■ **Catalysis**
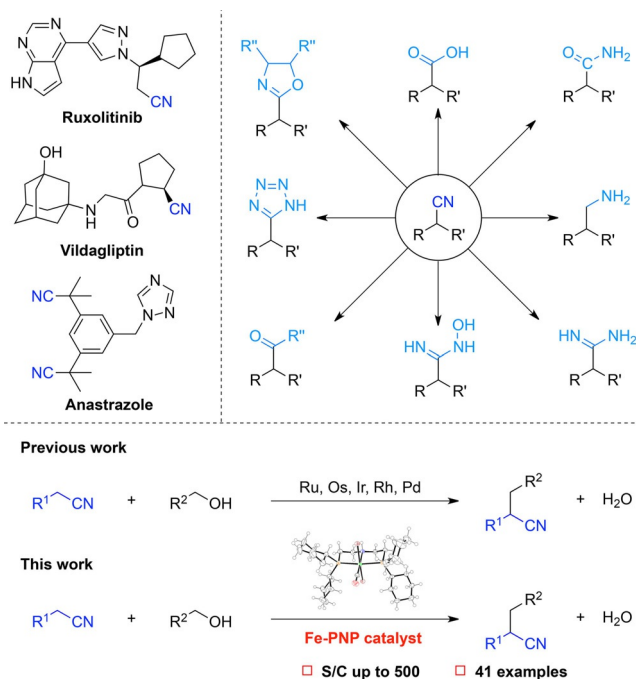
Iron-Catalyzed Alkylation of Nitriles with Alcohols

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Abstract: A general, efficient iron-catalyzed α-alkylation of nitriles with primary alcohols through a hydrogen-borrowing pathway has been developed, allowing a wide variety of alkylated nitriles to be readily accessible. Detailed mechanistic studies suggest that the reaction proceeds via an olefin intermediate with the turnover rate limited by the hydrogenation of the olefin with an iron hydride. Apart from participating in the alkylation, the nitrile is found to play an important role in promoting the formation of and stabilizing the active catalytic species.

Nitriles are versatile building blocks in organic synthesis. They can be easily transformed into a plethora of compounds, for example, amides, carboxylic acids, ketones, and oxazolines (Scheme 1).[1] Moreover, there are many drugs and natural products containing cyano groups.[2] Amongst the methods for the synthesis of nitrile compounds, the α-alkylation of alkyl nitriles with alcohols through a hydrogen-borrowing or hydrogen auto-transfer strategy[3] provides an environmentally benign route, with water as the only by-product. Transition-metal complexes, including Ru,[4] Os,[5] Rh,[6] Ir[7] and Pd,[8] have been reported to be effective catalysts for this reaction. Despite the progress, the replacement of noble-metal catalysts with those derived from earth-abundant base metals is attractive because it offers additional economic and ecological benefits.[9] Recently, Milstein and co-workers reported a remarkable example of Mn-catalyzed α-olefination of nitriles with alcohols through acceptorless dehydrogenation.[10] However, to the best of our knowledge, the α-alkylation of nitriles with alcohols catalyzed by base metals has not been reported. Here, we present the first examples of iron-catalyzed α-alkylation of nitriles with primary alcohols through a hydrogen-borrowing strategy (Scheme 1). The iron pincer catalyst showed even better per-

Scheme 1. The importance of nitrile compounds and past/present work on α-alkylation of nitriles with alcohols.

formance than some of the noble-metal catalysts in terms of substrate scope and catalytic activity.

Iron pincer complexes with PNP ligands have proven to be efficient catalysts for dehydrogenation[11] and hydrogenation[12] of a range of substrates. The dehydrogenation and hydrogenation abilities of these complexes render them possible candidates for hydrogen-borrowing catalysts. However, iron complexes,[9] and particularly the pincer variants,[9e] have rarely been used as catalysts in hydrogen-borrowing reactions. With these observations in mind, we examined Fe-PNP complexes for the alkylation of nitriles with alcohols, a reaction requiring both dehydrogenation and hydrogenation abilities of the catalyst.

