scheme 2. Control Experiments



mediated Meerwein–Ponndorf–Verley (MPV) hydrogenation pathway.[12]

Further investigations showed that the transfer hydrogenation can be finished in an hour by 20 mol % KOH. The deuterium labeling experiment utilizing benzyl alcohol-α,α-d_2 in the 2,3-diphenylacrylonitrile transfer hydrogenation resulted in a k_H/k_D ratio of 2.16 (Scheme 2E), indicating that the cleavage of the α-C–H bond of benzyl alcohol is a slow step. The H/D ratio is close to unit, which suggests that the deuterium at the benzyl position transfers to the β position of the nitrile group in the MPV process. However, a H/D ratio close to 1:4 was obtained in the α-alkylation of phenylacetonitrile with benzyl alcohol-α,α-d_2 (Scheme 2F). The incorporation of hydrogen infers that **A**-mediated dehydrogenation of primary alcohol may be reversible. A k_H/k_D ratio of 1.88 was acquired, which is in line with the result from the 2,3-diphenylacrylonitrile transfer hydrogenation. Different bases were also examined. Employing only 3 mol % KO^{t}Bu with or without **A** both gave a full conversion of 2,3-diphenylacrylonitrile in 24 h (Scheme 2G), suggesting that **A** might not play a crucial role in the α,β-unsaturated nitrile hydrogenation step.

Based on the mechanistic study, a plausible catalytic cycle is proposed as depicted in Scheme 3. Initial **A**-mediated primary alcohol dehydrogenation leads to aldehyde, which undergoes a nucleophilic attack by the nitrile substrate affording α,β-unsaturated nitrile in the presence of base. Finally, the α,β-unsaturated nitrile is reduced to the nitrile product via a base-mediated MPV pathway. To the best of our knowledge, such a mechanism has yet been revealed for the α-alkylation of nitriles. A more in-depth mechanistic investigation is ongoing in our laboratory.

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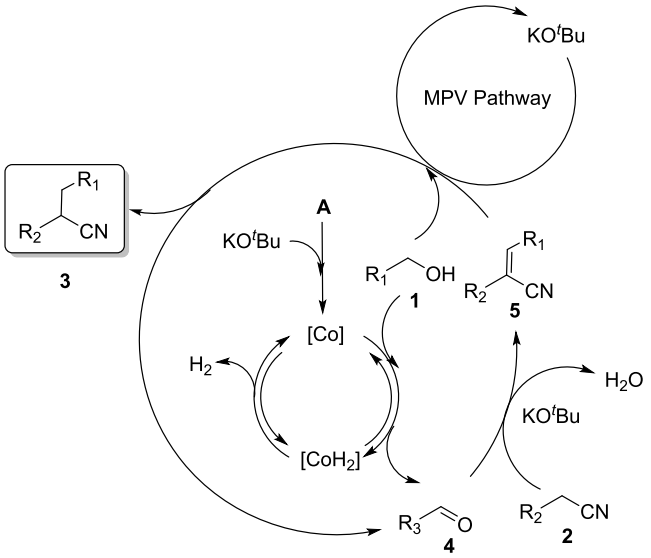
Scheme 3. Proposed Reaction Mechanism



CONCLUSIONS

In summary, we disclosed a well-defined molecular cobalt catalyst for the selective nitrile alkylation with primary alcohols to α-alkylated nitriles. Notably, this method is atom-efficient and environmentally friendly with water as the only byproduct. We expect this work will contribute to the development of base transition-metal catalysts in green synthesis.

EXPERIMENTAL SECTION

General Method. Unless otherwise is stated, all reactions were set up in an MBraun glovebox under an atmosphere of N_2. Anhydrous solvents were deoxygenated by sparging with N_2 and dried by passing through activated alumina columns of a Pure Solv solvent purification system. $CDCl_3$ was purchased from Cambridge Isotope Lab and dried over molecular sieves (4 Å). Cobalt complexes (**A**−**C**) were prepared according to our published procedures.[10a] Chemicals used in this paper were purchased from Sigma-Aldrich, Oakwood Chemical, or Fisher Scientific and used as received. NMR spectra were recorded on a JEOL Unity 500 or 300 MHz spectrometer. ^{1}H NMR spectra were referenced to tetramethyl silane (0.00 ppm) using $CDCl_3$ as a solvent. ^{13}C NMR were referenced to solvent carbons at 77.0 ppm for $CDCl_3$. ^{19}F NMR spectra were referenced to fluorobenzene at −113.15 ppm. HRMS were acquired from the Mass Spectrometry and Proteomics Facility at University of Notre Dame.

General Procedure for the α-Alkylation of Nitriles with Aryl Primary Alcohols Using A. Inside a N_2-filled glovebox, a mixture of **A** (1.3 mol %), $KHBEt_3$ (3.5 mol %), KOH (20 mol %), nitrile (0.25 mmol), primary alcohol (0.5 mmol), and toluene (1.25 mL) was loaded into a 15 mL reaction vessel. The reaction vessel was sealed by a screw cap and brought out of the glovebox. The reaction tube was placed in a preheated oil bath at 140 °C for 24 h. After the reaction was finished and cooled down, the reaction mixture was filtered through a silica gel plug and the collected filtrate was concentrated by a rotavap. The obtained residue was purified by a silica gel column using ethyl acetate/hexane (1:20, v/v) as an eluent, giving the pure alkylated nitrile product.

General Procedure for the α-Alkylation of Nitriles with Aliphatic Primary Alcohols Using A. Inside a N_2-filled glovebox, a mixture of **A** (2.6 mol %), KO^{t}Bu (15 mol %), nitrile (0.25 mmol), primary alcohol (0.5 mmol), and toluene (1.25 mL) was loaded into a 15 mL reaction vessel. The reaction vessel was sealed by a screw cap and brought out of the glovebox. The reaction tube was placed in a preheated oil bath at 140 °C for 24 h. After the reaction was finished and cooled down, the reaction mixture was filtered through a silica gel plug and the collected filtrate was concentrated by a rotavap. The obtained residue was purified by a silica gel column using ethyl acetate/hexane (1:20, v/v) as an eluent, giving the pure alkylated nitrile product.

