Alkylation of Ketones Catalyzed by Bifunctional Iron Complexes: From Mechanistic Understanding to Application

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Cyclopentadienone iron dicarbonyl complexes were applied in the alkylation of ketones with various aliphatic and aromatic ketones and alcohols via the borrowing hydrogen strategy in mild reaction conditions. DFT calculations and experimental works highlight the role of the transition metal Lewis pairs and the base. These iron complexes demonstrated a broad applicability in mild conditions and extended the scope of substrates.

Alkylation of ketones usually involves halides or pseudohalides such as tosylate and triflate derivatives in the presence of a stoichiometric amount of a strong base.[1] Such methodology generates wastes, as all these electrophiles are prepared from alcohols, and requires the use of hazardous chemical materials. Synthetic chemists seek nowadays for more environmentally friendly ways to construct carbon–carbon bonds. In recent years, several efficient strategies were proposed for their creation: i) directly from two simple carbon–hydrogen bonds (catalytic dehydrogenative cross-coupling reaction),[2] and ii) from ketones and alcohols (hydrogen autotransfer or borrowing hydrogen strategy).[3] Carbon–carbon bond formation via the borrowing hydrogen strategy is a powerful strategy for the alkylation of ketones (Scheme 1).[3] Advantages of this approach are the use of easily-to-handle alcohols, as a source of alkylating reagents, and the formation of water as the sole byproduct. Indeed, following a simplified mechanism, the alcohol is initially oxidized (dehydrogenation step), and then an aldolization–dehydration step liberates an enone intermediate, which can be reduced into a ketone (Scheme 1).
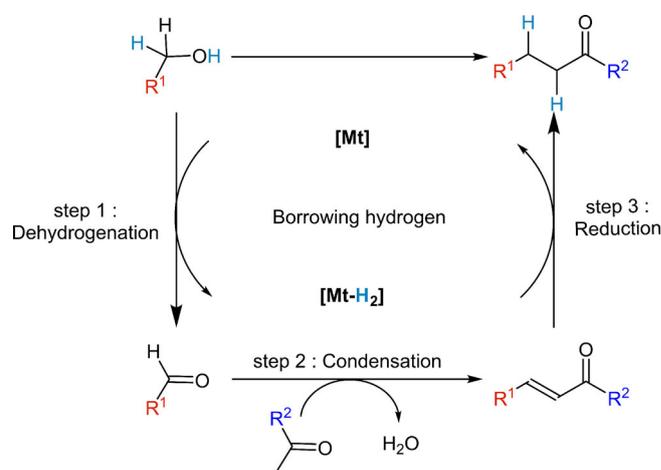
Scheme 1. Simplified accepted mechanism of alkylation of ketones.

Many efficient catalysts are based on expensive noble metals such as iridium,[4] ruthenium[5] or rhodium.[6] Owing to economic constraint and sustainability concerns, the replacement of platinum metals by first-row-based metals could be an attractive alternative. Recent reports described the use of iron,[7] cobalt[8] and manganese[9] as non precious metals in hydrogen autotransfer processes. However, all these complexes required a temperature threshold of 140 °C and/or expensive phosphine ligands. The scope of substrates could also be rather limited. As example, Darcel and co-workers showed recently that only aromatic ketones could be engaged in alkylation reactions in the presence of an in situ iron catalyst generated from Knölker's complex and triphenylphosphine.[10] Moreover, yields were moderate and no mechanism was proposed.[11] Then, even if these works pave the way to new opportunities in sustainable chemistry, some limitations were still present, a mechanistic understanding of this iron-catalyzed alkylation reaction and some improvement were needed.

In our ongoing work on iron-catalyzed reduction,[12] we have recently brought to light that cyclopentadienone iron tricar-

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bonyl complexes could be seen as "transition metal frustrated Lewis pairs".[13] Based on this approach, we synthesized the phosphine-free iron complex **Fe1** (Figure 1), bearing an electron rich cyclopentadienone ligand, and showed that **Fe1**
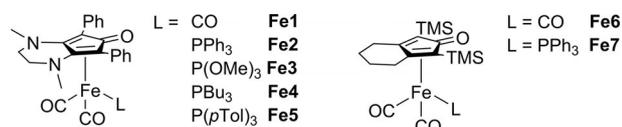

