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Iron-Catalyzed α-Alkylation of Ketones with Alcohols

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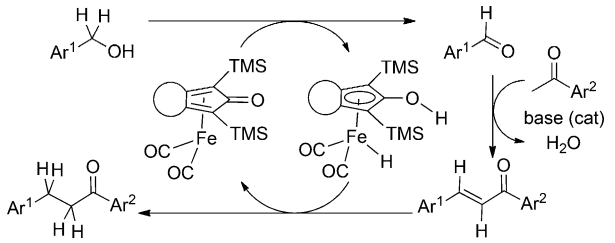
Abstract: *A general and benign iron-catalyzed α-alkylation reaction of ketones with primary alcohols has been developed. The key to success of the reaction is the use of a Knölker-type complex as catalyst (2 mol%) in the presence of Cs_2CO_3 as base (10 mol%) under hydrogen-borrowing conditions. Using 2-aminobenzyl alcohol as alkylation reagent allows for the "green" synthesis of quinoline derivatives.*

The selective α-functionalization of ketones with organohalides in the presence of a base is one of the most fundamental reactions to build up carbon–carbon bonds.[1] This method usually suffers from the use of stoichiometric amount of base, and the use of halides which leads to the formation of (over)stoichiometric amounts of waste. By contrast, owing to their availability and often lower prices, alcohols have emerged as interesting alternative alkylating reagents in the presence of suitable catalysts.[2] More specifically, using the so-called borrowing hydrogen or hydrogen autotransfer strategy,[2,3] an alcohol is dehydrogenated to the corresponding aldehyde or ketone, which in situ reacts with an enolate to form after dehydration the α,β-unsaturated ketone. Finally, this latter product is reduced to the desired alkylated ketone. Notably, in the overall process, the catalyst plays the role of a hydrogen shuttle.

Pioneering results using alcohols as alkylation reagents were reported by Guerbet more than one hundred years ago. In those initial studies, the "self" β-alkylation of primary alcohols proceeded in the presence of copper salts and base.[4] Later on, related catalytic anaerobic dehydrogenative coupling reactions starting from alcohols were reported using different noble metals such as ruthenium,[5] iridium,[6] or palladium.[7] Obviously, in terms of sustainability, such precious transition metals should be substituted by more eco-friendly, inexpensive, and widely abundant first row-based metals.

Among these metals, iron attracts significant attention and is considered as a valuable alternative.[8] In the last decade, iron catalysts have increasingly been used in C–C cross coupling reactions,[9] and especially in reductions.[10] With respect to the catalyst, Knölker-type complexes **1**[11] constitute convenient and stable precursors, which have been used by us and others for hydrogenations and hydrogen transfer reactions,[12] as well as for selective oxidations of alcohols.[13] So far, such complexes have scarcely been used in redox neutral processes. Meanwhile, acceptorless alcohol dehydrogenation reactions were recently described with iron pincer complexes using the so-called MACHO (PNP) ligand.[14] Furthermore, the synthesis of substituted amines by alkylation of the corresponding primary or secondary amines by alcohols was also just reported.[15] Herein, we demonstrate the first iron-catalyzed α-alkylation of ketones with alcohols in the presence of the complex **1** using a hydrogen borrowing strategy (Scheme 1).



Scheme 1. Iron-catalyzed α-alkylation of ketones with alcohols.

Based on the results using Knölker-type catalysts for both reduction and oxidation reactions, and for alkylation of amines,[15] we envisioned that such complexes can promote hydrogen transfer reactions using alcohols as alkylating reagent in the α-functionalization of ketones (Table 1).