Procedure for the α-Alkylation of 4-Methoxybenzonitrile with Methanol Using A. Inside a N_2-filled glovebox, a mixture of **A** (2.6 mol %), KO^{t}Bu (15 mol %), 4-methoxybenzonitrile (0.25 mmol), methanol (2.5 mmol), and toluene (1.25 mL) was loaded into a 15 mL reaction vessel. The reaction vessel was sealed by a screw cap and brought out of the glovebox. The reaction tube was placed in a preheated oil bath at 140 °C for 60 h. After the reaction was finished and cooled down, the reaction mixture was filtered through a silica gel plug and the collected filtrate was concentrated by a rotavap. The obtained residue was purified by a silica gel column using ethyl acetate/hexane (1:20, v/v) as an eluent, giving the pure alkylated nitrile product.

Procedure for the α-Alkylation of Phenylacetonitrile with Benzyl Alcohols Using B. Inside a N_2-filled glovebox, a mixture of **B** (1.3 mol %), $KHBEt_3$ (3.5 mol %), KOH (20 mol %), phenylacetonitrile (0.25 mmol), benzyl alcohol (0.5 mmol), and toluene (1.25 mL) was loaded into a 15 mL reaction vessel. The reaction vessel was sealed by a screw cap and brought out of the glovebox. The reaction tube was placed in a preheated oil bath at 140 °C for 24 h. After the reaction was finished and cooled down, the reaction mixture was filtered through a silica gel plug and the collected filtrate was concentrated by a rotavap. The obtained residue was purified by a silica gel column using ethyl acetate/hexane (1:20, v/v) as an eluent, giving the pure alkylated nitrile product.

Procedure for the α-Alkylation of Phenylacetonitrile with Benzyl Alcohols Using C. Inside a N_2-filled glovebox, a mixture of **C** (1.3 mol %), $KHBEt_3$ (3.5 mol %), KOH (20 mol %), phenylacetonitrile (0.25 mmol), benzyl alcohol (0.5 mmol), and toluene (1.25 mL) was loaded into a 15 mL reaction vessel. The reaction vessel was sealed by a screw cap and brought out of the glovebox. The reaction tube was placed in a preheated oil bath at 140 °C for 24 h. After the reaction was finished and cooled down, the reaction mixture was filtered through a silica gel plug and the collected filtrate was concentrated by a rotavap. The obtained residue was purified by a silica gel column using ethyl acetate/hexane (1:20, v/v) as an eluent, giving the pure alkylated nitrile product.

Procedure for the α-Alkylation of Phenylacetonitrile with Benzyl Alcohols Using A in 1.0 mmol Scale. Inside a N_2-filled glovebox, a mixture of **A** (1.3 mol %), $KHBEt_3$ (3.5 mol %), KOH (20 mol %), phenylacetonitrile (1.0 mmol), benzyl alcohol (2.0 mmol), and toluene (2.0 mL) was loaded into a 15 mL reaction vessel. The reaction vessel was sealed by a screw cap and brought out of the glovebox. The reaction tube was placed in a preheated oil bath at 140 °C for 24 h. After the reaction was finished and cooled down, the reaction mixture was filtered through a silica gel plug and the collected filtrate was concentrated by a rotavap. The obtained residue was purified by a silica gel column using ethyl acetate/hexane (1:20, v/v) as an eluent, giving the pure alkylated nitrile product: 166 mg (80%).

Procedure for Homogeneity Test. Inside a N_2-filled glovebox, a mixture of **A** (1.3 mol %), $KHBEt_3$ (3.5 mol %), KOH (20 mol %), phenylacetonitrile (0.25 mmol), benzyl alcohol (0.5 mmol), and toluene (1.25 mL) was loaded into a 15 mL reaction vessel and stirred at room temperature for 10 min. Mercury (125 mg, 0.625 mmol) was added to the vessel. The reaction vessel was sealed by a screw cap and brought out of the glovebox. The reaction tube was placed in a preheated oil bath at 140 °C for 24 h. After the reaction was finished and cooled down, the reaction mixture was filtered through a silica gel plug and the collected filtrate was concentrated by a rotavap. The obtained residue was purified by a silica gel column using ethyl acetate/hexane (1:20, v/v) as an eluent, giving the pure alkylated nitrile product.

Procedure for Condensation of Benzaldehyde and Phenylacetonitrile by KOH or A/$KHBEt_3$/KOH. Inside a N_2-filled glovebox, a mixture of **A** (0 or 1.3 mol %), $KHBEt_3$ (0 or 3.5 mol %), KOH (20 mol %), phenylacetonitrile (0.25 mmol), benzaldehyde (0.25 mmol), and toluene (1.25 mL) was loaded into a 15 mL

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reaction vessel. The reaction vessel was sealed by a screw cap and brought out of the glovebox. The reaction tube was placed in a preheated oil bath at 140 °C for 24 h. After the reaction was finished and cooled down, 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol) dissolved in diethyl ether was added to the reaction mixture, stirred, and filtered through a silica gel plug. The plug was washed with diethyl ether, and the collected filtrate was concentrated under vacuum using a rotavapor. The obtained residue was dissolved in $CDCl_3$ and subjected to NMR analysis.

Procedure for Transfer Hydrogenation of 2,3-Diphenylacrylonitrile with Benzyl Alcohol by A/KO^{t}Bu or KO^{t}Bu. Inside a N_2-filled glovebox, a mixture of **A** (1.3 mol %), KO^{t}Bu (3 mol %), 2,3-diphenylacrylonitrile (0.25 mmol), benzyl alcohol (0.5 mmol), and toluene (1.25 mL) was loaded into a 15 mL reaction vessel. The reaction vessel was sealed by a screw cap and brought out of the glovebox. The reaction tube was placed in a preheated oil bath at 140 °C for 24 h. After the reaction was finished and cooled down, 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol) dissolved in diethyl ether was added to the reaction mixture, stirred, and filtered through a silica gel plug. The plug was washed with diethyl ether, and the collected filtrate was concentrated under vacuum using a rotavapor. The obtained residue was dissolved in $CDCl_3$ and subjected to NMR analysis.