**Figure 1.** Complexes **Fe1**–**Fe7** evaluated in this work.

could improve the reaction conditions (lower temperature, higher chemical yields) and extend the scope of amines used in the reductive amination.[14] In this study, DFT calculations confirmed that **Fe1** facilitated both the hydrogen bond cleavage and the reduction step.[13] We anticipated that **Fe1** might also be more active than Knölker's complex or analogs in other reactions involving reduction. Alkylation of ketones via the borrowing hydrogen strategy is one of these reactions.[7]

To initiate this study and confirm that our complexes could also catalyze such alkylation, DFT calculations were undertaken based on the usually proposed and simplified mechanism (Schemes 1 and 2). After an initial dissociation of a ligand (CO or a phosphine, vide infra), dehydrogenation of the primary alcohol could liberate an aldehyde and the [Fe–H] iron–hydride complex **III**. An aldolization, followed by a dehydration step, could liberate an enone, which could be reduced by the [Fe–H] species (Scheme 2). The energy profiles of complexes **Fe2**–**Fe5** and known Knölker's type complexes (Complexes **Fe6** and **Fe7**, Figure 1) were compared in the key steps, namely, (i) the ligand dissociation, (ii) the dehydrogenation step, and (iii) the reduction of the enone (for details, see the Supporting Information). The free energies for **Fe1** and **Fe2** and **Fe6** and **Fe7** are reported in Scheme 2. The dissociation step under thermal conditions, leading to the unsaturated iron complexes, appears to be favored with PPh₃ compared to a CO ligand and facilitated with cyclopentadienone iron complex **Fe2** (14.5 kcal mol⁻¹

with **Fe2** vs. 22.9 kcal mol⁻¹ with **Fe1** or 16.4 kcal mol⁻¹ with **Fe7**, and 26.8 kcal mol⁻¹ with **Fe6**). The energy of dissociation is higher with P(OMe)₃ and PBu₃, and comparable with P(oTol)₃ (for details, see the Supporting Information). Dissociation of CO instead of a phosphine molecule is also not favored as the energy barrier is much higher (29.3 kcal mol⁻¹ from **Fe2** and 27.7 kcal mol⁻¹ from **Fe7**, respectively). DFT calculations also reveal a significant higher chemical hardness for the non-phosphine-based system **Fe1**, and thus an increased HOMO–LUMO gap. In the phosphine–iron series, **Fe3** displays the highest value (28.7 kcal mol⁻¹), and triphenylphosphine analogs **Fe2** and **Fe5** have the lowest one (27.1 kcal mol⁻¹). The chemical consequence is that **Fe1** and **Fe3** might be the less reactive species.

Decoordination of ligands can proceed not only thermally but also under photochemical conditions.[15] As Casey[16] and Berkessel[17] reported CO exchange in complex **Fe6** under UV light activation, the generation of **I** under these conditions was also calculated by DFT. Even though the photoexcited triplet state for **Fe1** and **Fe6** was found to be 17.4 and 26.1 kcal mol⁻¹ higher in energy than the singlet ground state, respectively, the next CO dissociation in intermediate **I** is then facilitated, requiring only 9.3 and 1.0 kcal mol⁻¹, respectively. On the other hand, from the phosphine-based complexes **Fe2** and **Fe7**, the triplet species were placed 24.9 and 14.2 kcal mol⁻¹ above in energy than the singlet ground state, respectively. However, even more interestingly, this photoexcitation led to intermediate **I** very easily because the triplet state was then much favored. With respect to the thermal process, the photoexcited step was favored by 18.4 and 8.2 kcal mol⁻¹, respectively.