Indeed, in a preliminary experiment with acetophenone (1 equiv) and benzylalcohol (1.5 equiv) in the presence of 5 mol% of the complex **1** as the pre-catalyst and 30 mol% of K_2CO_3 at 140 °C, 1,3-diphenylpropan-1-one **5a** was obtained in 55% GC-yield together with 1-phenylethanol **6a** (32% GC-yield), resulting from the reduction of acetophenone, which indicates that hydrogen transfer did occur during the reaction (Table 1, entry 1). When using Cs_2CO_3 (30 mol%) as the base, the reactivity was increased and 62% of the desired α-alkylated product **5a** was obtained after 24 h with 38% of **6a** (Table 1, entry 2; Supporting Information, Table S3). Variation of the nature of the iron complex by substituting one CO ligand by PPh_3 (complex **2**), and acetonitrile (complex **3**), or by modifying the cyclopentadienone ligand (complex **4**) led to active catalysts, but with lower chemoselectivities (yields **5a**/**6a** from 33/18 to 45/30; Table 1, entries 3–5). Notably, the cyclopentadienone motif is crucial for the activity of the catalyst because when $Fe_2(CO)_9$ was used as the precatalyst, no activity was observed even at prolonged reaction time (48 h; Table 1, entry 6). Interestingly, when

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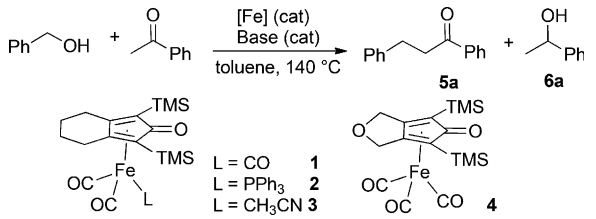
Table 1: Iron-catalyzed α-alkylation of acetophenone with benzylalcohol: Variation of reaction parameters.[a]



Entry	Complex (mol%)	Base (mol%)	*t* [h]	Yield [%] **5a**[b]	Yield [%] **6a**[b]
1	**1** (5)	K_2CO_3 (30)	36	55	32
2	**1**(5)	Cs_2CO_3 (30)	24	62	38
3	**2** (2)	Cs_2CO_3 (10)	24	46	24
4	**3** (2)	Cs_2CO_3 (10)	24	33	18
5	**4** (2)	Cs_2CO_3 (10)	24	45	30
6	$Fe_2(CO)_9$ (5)	Cs_2CO_3 (10)	48	0	0
7	**1**(2)	Cs_2CO_3 (10)	24	61	29
8[c]	**1** (2)	Cs_2CO_3 (10)	24	74	20
9[c]	**2** (2)	Cs_2CO_3 (10)	24	44	10
10[c,d]	**1** (2)	Cs_2CO_3 (10)	24	80	6
11[c,e]	**1** (2)	Cs_2CO_3 (10)	24	0	0
12	**1** (10)	–	24	0	5
13	–	Cs_2CO_3 (15)	24	0	0

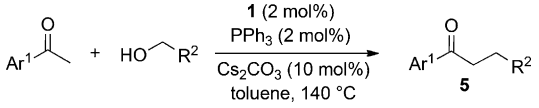
[a] acetophenone (0.5 mmol), benzyl alcohol (0.75 mmol, 1.5 equiv), [Fe] (2–10 mol%), base (10–30 mol%), toluene (1 mL), 140°C. [b] Yields determined by GC analysis. [c] 1.3 equiv of benzyl alcohol was used. [d] 2 mol% of PPh_3 was used as an additive. [e] Reaction under neat conditions at 140°C.

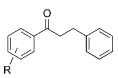
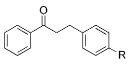
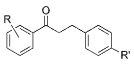
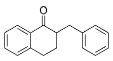
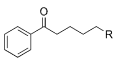
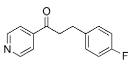
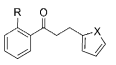
decreasing the catalytic amount of the iron complex **1** (2 mol%) and of the base Cs_2CO_3 (10 mol%) in the presence of 1.5 equiv of benzyl alcohol, 61% of **5a** and 29% of **6a** was obtained (Table 1, entry 7). When lowering the amount of benzyl alcohol to 1.3 equiv, the chemoselectivity was improved notably with a decrease of the amount of 1-phenylethanol **6a**: catalyst **1** (**5a**: 74% and **6a**: 20%) and catalyst **2** (**5a**: 44% and **6a**: 10%) (Table 1, entries 8 and 9 vs 7 and 3, respectively).[16] Finally, a significant breakthrough was obtained using a catalytic system generated in situ from the Knölker complex **1** (2 mol%) and PPh_3 (2 mol%) under similar conditions to those in the entry 8, and 80% of the α-alkylated product **5a** was obtained with only 6% of **6a** (Table 1, entry 10). Interestingly, the nature of the phosphine is also important: with 2 mol% of P(*o*-Tol)$_3$ or P(2-methylfuryl)$_3$, similar results were achieved, whereas in the presence of 2 mol% of PCy_3, $PPhMe_2$, or $P(OPh)_3$, less active and selective transformations were observed (Supporting Information, Table S4).