Procedure for Transfer Hydrogenation of 2,3-Diphenylacrylonitrile with Benzyl Alcohol by KOH or A/KHBEt$_3$/KOH. Inside a N_2-filled glovebox, a mixture of **A** (0 or 1.3 mol%), $KHBEt_3$ (0 or 3.5 mol %), KOH (20 mol %), 2,3-diphenylacrylonitrile (0.25 mmol), benzyl alcohol (0.5 mmol), and toluene (1.25 mL) was loaded into a 15 mL reaction vessel. The reaction vessel was sealed by a screw cap and brought out of the glovebox. The reaction tube was placed in a preheated oil bath at 140 °C for 24 h. After the reaction was finished and cooled down, 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol) dissolved in diethyl ether was added to the reaction mixture, stirred, and filtered through a silica gel plug. The plug was washed with diethyl ether, and the collected filtrate was concentrated under vacuum using a rotavapor. The obtained residue was dissolved in $CDCl_3$ and subjected to NMR analysis.

Deuterium Labeling Experiment for the Transfer Hydrogenation of 2,3-Diphenylacrylonitrile with Benzyl Alcohol or Benzyl Alcohol-α,α-d_2 by KOH. Inside a N_2-filled glovebox, a mixture of KOH (20 mol %), 2,3-diphenylacrylonitrile (0.25 mmol), benzyl alcohol or benzyl alcohol-α,α-d_2 (0.5 mmol), and toluene (1.25 mL) was loaded into a 15 mL reaction vessel. The reaction vessel was sealed by a screw cap and brought out of the glovebox. The reaction tube was placed in a preheated oil bath at 140 °C for 15 min. After the reaction was finished and cooled down, 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol) dissolved in diethyl ether was added to the reaction mixture, stirred, and filtered through a silica gel plug. The plug was washed with diethyl ether, and the collected filtrate was concentrated under vacuum using a rotavapor. The obtained residue was dissolved in $CDCl_3$ and subjected to NMR analysis.

Deuterium Labeling Experiment for the α-Alkylation of Phenylacetonitrile with Benzyl Alcohols or Benzyl Alcohol-α,α-d_2 by A/KHBEt$_3$/KOH. Inside a N_2-filled glovebox, a mixture of **A** (1.3 mol %), $KHBEt_3$ (3.5 mol %), KOH (20 mol %), phenylacetonitrile (0.25 mmol), benzyl alcohol or benzyl alcohol-α,α-d_2 (0.5 mmol), and toluene (1.25 mL) was loaded into a 15 mL reaction vessel. The reaction vessel was sealed by a screw cap and brought out of the glovebox. The reaction tube was placed in a preheated oil bath at 140 °C for 6 h. After the reaction was finished and cooled down, 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol) dissolved in diethyl ether was added to the reaction mixture, stirred, and filtered through a silica gel plug. The plug was washed with diethyl ether, and the collected filtrate was concentrated under vacuum using a rotavapor. The obtained residue was dissolved in $CDCl_3$ and subjected to NMR analysis.

2,3-Diphenylpropanenitrile[8d] ***(3a)***. White solid; 44 mg (85%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37−7.25 (m, 8H), 7.14−7.13 (m, 2H), 3.99 (dd, 1H, J = 8.4, 6.4 Hz), and 3.21−3.11 (m, 2H); and $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 136.3, 135.3, 129.2, 129.1, 128.7, 128.2, 127.5, 127.4, 120.4, 42.2, and 39.8.

3-(4-Methoxyphenyl)-2-phenylpropanenitrile[8d] ***(3b)***. White solid; 45 mg (75%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37−7.31 (m, 3H), 7.26−7.25 (m, 2H), 7.04 (d, 2H, J = 10.5 Hz), 6.82 (d, 2H, J = 10.9 Hz), 3.96 (t, 1H, J = 7.7 Hz), 3.79 (s, 3H), and 3.16−3.07 (m, 2H); and $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 158.9, 135.3, 130.3, 129.0, 128.4, 128.2, 127.5, 120.5, 114.0, 55.3, 41.5, and 40.1.

3-(4-Isopropylphenyl)-2-phenylpropanenitrile[8f] ***(3c)***. White solid; 44 mg (70%); m.p. 65−67 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38−7.33 (m, 3H), 7.30−7.28 (m, 2H), 7.16 (d, 2H, J = 8.1 Hz), 7.09 (d, 2H, J = 8.1 Hz), 3.97 (dd, 1H, J = 8.7, 6.2 Hz), 3.18−3.07 (m, 2H), 2.93−2.84 (m, 1H), and 1.24 (d, 6H, J = 6.9 Hz); and $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 148.1, 135.5, 133.7, 129.1, 129.0, 128.2, 127.5, 126.7, 120.5, 41.9, 40.0, 33.8, and 24.0.

3-(4-Chlorophenyl)-2-phenylpropanenitrile[8b] ***(3d)***. White solid; 45 mg (74%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38−7.33 (m, 3H), 7.27−7.23 (m, 4H), 7.04 (d, 2H, J = 8.4 Hz), 3.99 (dd, 1H, J = 7.9, 6.5 Hz), and 3.18−3.10 (m, 2H); and $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 134.8, 134.6, 133.4, 130.6, 129.1, 128.8, 128.4, 127.5, 120.1, 41.5, and 39.6.

3-(Benzo[d][1,3]dioxol-5-yl)-2-phenylpropanenitrile[8f] ***(3e)***. Colorless oil; 39 mg (62%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37−7.33 (m, 3H), 7.27−7.26 (m, 2H), 6.73 (d, 1H, J = 7.9 Hz), 6.62−6.60 (m, 2H), 5.94 (s, 2H), 3.95 (dd, 1H, J = 8.3, 6.5 Hz), and 3.13−3.03 (m, 2H); and $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 147.8, 146.9, 135.2, 130.0, 129.1, 128.3, 127.5, 122.5, 120.4, 109.5, 108.4, 101.1, 42.0, and 40.1.