Then, the dehydrogenation step from benzyl alcohol is kinetically facile because the barriers are located at 12.6 and 8.5 kcal mol⁻¹ from **I** (Scheme 2 and Supporting Information). Interestingly, the hydride species **III** formed from the new iron complex is less stable than the one from Knölker's complex (the destabilization is 2.2 kcal mol⁻¹), but the transition states are comparable in both cases (Scheme 2 and Supporting Information). An aldolization–crotonization reaction between the
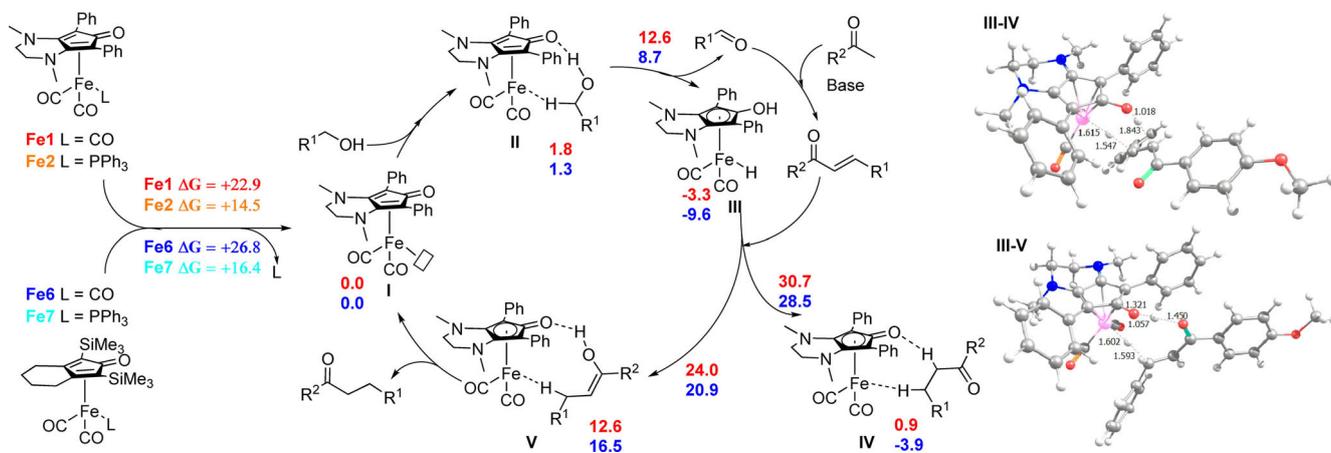
Scheme 2. Free-energy profiles for alkylation of ketones by complexes **Fe1**–**Fe7** (energies in kcal mol⁻¹; for clarity, only the Lewis schemes for the set of complexes **Fe1**–**Fe5** are depicted in the catalytic cycle. 3D sketches of the transition states of **III**→**IV** and **III**→**V** are included with relevant distances in Å (see the Supporting Information for all the other computed species).

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generated aldehyde and the enolate, formed by deprotonation of the ketone, liberated the corresponding enone (Scheme 2).

The key step in the overall mechanism is the reduction of the enone. Two pathways were calculated. The first one involves an initial interaction between the alkene, the hydride species, and the hydroxyl function (intermediate **IV**, Scheme 2), followed by the addition of both hydrogen atoms. The second one goes, first, through interactions between the iron complex and the enone (intermediate **V**, Scheme 2), followed by a 1,4-type addition. Even though the second pathway is lower in energy for both sets of iron complexes (27.3 and 30.5 kcal mol^{-1} from **III** to **V** vs. 34.0 and 38.1 kcal mol^{-1} from **III** to **IV** for **Fe1–Fe5** and **Fe6** and **Fe7**, respectively), the energy barriers are high. The transition states are again comparable in
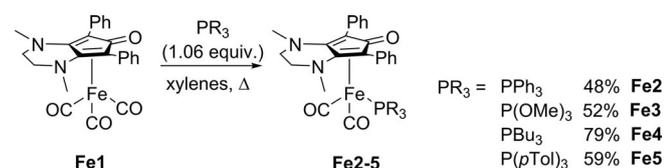
Scheme 3. Synthesis of complexes **Fe2–Fe5**.

PR$_3$ = PPh$_3$ 48% **Fe2**
P(OMe)$_3$ 52% **Fe3**
PBu$_3$ 79% **Fe4**
P(pTol)$_3$ 59% **Fe5**

both cases, and disfavored by approximately 3 kcal mol^{-1} for the Knölker's catalyst (see Scheme 2 and Supporting Information).

Having found theoretically that **Fe1**, **Fe2**, and **Fe5** could be active complexes in alkylation of ketones, we started evaluating their catalytic activity in the alkylation of ketones. New precatalysts **Fe2–Fe5** were prepared by the treatment of **Fe1** with the corresponding phosphine (Scheme 3). All these complexes were isolated in moderate to good yields (48–79%) and fully characterized.

To unambiguously establish the atom connectivity, single crystals were grown by slow diffusion of pentane in dichloromethane. Suitable single crystals were obtained and subjected to X-ray diffraction (XRD) analysis. Thermal ellipsoid representations are shown in Figure 2.

In all these complexes, the phosphorous ligand is located underneath the carbonyl function of the cyclopentadienone. Such conformation minimizes the steric hindrance with the phenyl substituent and the amino bridge, which bent to the metal. Interestingly, the Fe–P bond length is shorter in **Fe3** (2.1839(5) Å) than in the other complexes (2.2682(4) Å, 2.2552(4) Å, and 2.2609(5) Å in **Fe2**, **Fe4**, and **Fe5**, respectively). This may reflect an easier dissociation of the phosphine ligand as also suggested by the DFT calculations and by the Mayer bond orders (MBO).