Obviously, no coupling occurred in the absence of iron catalyst or Cs_2CO_3 as the base, or when the reaction was performed in neat conditions (Table 1, entries 11–13).

To demonstrate the general scope of this method, reactions of various arylalkylketones with primary alcohols were investigated using the optimized conditions (2 mol% of complex **1**, 2 mol% PPh_3, 10 mol% Cs_2CO_3, 1 equiv of ketone, and 1.3 equiv of alcohol in toluene at 140°C for 24 h) (Table 2; Supporting Information, Figure S5).

Table 2: Scope of the iron-catalyzed α-alkylation of ketones with alcohols.[a]



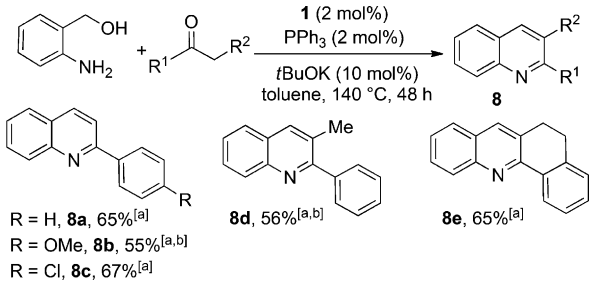
Entry			*t* [h]	NMR-yield[b] (Isolated)[c] **5** [%]
1		R = H, **5a**	24	80 (60)
2		R = *p*-OMe, **5b**	48	80 (57)
3		R = *p*-Me, **5c**	24	68 (58)
4		R = *o*-Me, **5d**	48	92 (72)
5		R = *p*-Cl, **5e**	24	78 (71)
6		R = *p*-Br, **5f**	48	57 (36)
7		R = *p*-F, **5g**	48	67 (52)
8		R = *p*-CF_3, **5h**	48	50 (38)
9		Ar = 2,4,6-Me_3-C_6H_2, **5i**	48	59 (51)
10		Ar = 2-naphthyl, **5j**	48	76 (60)
11		R = OMe, **5k**	48	63 (51)
12		R = *i*Pr, **5l**	24	75 (59)
13		R = Cl, **5m**	48	76 (55)
14		R = F, **5n**	24	73 (62)
15		R = *p*-Cl, R′ = F, **5o**	24	80 (59)
16		R = *o*-Me, R′ = Me, **5p**	48	70 (56)
17			24	0
18[d]		**5q**	48	72 (50)
19		R = Ph, **5r**	48	47 (42)
20		R = Me, **5s**	48	70 (55)
21		**5t**	48	54 (43)
22		R = Me, X = S, **5u**	48	70 (46)
23[d]		R = H, X = O, **5v**	48	(19)

[a] Reaction conditions: ketone (1 mmol), alcohol (1.3 mmol), complex **1** (0.02 mmol, 2 mol%), PPh_3 (0.02 mmol, 2 mol%), Cs_2CO_3 (0.1 mmol, 10 mol%), toluene (2 mL), 140°C. [b] ^{1}H NMR-yields in the crude mixture. [c] Yield of isolated product. [d] *t*BuOK (10 mol%) was used as the base.

In all of these cases, the α-alkylated derivative **5** was obtained as the major product with small amounts of the alcohols resulting from the reduction of the starting material and/or the formed ketones. The substitution on the aryl ring Ar^1 of arylmethylketones has no noticeable effect on the efficiency of the reaction. With both electron-withdrawing (Table 2, entries 5–8) and electron-donating substituents (Table 2, entries 2–4, 9), the α-alkylated ketones were obtained in 50–92% ^{1}H NMR-yields (36–72% yields of isolated product) with 0–20% of the reduced compounds from the starting and/or the formed ketones. α-Tetralone in the presence of benzyl alcohol led specifically to the α-alkylated-α-tetralone in 50% isolated yield after 48 h (Table 2, entries 17, 18). Similarly, there is no significant effect of the substitution of the aryl ring R^2 on the benzyl