3-(Furan-2-yl)-phenylpropanenitrile[8b] ***(3f)***. Pale yellow oil; 28 mg (56%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40−7.31 (m, 4H), 7.30−7.27 (m, 2H), 6.29 (dd, 1H, J = 3.1, 2.0 Hz), 6.11 (d, 1H, J = 3.4 Hz), 4.15 (dd, 1H, J = 8.5, 6.6 Hz), and 3.30−3.13 (m, 2H); and $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 150.0, 142.2, 134.9, 129.1, 128.4, 127.3, 120.1, 110.5, 108.2, 37.1, and 34.7.

2-(4-Methoxyphenyl)-3-phenylpropanenitrile[8d] ***(3g)***. White Solid; 53 mg (90%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.29−7.25 (m, 3H), 7.17−7.12 (m, 4H), 6.87 (d, 2H, J = 8.6 Hz), 3.95 (dd, 1H, J = 8.2, 6.6 Hz), 3.80 (s, 3H), and 3.19−3.08 (m, 2H); and $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 159.5, 136.4, 129.3, 128.7, 128.6, 127.3, 127.3, 120.6, 114.4, 55.4, 42.3, and 39.0.

2-(Benzo[d][1,3]dioxol-5-yl)-3-phenylpropanenitrile[8f] ***(3h)***. Colorless oil; 49 mg (78%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32−7.26 (m, 3H), 7.15−7.13 (m, 2H), 6.76−6.75 (m, 2H), 6.69 (dd, 1H, J = 8.1, 1.7 Hz), 5.98 (s, 2H), 3.90 (dd, 1H, J = 8.2, 6.5 Hz), and 3.19−3.07 (m, 2H); and $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 148.2, 147.6, 136.3, 129.2, 128.9, 128.7, 127.4, 121.0, 120.4, 108.6, 107.9, 101.4, 42.3, and 39.5.

2-(4-Fluorophenyl)-3-phenylpropanenitrile[8f] ***(3i)***. White solid; 42 mg (75%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.31−7.26 (m, 3H), 7.21−7.19 (m, 2H), 7.10 (dd, 2H, J = 7.6, 1.5 Hz), 7.03 (t, 2H, J = 8.6 Hz), 3.99 (dd, 1H, J = 7.8, 6.9 Hz), and 3.21−3.09 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 162.5 (d, J_{C-F} = 247.5 Hz), 135.9, 131.0 (d, J_{C-F} = 6.0 Hz), 129.3 (d, J_{C-F} = 6.0 Hz), 129.2, 128.7, 127.5, 120.2, 116.0 (d, J_{C-F} = 21.8 Hz), 42.2, and 39.0; and ^{19}F NMR (283 MHz, $CDCl_3$): δ −113.4.

2-(4-Chlorophenyl)-3-phenylpropanenitrile[8d] ***(3j)***. White Solid; 42 mg (70%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33−7.25 (m, 5H), 7.16 (d, 2H, J = 8.5 Hz), 7.10 (dd, 2H, J = 7.6, 1.7 Hz), 3.99 (dd, 1H, J = 7.8, 6.8 Hz), and 3.21−3.08 (m, 2H); and $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 134.7, 133.2, 132.5, 128.1, 128.1, 127.8, 127.6, 126.4, 118.8, 40.9, and 38.1.

3-Phenyl-2-(3-(trifluoromethyl)phenyl)propanenitrile ***(3k)***. Colorless oil; 38 mg (55%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.60 (d, 1H, J = 7.7 Hz), 7.49(t, 1H, J = 8.0 Hz), 7.46−7.44 (m, 2H), 7.32−7.28 (m, 3H), 7.11 (dd, 2H, J = 7.4, 1.8 Hz), 4.08 (dd, 1H, J = 8.1, 6.5 Hz), and 3.25−3.13 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 136.2, 135.5, 131.5 (q, J_{C-F} = 33.1 Hz), 130.9, 129.6, 129.2, 128.8, 127.7, 125.9 (q, J_{C-F} = 272.0 Hz), 125.2 (d, J_{C-F} = 3.7 Hz), 124.5 (d, J_{C-F} = 3.7 Hz), 119.6, 42.0, and 39.6; ^{19}F NMR (283 MHz, $CDCl_3$):

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δ −62.6; HRMS (ESI+): m/z $[M]^+$ calcd for $C_{16}H_{12}NF_3$, 275.0922; found 275.0912.

4-(Benzyl-cyano-methyl)-benzonitrile (**3l**). White solid; 33 mg (57%); m.p. 84 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65 (d, 2H, J = 8.4 Hz), 7.34 (d, 2H, J = 8.4 Hz), 7.30-7.27 (m, 3H,), 7.07 (dd, 2H, J = 7.0, 2.3 Hz), 4.08 (t, 1H, J = 7.2 Hz), and 3.19 (ddd, 2H, J = 20.3, 13.6, 7.2 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 140.2, 135.2, 132.8, 129.2, 128.8, 128.5, 127.8, 119.2, 118.1, 112.6, 41.8, and 39.7; HRMS (ESI+): m/z $[M]^+$ calcd for $C_{16}H_{13}N_2$, 233.1073; found 233.1077.

3-Phenyl-2-(o-tolyl)propanenitrile[6l] (**3m**). Colorless oil; 39 mg (70%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44−7.42 (m, 1H), 7.33−7.27 (m, 3H), 7.25−7.22 (m, 2H), 7.18−7.16 (m, 3H), 4.15 (dd, 1H, J = 8.9, 6.0 Hz), 3.18−3.06 (m, 2H), and 2.26 (s, 3H); and $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 136.6, 135.1, 133.7, 131.0, 129.1, 128.7, 128.3, 127.7, 127.4, 126.9, 120.7, 41.0, 36.6, and 19.0.

3-Phenyl-2-(pyridin-3-yl)propanenitrile[6c] (**3n**). Colorless solid; 31 mg (60%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.59 (dd, 1H, J = 4.9, 1.5 Hz), 8.46 (d, 1H, J = 2.4 Hz), 7.61−7.55 (m, 1H), 7.35−7.27 (m, 4H), 7.11 (dd, 2H, J = 7.4, 1.8 Hz), 4.06 (t, 1H, J = 7.2 Hz), and 3.26−3.13 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 149.7, 148.9, 135.4, 135.0, 131.0, 129.3, 128.8, 127.8, 123.7, 119.4, 41.9, and 37.3.