As a model reaction, the iron-catalyzed alkylation of 4-methoxyacetophenone (1 equiv.) with benzyl alcohol (1.3 equiv.) was optimized in toluene in the presence of 10 mol% cesium carbonate as a base (Table 1). After screening various reaction parameters, the optimal conditions for the alkylation were a reaction time of 16 h (overnight reaction) at 90°C in the presence of **Fe2** or **Fe5**. To our delight, and as calculated by DFT, precatalyst **Fe2** was more active thermally and provided the al-
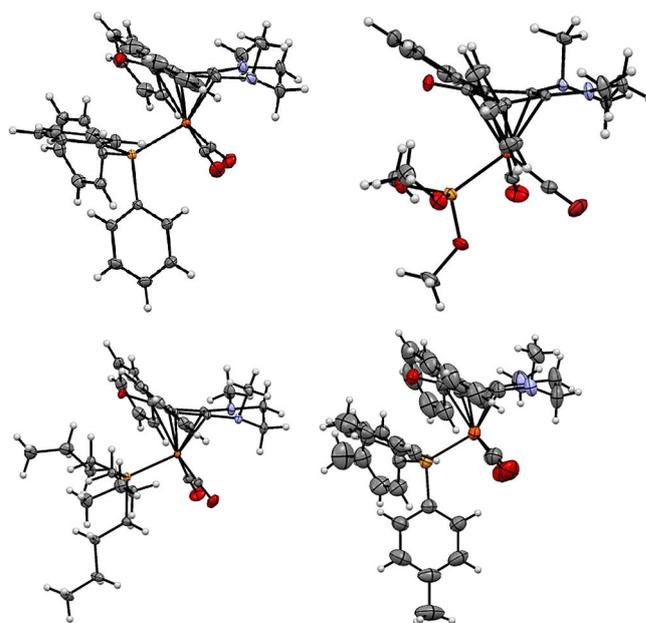
**Table 1.** Optimization of the reaction conditions.[a]

Entry	[Fe]	PPh$_3$ [mol%]	Temp. [°C]	Time [h]	Conv. [Yield][b] [%]
1	**Fe1**	0	140	24	100 [95]
2	**Fe1**	2	140	24	100 [94]
3	**Fe1**	2	100	24	100 [89]
4	**Fe1**	0	90	24	48 [45]
5	**Fe1**	4	90	24	81 [65]
6[c]	**Fe1**	2	90	24	54
7	**Fe1**	2	80	54	68.5
8[c]	**Fe1**	2	80	54	56
9[c]	**Fe1**	2	65	24	25
10	**Fe2**	0	90	24	100 [93]
11	**Fe2**	0	90	9.5	95
12	**Fe2**	0	90	7.5	94.5
13	**Fe2**	0	90	16	100 [95]
14	–	2	90	36	0
15[d]	**Fe2**	0	90	16	0
16[e]	**Fe2**	0	90	16	0
17[f]	**Fe2**	0	90	16	0
18[g]	**Fe2**	0	90	16	100
19	**Fe3**	0	90	16	0
20	**Fe4**	0	90	16	71
21[h]	**Fe1**	0	90	16	100 [96]
22[h]	**Fe1**	0	70	16	20
23[h]	**Fe1**	0	50	16	0
24[i]	**Fe1**	0	r.t.	16	0

[a] General conditions: carbonyl derivative (1 mmol), alcohol (1.2 mmol), complex **Fe** (2 mol%), Cs$_2$CO$_3$ (10 mol%), and phosphine (x mol%) in toluene (2 mL). [b] Conversion was determined by ^{1}H NMR analysis of the crude mixture; yield was based on the purified product. [c] With Me$_3$NO (2 mol%). [d] Without Cs$_2$CO$_3$. [e] With Na$_2$CO$_3$ (10 mol%). [f] With K$_2$CO$_3$ (10 mol%). [g] With CsOH (10 mol%). [h] UV-A irradiation for 2 h then heating. [i] UV-A irradiation for 16 h.

kylated ketone in complete conversion and 95% yield. Interestingly, and in sharp contrast with the alkylation catalyzed by Knölker's complex,[10] the selectivity of the transformation was complete and no by-product (such as from competitive direct reduction of the ketone) was observed; the reaction temperature and reaction times were lower.