Iron complexes **1–4** were prepared and initially examined as catalyst candidates for the model alkylation of phenylacetonitrile (**6**) with 4-methylbenzyl alcohol (**5**) (Scheme 2). After screening a variety of conditions including complexes **1–4** and other metal compounds (see the Supporting Information for details), complex **3**, with cyclohexyl substituents on the phosphorus atoms, was found to be most effective in catalyzing the model reaction. Thus, under the catalysis of **3** (1 mol%) in the presence of the activating NaBHEt₃ (2 mol%) and NaOH

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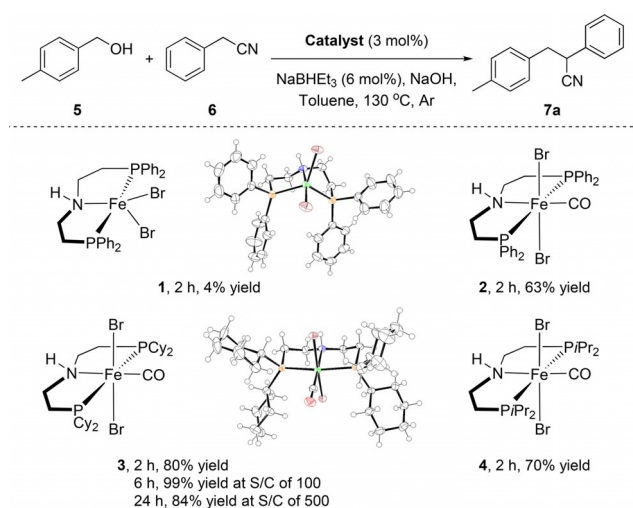
Scheme 2. Fe-PNP complexes catalyzed the α-alkylation of nitriles with primary alcohols and the X-ray structures of **1** and **3**. See the Supporting Information for detailed conditions.

(1 equivalent), **7a** was obtained in an NMR yield of 99% in toluene at 130 °C under Ar in 6 h, and the substrate-to-catalyst ratio could be raised to 500 (Scheme 2). Slightly lower activities were observed by replacing the cyclohexyl substituents of **3** with phenyl (**2**) or isopropyl (**4**) variants. Complex **1**, without the CO ligand, was essentially inactive. The molecular structures of **1** and **3** were confirmed by single-crystal X-ray diffraction.

With the optimized reaction conditions in hand, the scope of the alkylation reaction was explored (Scheme 3). The α-alkylation of **6** with various alcohols was first examined with **3** as the catalyst (1 mol%), NaBHEt$_3$ (2 mol%) as the activating agent and NaOH as the base (1 equivalent). In general, both benzylic and aliphatic alcohols reacted well to afford the corresponding alkylated products in good to excellent yields. For benzylic alcohols, electron-donating substituents tend to impart slightly better activity than electron-withdrawing ones (**7a**–**7k**), and good yields were still obtained for sterically bulky substrates (**7d**, **7e**). The presence of a morpholine moiety on the phenyl ring of benzyl alcohol was tolerated (**7k**). Aliphatic alcohols generally gave lower yields of the desired α-alkylated products (**7l**–**7v**) and further optimization of reaction conditions was required in some cases (**7l**, **7m**, **7n**, **7t**). Despite extensive effort of optimization, the yield for the reaction of methanol with 2-naphthylacetonitrile was only 26% (**7l**); however, significantly higher yields were obtained with longer chain aliphatic alcohols (**7m**–**7o**). Interestingly, complex **2** gave better results than **3** for some of aliphatic alcohols (**7n**, **7t**). These results indicate that fine-tuning of the steric and electronic properties of the catalyst is necessary to suit reactivity of different substrates in hydrogen-borrowing reactions, which require a subtle balance of the dehydrogenation/hydrogenation abilities of the catalyst. Sterically bulkier aliphatic alcohols also reacted (**7p**–**7r**), albeit affording a lower yield in the case of cyclopropylmethanol (**7q**). Notably, both unsaturated and amino alcohols are viable substrates, with the C=C

double bond and the amino unit remaining intact in the product (**7u**–**7v**). The compound **7v** could be hydrolyzed to an amino acid **7w** in high yield (see the Supporting Information), which is a unique gamma-aminobutyric acid derivative and may find applications in biological studies.[13]