2-(Naphthalen-2-yl)-3-phenylpropanenitrile (**3o**). White solid; 46 mg (71%); m.p. 95−96 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.86−7.83 (m, 2H), 7.81−7.79 (m, 1H), 7.73 (d, 1H, J = 1.3 Hz), 7.51 (dd, 2H, J = 6.1, 3.2 Hz), 7.35 (dd, 1H, J = 8.5, 1.8 Hz), 7.31-7.26 (m, 3H), 7.16 (dd, 2H, J = 7.6, 1.8 Hz), 4.17 (dd, 1H, J = 8.2, 6.5 Hz), and 3.30−3.21 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 136.3, 133.3, 132.9, 132.5, 129.3, 129.0, 128.7, 127.9, 127.8, 127.5, 126.7, 126.7, 126.6, 125.0, 120.4, 42.2, and 40.0; HRMS (ESI+): m/z $[M]^+$ calcd for $C_{19}H_{15}N$, 257.1204; found 257.1212.

2,3-bis(Benzo[d][1,3]dioxol-5-yl)propanenitrile (**3p**). Colorless oil; 44 mg (60%); m.p. 64−66 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.69 (dd, 3H), 6.62−6.58 (m, 2H), 5.98 (s, 2H), 5.95 (s, 2H), 3.85 (dd, 1H, J = 8.2, 6.6 Hz), and 3.09−2.99 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 148.2, 147.8, 147.6, 146.9, 129.9, 128.8, 122.5, 121.0, 120.4, 109.5, 108.6, 108.4, 107.9, 101.4, 101.1, 42.0, and 39.7; HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{17}H_{13}NNaO_4$, 318.0737; found 318.0735.

2-(4-Methoxyphenyl)-3-(p-tolyl)propanenitrile[8d] (**3q**). Colorless oil; 50 mg (80%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.17 (d, 2H, J = 8.7 Hz), 7.10 (d, 2H, J = 7.9 Hz), 7.02 (d, 2H, J = 8.0 Hz), 6.87 (d, 2H, J = 8.6 Hz), 3.92 (dd, 1H, J = 8.3, 6.5 Hz), 3.81 (s, 3H), 3.15−3.04 (m, 2H), and 2.32 (s, 3H); and $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 159.4, 137.0, 133.4, 129.3, 129.1, 128.7, 127.4, 120.7, 114.4, 55.4, 41.9, 39.2, and 21.1.

2-(4-Methoxyphenyl)-3-(o-tolyl)propanenitrile (**3r**). Colorless oil; 36 mg (57%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.22−7.08 (m, 6H), 6.87 (d, 2H, J = 8.6 Hz), 3.91 (dd, 1H, J = 8.5, 6.6 Hz), 3.81 (s, 3H), 3.23−3.07 (m, 2H), and 2.22 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 159.5, 136.3, 134.8, 130.6, 130.1, 128.6, 127.5, 126.3, 120.8, 114.4, 55.4, 39.6, 38.0, and 19.3; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{17}H_{18}NO$, 252.1382; found 252.1374.

3-(4-Isopropylphenyl)-2-(4-methoxyphenyl)-phenylpropanenitrile[8d] (**3s**). White solid; 55 mg (79%); m.p. 67−69 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.19 (d, 2H, J = 8.7 Hz), 7.16 (d, 2H, J = 8.1 Hz), 7.08 (d, 2H, J = 8.1 Hz), 6.88 (d, 2H, J = 8.7 Hz), 3.92 (dd, 1H, J = 8.7, 6.2 Hz), 3.81 (s, 3H), 3.15−3.04 (m, 2H), 2.93−2.84 (m, 1H), and 1.24 (d, 6H, J = 6.9 Hz); and $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 159.4, 148.0, 133.8, 129.1, 128.6, 127.5, 126.7, 120.8, 114.4, 55.4, 42.0, 39.2, 33.8, and 24.0.

3-(Furan-2-yl)-2-(4-methoxyphen-yl)propanenitrile (**3t**). Colorless oil; 28 mg (50%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38−7.32 (m, 1H), 7.19 (d, 2H, J = 8.7 Hz), 6.88 (d, 2H, J = 8.6 Hz), 6.29 (dd, 1H, J = 3.1, 1.9 Hz), 6.11 (d, 1H, J = 3.7 Hz), 4.09 (dd, 1H, J = 8.3, 6.7 Hz), 3.81 (s, 3H), and 3.27−3.10 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 159.6, 150.1, 142.1, 128.4, 126.9, 120.4, 114.5, 110.5, 108.2, 55.4, 36.3, and 34.8; HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{14}H_{13}NNaO_2$, 250.0838; found 250.0840.

3-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)propanenitrile (**3u**). Pale yellow oil; 68 mg (92%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.18(d, 2H, J = 8.7 Hz), 6.88 (d, 2H, J = 8.6 Hz), 6.36 (t, 2H, J = 2.2 Hz), 6.28 (d, 2H, J = 2.3 Hz), 3.94 (dd, 1H, J = 8.3, 6.5 Hz), 3.81 (s, 3H), 3.74 (s, 6H), and 3.13−3.01 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 160.9, 159.5, 138.7, 128.7, 127.3, 120.7, 114.4, 107.3, 99.49, 55.4, 55.3, 42.6, and 38.8; HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{18}H_{19}NNaO_3$, 320.1257; found 320.1256.

2-(4-Methoxyphenyl)-3-(naphthal-en-2-yl)propanenitrile[8d] (**3v**). Pale yellow oil; 63 mg (88%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.84−7.80 (m, 1H), 7.77 (d, 2H, J = 8.0 Hz), 7.60 (s, 1H), 7.49−7.43 (m, 2H), 7.23 (dd, 1H, J = 8.3, 1.8 Hz), 7.18 (d, 2H, J = 8.7 Hz), 6.86 (d, 2H, J = 8.6 Hz), 4.05 (dd, 1H, J = 8.1, 6.7 Hz), 3.80 (s, 3H), and 3.36−3.24 (m, 2H); and $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 159.5, 133.9, 133.4, 132.6, 128.7, 128.3, 128.2, 127.8, 127.7, 127.2, 126.2, 125.9, 120.7, 114.4, 55.4, 42.5, and 39.0.