alcohol derivatives. Consequently, alcohols with both electron-donating (Table 2, entries 11,12,16) and electron-withdrawing substituents (Table 2, entries 13–15,21) gave the corresponding α-alkylated ketones in 51–62% yields of isolated product. Furthermore, bio-based and synthetically more interesting alcohols such as butan-1-ol and 3-phenylpropan-1-ol could be used, and led to the corresponding ketones in 55 and 42% yields of isolated products, respectively (Table 2, entries 19–20). Methanol was unfortunately not suitable for this transformation, probably owing to the more difficult dehydrogenation reaction of this alcohol. More gratifyingly, heteroaromatic methylketones, such as 3-pyridylmethylketone or heteroaromatic alcohols such as 2-thienylethanol, performed well in this reaction (Table 2, entries 21 and 22).[17]

Following the general hydrogen-borrowing concept, our iron-catalyzed method allows also for the synthesis of quinoline derivatives. Based on the classic Friedländer annulation reaction, quinolines can be prepared in a straightforward manner from 2-aminobenzaldehyde and various ketones.[18] In general, self-aldol condensation by-products and the low stability of 2-aminobenzaldehyde are some of the challenges of this reaction. Using the more stable 2-aminobenzyl alcohol in the presence of a catalytic amount of base under hydrogen-borrowing conditions is an advantage to perform this reaction[19] compared to reactions in the presence of stoichiometric amounts of base.[20] Using the optimal conditions developed for α-alkylation described above, 2-aminobenzylalcohol **7** (1.3 equiv) reacted with 1 equiv of acetophenone to give the corresponding quinoline derivative **8a** in 63% yield of isolated product. The only other product detected in this sequence was 2-phenylethanol (Scheme 2).



Scheme 2. Iron-catalyzed modified Friedländer annulation reaction. [a] Yields of isolated products. [b] 30 mol% of *t*BuOK was used.

Using *t*BuOK (10 mol%) as the base permitted to obtain **8a** in 65% yield of isolated product. Furthermore, 2-aminobenzylalcohol **7** reacted with *p*-OMe- and *p*-Cl-substituted acetophenones to afford the corresponding quinolines **8b** and **8c** in 55 and 67% yields, respectively.[21] Similarly, propiophenone yielded the corresponding quinoline **8d** in 56% yield. Finally, 5,6-dihydrobenzo[c]acridine **8e** was obtained in 65% starting from inexpensive α-tetralone.

In conclusion, we have developed the first iron-catalyzed α-alkylation of ketones with primary alcohols in the presence of a catalytic amount of base. The key to success for this novel transformation is the use of a Knölker-type iron complex as catalyst. The optimized catalytic system permitted the development of the first iron-catalyzed Friedländer annulation reaction starting from 2-aminobenzyl alcohols. Notably, this method is not only of interest for organic synthesis, but also permits the green valorization of bio-based alcohols.

Experimental Section

Typical procedure for Fe-catalyzed α-alkylation of ketones with primary alcohols: an oven-dried 10 mL Schlenk tube, equipped with a stirring bar, was charged with acetophenone (120 mg, 1 mmol), benzyl alcohol (1.3 mmol), iron complex **1** (8.4 mg, 0.02 mmol), PPh_3 (5.2 mg, 0.02 mmol), Cs_2CO_3 (32.4 mg, 0.1 mmol), and toluene (2 mL). Under argon, the mixture was stirred at RT for 2 min, then was placed into a pre-heated oil bath at 140 °C and stirred for 24–48 h. The reaction mixture was cooled to RT, then diluted with ethyl acetate and washed with brine solution. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (*n*-pentane/diethylether).

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Keywords: alkylation · borrowing hydrogen · homogeneous catalysis · Friedländer reaction · iron catalysts

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[16] Noticeably, under similar experimental conditions, the temperature of the reaction had a significant influence: at 100 °C, only 11% conversion was obtained whereas at 120 °C, 85% conversion can be reached with 72% of **5a** and 6% of 1-phenylethanol **6a**.

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