The scope of the reaction was further examined by reacting other nitrile compounds with **5** (Scheme 3). A variety of arylacetonitriles containing both electron-withdrawing and electron-donating substituents were successfully alkylated with **5** in good to excellent yields (**8a**–**8g**). 2-(Phenylsulfonyl)acetonitrile was also a viable substrate, and the corresponding product **8h** could be further functionalized.[14] However, aliphatic nitriles, such as acetonitrile and phenylpropanenitrile, gave poor yields in the alkylation reaction (**8i**, **8j**), probably as a result of the high pK_a values of the protons adjacent to the cyano group (pK_a = 31 for acetonitrile vs. 22 for phenylacetonitrile in DMSO).

Another appealing feature of the Fe-catalyzed system is that heterocyclic substrates are well tolerated (Scheme 3). Thus, unprotected indole- (**9a**–**9d**), furan- (**9e**) and pyridine-bearing alcohols (**9f**–**9i**) all proved to be viable. These substrates are problematic even for some noble-metal catalysts.[4–8]

The remarkable ability of the iron complexes in catalyzing the alkylation prompted us to look into the reaction mechanism. Monitoring of the alkylation of **6** with **5** catalyzed by complexes **2**–**4** revealed an olefin intermediate **10** and a kinetic profile typical of a sequential reaction (Scheme 4, see also Scheme 5). Based on the information gained from this scheme and the literature,[4–8] the alkylation is proposed to proceed through the dehydrogenation of **5** to give 4-methylbenzaldehyde, which condenses with **6** under basic conditions to form **10**, hydrogenation of which affords **7a**. Considering that the alkylation is performed under a nitrogen atmosphere, the formation of **10** indicates that hydrogen gas is released. Indeed, hydrogen gas was detected from the head gas of the reaction of **5** with **6** catalyzed by **3** (see section 5.2 in the Supporting Information). Together with the faster initial rates for the formation of **10** than for **7a**, the accumulation of **10** suggests that the turnover rate of the alkylation may be limited by the step of hydrogenation.