2-(4-Methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)-propanenitrile[8d] (**3w**). Colorless oil; 55 mg (72%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.55 (d, 2H, J = 8.1 Hz), 7.23 (d, 2H, J = 8.1 Hz), 7.15 (d, 2H, J = 8.7 Hz), 6.88 (d, 2H, J = 8.6 Hz), 3.9 (t, 1H, J = 7.5 Hz), 3.81 (s, 3H), and 3.24−3.15 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 159.6, 140.2, 129.7, 128.6, 126.5, 125.6 (q, J_{C-F} = 3.7 Hz), 124.1 (q, J_{C-F} = 270.0 Hz), 120.2, 114.5, 55.4, 41.9, and 38.6; and ^{19}F NMR (283 MHz, $CDCl_3$): δ −62.4.

2-(4-Methoxyphenyl)hept-6-enenitrile (**3x**). Colorless oil; 44 mg (82%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.23 (d, 2H, J = 8.6 Hz), 6.90 (d, 2H, J = 8.6 Hz), 5.75 (ddt, 1H, J = 16.9, 10.1, 6.7 Hz), 5.07−4.89 (m, 2H), 3.81 (s, 3H) 3.73 (dd, 1H, J = 8.2, 6.5 Hz), 2.09 (q, 2H, J = 7.1 Hz), 1.96−1.76 (m, 2H), and 1.63−1.45 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 159.4, 137.6, 128.4, 127.9, 121.1, 115.4, 114.5, 55.4, 36.5, 35.3, 33.0, and 26.1; HRMS (ESI+): m/z $[M]^+$ calcd for $C_{14}H_{18}NO$, 216.1383; found 216.1388.

2-(4-Methoxyphenyl)tetradecanenitrile (**3y**). Colorless oil; 75 mg (95%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.23 (d, 2H, J = 8.7 Hz), 6.90 (d, 2H, J = 8.6 Hz), 3.81 (s, 3H), 3.71 (dd, 1H, J = 8.5, 6.3 Hz), 1.93−1.78 (m, 2H), 1.50−1.37 (m, 2H), 1.30−1.25 (m, 18H), and 0.88 (t, 3H, J = 6.9 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 158.4, 127.5, 127.3, 120.3, 113.5, 54.5, 35.7, 35.1, 31.0, 28.8, 28.7, 28.6, 28.5, 28.5, 28.1, 26.1, 21.8, and 13.2; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{21}H_{34}NO$, 316.2635; found 316.2631.

2-(4-Methoxyphenyl)tridecanenitrile (**3z**). Colorless oil; 64 mg (85%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.23 (d, 2H, J = 8.7 Hz), 6.90 (d, 2H, J = 8.8 Hz), 3.81 (s, 3H), 3.71 (dd, 1H, J = 8.5, 6.4 Hz), 1.93−1.78 (m, 2H), 1.50−1.37 (m, 2H), 1.31−1.25 (m, 16H), and 0.88 (t, 3H, J = 6.9 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 159.4, 128.4, 128.2, 121.3, 114.5, 55.4, 36.7, 36.0, 32.0, 29.7, 29.7, 29.6, 29.4, 29.0, 29.0, 27.1, 22.8, and 14.2; HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{20}H_{31}NNaO$, 324.2297; found 324.2289.

2-(4-Methoxyphenyl)undecanenitrile[8d] (**3aa**). Colorless oil; 62 mg (91%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.23 (d, 2H, J = 8.7 Hz), 6.90 (d, 2H, J = 8.8 Hz), 3.81 (s, 3H), 3.71 (dd, 1H, J = 8.5, 6.3 Hz), 1.93−1.78 (m, 2H), 1.50−1.37 (m, 2H), 1.30−1.25 (m, 12H), and 0.88 (t, 3H, J = 6.9 Hz); and $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 159.3, 128.4, 128.1, 121.2, 114.4, 55.4, 36.6, 36.0, 31.9, 29.5, 29.3, 29.3, 29.0, 27.0, 22.7, and 14.1.

2-(4-Methoxyphenyl)decanenitrile (**3ab**). Colorless oil; 58 mg (90%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.23 (d, 2H, J = 8.7 Hz), 6.90 (d, 2H, J = 8.7 Hz), 3.81 (s, 3H), 3.71 (dd, 1H, J = 8.3, 6.5 Hz), 1.93−1.78 (m, 2H), 1.51−1.38 (m, 2H), 1.30−1.25 (m, 10H), and 0.87 (t, 3H, J = 6.8 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 159.3, 128.4, 128.1, 121.2, 114.4, 55.4, 36.6, 36.0, 31.8, 29.3, 29.2, 29.0, 27.0, 22.6, and 14.1; HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{17}H_{25}NNaO$, 282.1828; found 282.1824.

2-(4-Methoxyphenyl)hexanenitrile[8d] (**3ac**). Colorless oil; 45 mg (88%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.24 (d, 2H, J = 8.7 Hz), 6.90 (d, 2H, J = 8.8 Hz), 3.81 (s, 3H), 3.71 (dd, 1H, J = 8.5, 6.4 Hz), 1.94−1.79 (m, 2H), 1.47−1.31 (m, 4H), and 0.90 (t, 3H, J = 7.2 Hz); and $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 158.2, 127.3, 127.0, 120.1, 113.3, 54.3, 35.5, 34.6, 28.0, 21.0, and 12.7.

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2-(4-Methoxyphenyl)butanenitrile[8d] ***(3ad)***. Colorless oil; 35 mg (79%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.24 (d, 2H, J = 8.5 Hz), 6.90 (d, 2H, J = 8.8 Hz), 3.81 (s, 3H), 3.68 (dd, 1H, J = 7.8, 6.6 Hz), 1.95−1.87 (m, 2H), and 1.06 (t, 3H, J = 7.4 Hz); and ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 159.3, 128.4, 127.8, 121.0, 114.4, 55.4, 38.2, 29.3, and 11.5.

2-(4-Methoxyphenyl)propanenitrile[8a] ***(3ae)***. Yellowish oil; 33 mg (80%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.28−7.25 (m, 2H), 6.93−6.88 (m, 2H), 3.85 (q, 1H, J = 7.3 Hz), 3.81 (s, 3H), and 1.62 (d, 3H, J = 7.1 Hz); and ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 159.4, 129.1, 127.9, 121.8, 114.5, 55.4, 30.5, and 21.5.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01822.

Copies of the ^{1}H, ^{13}C{^{1}H}, and ^{19}F NMR spectra for all product copies of the ^{1}H NMR spectra for the deuterium labeling experiments (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Mowry, D. T. The Preparation of Nitriles. *Chem. Rev.* **1948**, *42*, 189−283. (b) López, R.; Palomo, C. Cyanoalkylation: Alkylnitriles in Catalytic C−C Bond-Forming Reactions. *Angew. Chem., Int. Ed.* **2015**, *54*, 13170−13184. (c) Kurono, N.; Ohkuma, T. Catalytic Asymmetric Cyanation Reactions. *ACS Catal.* **2016**, *6*, 989−1023.

(2) Hartwig, J. *Organotransition Metal Chemistry: From Bonding to Catalysis*; University Science Books, 2009.

(3) (a) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Organic Reactions*; John Wiley & Sons, Inc: New York, 1984. (b) Taber, D. F.; Kong, S. Alkylation of Acetonitrile. *J. Org. Chem.* **1997**, *62*, 8575−8576.

(4) For reviews on borrowing hydrogen (BH) methodology, see: (a) Guillena, G.; Ramln, D. J.; Yus, M. Hydrogen Autotransfer in the N-Alkylation of Amines and Related Compounds using Alcohols and Amines as Electrophiles. *Chem. Rev.* **2010**, *110*, 1611−1641. (b) Gunanathan, C.; Milstein, D. Applications of Acceptorless Dehydrogenation and Related Transformations in Chemical Synthesis. *Science* **2013**, *341*, No. 1229712. (c) Crabtree, R. H. Homogeneous Transition Metal Catalysis of Acceptorless Dehydrogenative Alcohol Oxidation: Applications in Hydrogen Storage and to Heterocycle Synthesis. *Chem. Rev.* **2017**, *117*, 9228−9246. (d) Alig, L.; Fritz, M.; Schneider, S. First-Row Transition Metal (De)-Hydrogenation Catalysis Based On Functional Pincer Ligands. *Chem. Rev.* **2019**, *119*, 2681−2751. (e) Irrgang, T.; Kempe, R. 3d-Metal Catalyzed N- and C-Alkylation Reactions via Borrowing Hydrogen or Hydrogen Autotransfer. *Chem. Rev.* **2019**, *119*, 2524−2549. (f) Ai, W.; Zhong, R.; Liu, X.; Liu, Q. Hydride Transfer Reactions Catalyzed by Cobalt Complexes. *Chem. Rev.* **2019**, *119*, 2876−2953. (g) Junge, K.; Papa, V.; Beller, M. Cobalt−Pincer Complexes in Catalysis. *Chem. - Eur. J.* **2019**, *25*, 122−143.

(5) For selective examples on BH methodology, see: (a) Zhang, G.; Hanson, S. K. Cobalt-Catalyzed Acceptorless Alcohol Dehydrogenation: Synthesis of Imines from Alcohols and Amines. *Org. Lett.* **2013**, *15*, 650−653. (b) Mukherjee, A.; Nerush, A.; Leitus, G.; Shimon, L. J. W.; Ben-David, Y.; Espinosa Jalapa, N. A.; Milstein, D. Manganese-Catalyzed Environmentally Benign Dehydrogenative Coupling of Alcohols and Amines to Form Aldimines and H_2: A Catalytic and Mechanistic Study. *J. Am. Chem. Soc.* **2016**, *138*, 4298−4301. (c) Elangovan, S.; Neumann, J.; Sortais, J.-B.; Junge, K.; Darcel, C.; Beller, M. Efficient and selective N-alkylation of amines with alcohols catalysed by manganese pincer complexes. *Nat. Commun.* **2016**, *7*, No. 12641. (d) Rösler, S.; Ertl, M.; Irrgang, T.; Kempe, R. Cobalt-Catalyzed Alkylation of Aromatic Amines by Alcohols. *Angew. Chem., Int. Ed.* **2015**, *54*, 15046−15050. (e) Yan, T.; Feringa, B. L.; Barta, K. Iron catalysed direct alkylation of amines with alcohols. *Nat. Commun.* **2014**, *5*, No. 5602. (f) Samuelsen, S.; Santilli, C.; Ahlquist, M. S. G.; Madsen, R. Development and mechanistic investigation of the manganese(III) salen-catalyzed dehydrogenation of alcohols. *Chem. Sci.* **2019**, *10*, 1150−1157.

(6) For selective examples, see: (a) Li, F.; Zou, X.; Wang, N. Direct Coupling of Arylacetonitriles and Primary Alcohols to α-Alkylated Arylacetamides with Complete Atom Economy Catalyzed by a Rhodium Complex-Triphenylphosphine-Potassium Hydroxide System. *Adv. Synth. Catal.* **2015**, *357*, 1405−1415. (b) Li, J.; Liu, Y.; Tang, W.; Xue, D.; Li, C.; Xiao, J.; Wang, C. Atmosphere-Controlled Chemoselectivity: Rhodium-Catalyzed Alkylation and Olefination of Alkylnitriles with Alcohols. *Chem. - Eur. J.* **2017**, *23*, 14445−14449. (c) Löfberg, C.; Grigg, R.; Whittaker, M. A.; Keep, A.; et al. Efficient Solvent-Free Selective Monoalkylation of Arylacetonitriles with Mono-, Bis-, and Tris-primary Alcohols Catalyzed by a Cp*Ir Complex. *J. Org. Chem.* **2006**, *71*, 8023−8027. (d) Morita, M.; Obora, Y.; Ishii, Y. Alkylation of active methylene compounds with alcohols catalyzed by an iridium complex. *Chem. Commun.* **2007**, 2850−2852. (e) Buil, M. L.; Esteruelas, M. A.; Herrero, J.; Izquierdo, S.; Pastor, I. M.; Yus, M. Osmium Catalyst for the Borrowing Hydrogen Methodology: α-Alkylation of Arylacetonitriles and Methyl Ketones. *ACS Catal.* **2013**, *3*, 2072−2075. (f) Motokura, K.; Nishimura, D.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. A. A Ruthenium-Grafted Hydrotalcite as a Multifunctional Catalyst for Direct α-Alkylation of Nitriles with Primary Alcohols. *J. Am. Chem. Soc.* **2004**, *126*, 5662−5663. (g) Corma, A.; Ródenas, T.; Sabater, M. J. Monoalkylations with alcohols by a cascade reaction on bifunctional solid catalysts: Reaction kinetics and mechanism. *J. Catal.* **2011**, *279*, 319−327.