The proposed mechanism above is supported by further experiments. Thus, the isolated olefin intermediate **10′** was reduced by benzyl alcohol or H$_2$ under the catalysis of **3**, affording **7b** as expected from the intermediary role of **10′** (see section 5.3 in the Supporting Information). When the alkylation of nitrile **6** by benzyl alcohol is compared with that by α,α-d$_2$-benzyl alcohol, a significant kinetic isotope effect is revealed for the formation of **7b**, but only an insignificant one for that of its olefin intermediate (see section 5.4 in the Supporting Information), corroborating olefin hydrogenation as the rate-limiting step. Interestingly, it is noted that whereas the complexes **2**–**4** show similar initial rates in forming **7a**, **2** appears to be significantly less active in catalyzing the dehydrogenation of **5** from which **7a** results. Thus, the lower alkylation yield observed with **2** in Scheme 2 can be ascribed to its lower activity in alcohol dehydrogenation.
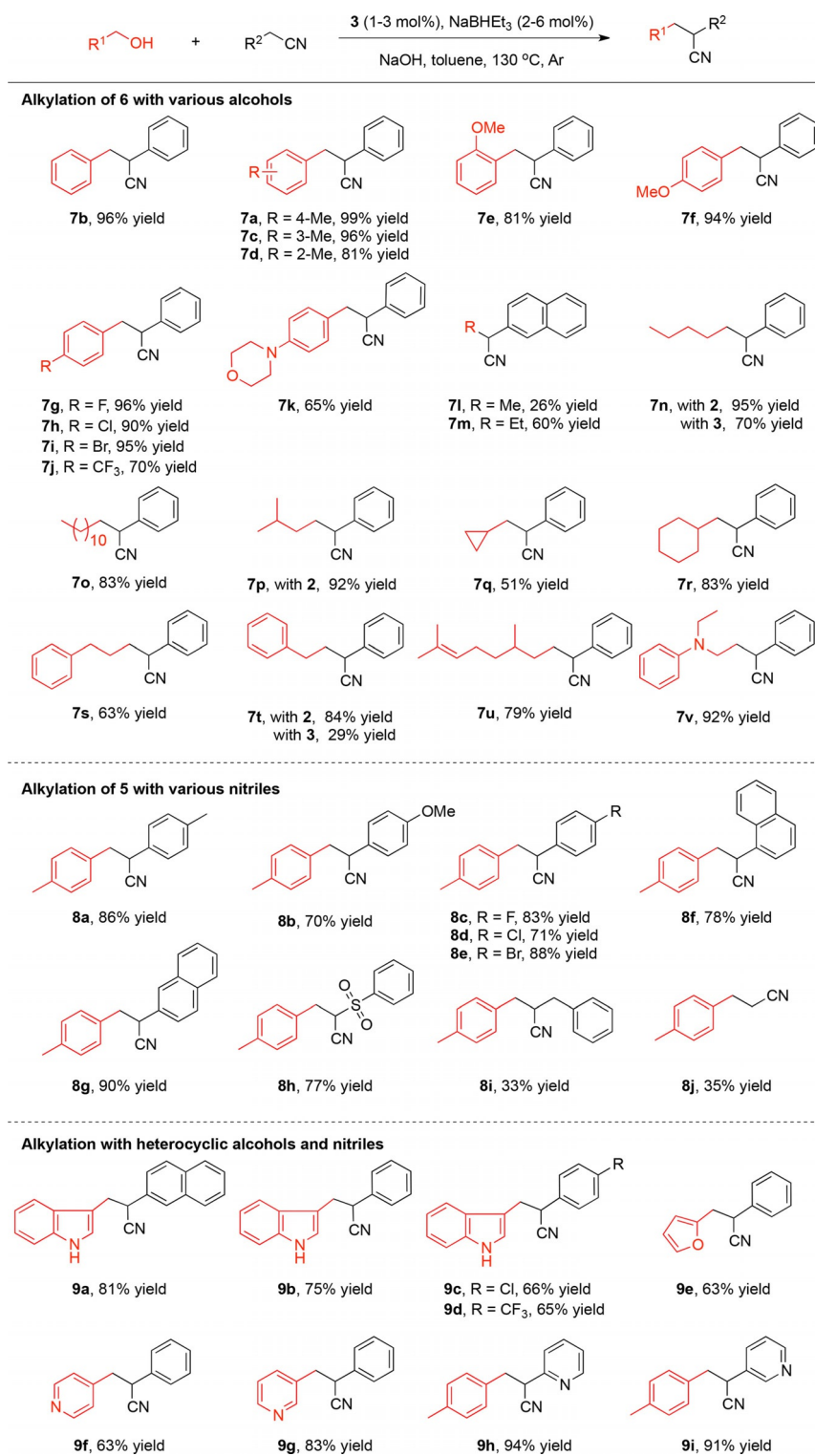
Scheme 3. α-Alkylation of nitriles (black) with primary alcohols (red). See the Supporting Information for detailed conditions.

A key mechanistic question is what happens to the Fe complex during the reaction. Toward this end, we carried out extensive studies by using NMR, IR and HRMS. In the catalytic reaction, the Fe catalyst was first activated by NaBHEt₃. As shown in Scheme S12 (Supporting Information), dissolving **3** in toluene afforded a clear blue solution, which gave an absorp-

tion peak at 1944 cm^{-1} in the IR spectrum, corresponding to the stretching absorption of CO ligand, and a single peak at δ 60.7 ppm in the ^{31}P NMR spectrum. Addition of 2 equiv of NaBHEt₃ to this solution led to an immediate color change from blue to red. In the ^{1}H NMR spectrum, two sets of hydride signals were detected at δ −9.3 ppm (multiplet) and

Scheme 4. Kinetic profiles for the reaction of **5** with **6** catalyzed by the Fe-PNP complexes **2**, **3** and **4**. See the Supporting Information for detailed conditions.

further support for the structures. Thus, the absorptions at 1795 and 1850 cm^{-1} in the IR spectrum (Scheme S12) fit with the previously reported data for CO stretching in **13**,[16] and peaks corresponding to **12** and **13** were detected by HRMS. In addition, HRMS indicated the formation of the species **17**. Clearly, treatment of **3** with NaBHEt$_3$ affords a complex mixture.