(7) Bullock, R. M. *Catalysis Without Precious Metals*; Wiley-VCH: Weinheim, 2010.

(8) For Co case, see: (a) Liu, Z.; Yang, Z.; Yu, X.; Zhang, H.; Yu, B.; Zhao, Y.; Liu, Z. Methylation of C(sp^3)−H/C(sp^2)−H Bonds with Methanol Catalyzed by Cobalt System. *Org. Lett.* **2017**, *19*, 5228−5231. For Fe case, see: (b) Ma, W.; Cui, S.; Sun, H.; Tang, W.; Xue, D.; Li, C.; Fan, J.; Xiao, J.; Wang, C. Iron-Catalyzed Alkylation of Nitriles with Alcohols. *Chem. - Eur. J.* **2018**, *24*, 13118−13123. For Mn cases, see: (c) Chakraborty, S.; Das, U. K.; Ben-David, Y.; Milstein, D. Manganese Catalyzed α-Olefination of Nitriles by Primary Alcohols. *J. Am. Chem. Soc.* **2017**, *139*, 11710−11713. (d) Jana, A.; Reddy, C. B.; Maji, B. Manganese Catalyzed α-Alkylation of Nitriles with Primary Alcohols. *ACS Catal.* **2018**, *8*, 9226−9231. (e) Borghs, J. C.; Tran, M. A.; Sklyaruk, J.; Rueping, M.; Osama El-Sepelgy, O. Sustainable Alkylation of Nitriles with Alcohols by

Manganese Catalysis. *J. Org. Chem.* **2019**, *84*, 7927−7935. For Ni case, see: (f) Bera, S.; Bera, A.; Banerjee, D. Nickel-catalyzed hydrogen-borrowing strategy: chemo-selective alkylation of nitriles with alcohols. *Chem. Commun.* **2020**, *56*, 6850−6853. For a very recent case with secondary alcohols mediated by a Co catalyst, see: (g) Chakraborty, P.; Garg, N.; Manoury, E.; Poli, R.; Sundararaju, B. C-Alkylation of Various Carbonucleophiles with Secondary Alcohols under Co^{III}-Catalysis. *ACS Catal.* **2020**, *10*, 8023−8031.

(9) Roy, B. C.; Ansari, I. A.; Samim, S. A.; Kundu, S. Base-Promoted α-Alkylation of Arylacetonitriles with Alcohols. *Chem. Asian J.* **2019**, *14*, 2215−2219.

(10) (a) Xu, S.; Alhthlol, L. M.; Paudel, K.; Reinheimer, E.; Tyer, D. L.; Taylor, D. K.; Smith, A. M.; Holzmann, J.; Lozano, E.; Ding, K. Tripodal N,P Mixed-Donor Ligands and Their Cobalt Complexes: Efficient Catalysts for Acceptorless Dehydrogenation of Secondary Alcohols. *Inorg. Chem.* **2018**, *57*, 2394−2397. (b) Paudel, K.; Pandey, B.; Xu, S.; Taylor, D. K.; Tyer, D. L.; Torres, C. L.; Gallagher, S.; Kong, L.; Ding, K. Cobalt-Catalyzed Acceptorless Dehydrogenative Coupling of Primary Alcohols to Esters. *Org. Lett.* **2018**, *20*, 4478−4481. (c) Pandey, B.; Xu, S.; Ding, K. Selective Ketone Formations via Cobalt-Catalyzed β-Alkylation of Secondary Alcohols with Primary Alcohols. *Org. Lett.* **2019**, *21*, 7420−7423.

(11) We cannot exclude the possibility that the α,β-unsaturated nitrile is not in the free form but coordinates to the metal center. See the recent DFT study: Luque-Urrutia, J. A.; Solà, M.; Milstein, D.; Poater, A. Mechanism of the Manganese-Pincer-Catalyzed Acceptorless Dehydrogenative Coupling of Nitriles and Alcohols. *J. Am. Chem. Soc.* **2019**, *141*, 2398−2403.

(12) For selective examples, see: (a) Walling, C.; Bollyky, L. Homogeneous Hydrogenation in the Absence of Transition-Metal Catalysts. *J. Am. Chem. Soc.* **1964**, *86*, 3750−3752. (b) Berkessel, A.; Schubert, T. J. S.; Müller, T. N. Hydrogenation without a Transition-Metal Catalyst: On the Mechanism of the Base-Catalyzed Hydrogenation of Ketones. *J. Am. Chem. Soc.* **2002**, *124*, 8693−8698. (c) Polshettiwar, V.; Varma, R. S. Revisiting the Meerwein−Ponndorf−Verley reduction: a sustainable protocol for transfer hydrogenation of aldehydes and ketones. *Green Chem.* **2009**, *11*, 1313−1316. (d) Duali, A.; Majoral, J.; Caminade, A.; Taillefer, M. NaOH-Promoted Hydrogen Transfer: Does NaOH or Traces of Transition Metals Catalyze the Reaction? *ChemCatChem* **2009**, *1*, 504−509. (e) Bauer, H.; Alonso, M.; Färber, C.; Elsen, H.; Pahl, J.; Causero, A.; Ballmann, G.; Proft, F. D.; Harder, S. Imine hydrogenation with simple alkaline earth metal catalysts. *Nat. Catal.* **2018**, *1*, 40−47.

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