More insightful observations were made upon introduction of the substrates. Thus, mixing **3** with NaBHEt$_3$ for 15 min in [D$_8$]toluene followed by addition of alcohol **5** gave rise to only one major hydride peak at δ −23.3 ppm in the ^{1}H NMR spectrum (Scheme S13, Supporting Information); the ^{31}P NMR showed a peak at δ 84.8 ppm. In the IR spectrum, a new CO stretching peak was observed at 1902 cm^{-1} (Scheme S12, Supporting Information). We tentatively attribute these observations to complex **15** resulting from the protonation of **12** by **5** (Scheme 5). However, the corresponding HRMS only showed peaks assignable to **12** and **13**, presumably due to the instability of **15**. Remarkably, introducing the nitrile **6**, instead of alcohol **5**, led to the formation of only one observable species **14**, according to the ^{1}H NMR (δ −19.1 ppm), ^{31}P NMR (δ 86.2 ppm), IR (1920 cm^{-1}) and HRMS ([M+H]$^+$, 667.3595) (see sections 5.5.1–5.5.4 in the Supporting Information).[17] Further ^{1}H NMR, ^{31}P NMR and HRMS experiments confirmed that addition of nitrile **6** to the mixture of complexes **11 a/11 b**, **12**, **13**, **17** and

−25.1 ppm (Scheme S13, Supporting Information); the ^{31}P NMR spectrum showed peaks at δ 106.5, 106.3 and 105.9 ppm. Based on the study of Hazari, Schneider[15] and Jones[11c] and their co-workers, these resonances can be tentatively assigned to the complexes **11 a**, **11 b** and **12** (Scheme 5). The ^{31}P NMR spectrum also revealed a peak at δ 98.0 ppm, assignable to **13**,[15] and a signal from the free ligand. IR and HRMS provided

Scheme 5. Proposed mechanism for the alkylation of nitriles, including various spectroscopically detected species (Ar = p-methylphenyl).

The mechanism of how **13** and **17** are formed is not yet clear. A tentative pathway is shown in Scheme 5. **11 b** may undergo reductive elimination of H_2 to afford a zero-valent complex **16**, disproportionation of which would result in **13** and **17**. The latter is not expected to be stable, decomposing to the free ligand and undefined iron species. On the other hand, the hydride in **11 a/11 b** could be protonated by the neighboring N−H proton, affording **12**. All these species are likely to be in equilibrium, and when **6** (in large excess) is introduced, the equilibria are driven to favoring the formation of **14**.

Based on the studies above and the literature, a proposed mechanism for the alkylation, exemplified by that of **5** with **6**, is shown in Scheme 5. The activation of **3** in toluene with NaBHEt₃ results in the formation of a complex mixture, which is converted into the complex **14** upon introducing **6**, with **14** in equilibrium with **12**. Protonation of the latter with **5** affords **15**, from which β-hydrogen elimination takes place, releasing one molecule of benzaldehyde while generating **11 a**.[11c,d] The benzaldehyde condenses with **6** with the aid of a base to produce the olefin intermediate **10**, which is reduced by **11 a** to give the alkylated product **7 a**, while regenerating **12**. The species involved in the catalytic cycle are probably in equilibrium with each other through the dissociation/association of substrates, aldehydes and H_2. As mentioned, the catalysis appears to be rate-limited by the hydrogenation of **10**. This remains, however, largely hypothetical, without measuring the rate constants and/or calculating the energy barriers of catalytic cycle.

In summary, the first Fe-catalyzed α-alkylation of nitriles with primary alcohols through a hydrogen-borrowing pathway has been developed. The catalytic system shows a broad substrate scope and high activity. Mechanistic studies showed that the reaction proceeds sequentially, involving the intermediary of an olefin. Significantly, the commonly adopted procedure of catalyst activation with boron hydrides leads to a complex mixture of iron species, and it is the nitrile substrate that converts these species into an active hydride catalyst.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

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[17] Further evidence supporting the formation of **14** is found in section 5.5.6, Supporting Information.