Evaluation of the complexes **Fe2–Fe5** in the model reaction highlighted the role of the phosphine ligand. Whereas **Fe2** and **Fe5** bearing a triaryl-phosphine showed excellent activities at 90°C, **Fe3** and **Fe4** bearing electron-rich phosphine or electron-poor phosphite, respectively, showed lower to no conversions (Table 1, entries 10–13, 19–21,). Moreover, to gain deeper insight, dissociation of the phosphine ligand was also analyzed by ^{31}P NMR for all the complexes **Fe2–Fe5**. Whereas ^{31}P NMR of **Fe2** or **Fe5** showed a ligand dissociation starting at 70°C, free phosphine appeared only at 90°C with **Fe4** and no ligand release was observed even at 110°C with **Fe3** (for details, see the Supporting Information). A base was clearly necessary for the formation of the enolate (entries 15–18), but the nature of the cation is crucial. Sodium or potassium carbonate does not provide any product under the same reaction conditions (entries 15, 16). Such difference of behavior might result from their solubility in toluene. Cesium hydroxide as base allowed also the formation of the alkylated ketone in complete conversion (entry 18). Activation of the tricarbonyl iron complex **Fe1** under photolytic conditions was also evaluated (entries 21–24). The irradiation of complex **Fe1** with UV-A light for 2 h, followed by heating overnight, led to the alkylated ketone in comparable yields than in thermal conditions (entries 5, 9, 13 vs. entries 21–23). The sole UV-light activation did not provide any product (Table 1, entry 24) and show the rate-limiting step is the reduction of the alkene.

All these results were in line with the DFT calculations (see below) and explained the higher activities of **Fe1**, **Fe2**, and **Fe5**. Both thermal or photolytic activation can be used for the initiation, but a temperature threshold is required for the aldolization–crotonization step and the reduction of the enone. However, based on DFT calculations, such process seems unlikely and thermodynamically unfeasible in these conditions, as the upper energy barrier defined by the transition state **III→V** requires at least 37.7 kcal mol^{-1} from the starting complexes, especially for **Fe1** (46.9 kcal mol^{-1}), and is too high to account for the observed reaction rates. In the overall mechanism, the base was initially considered for the deprotonation of the ketone. However, Casey determined the acidity of the OH proton in trimethylsilyl-substituted hydroxycyclopentadienyl ruthenium or iron hydrides, and the corresponding pK_a was found to be 19–21, comparable to the pK_a of ketones.[16] The base might also deprotonate the hydroxyl function in **III** (Scheme 4). The corresponding intermediate is thermodynamically more stable, and the overall oxidation process is now exothermic (5.9 and 9.4 kcal mol^{-1} for the hydride cesium alkoxides of complexes **Fe1–Fe5** and **Fe6** and **Fe7**, respectively, Scheme 4). The base-assisted reduction also dramatically de-
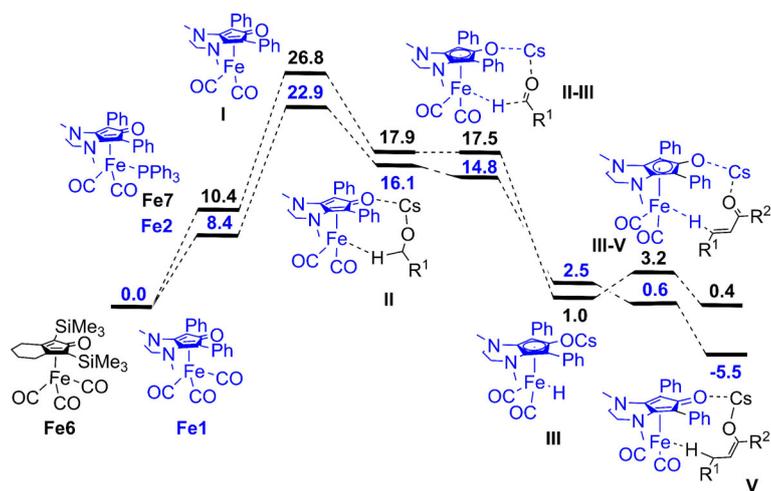
Scheme 4. Free-energy profiles for the alkylation of ketones by complexes **Fe1–Fe7** assisted by Cs$_2$CO$_3$ as a base (energies in kcal mol^{-1}; for clarity, only the Lewis schemes for the set of complexes **Fe1–Fe5** are depicted in the catalytic cycle (see Supporting Information for all the other computed species).

creased the barriers in reduction. The activation barrier is 2.2 kcal mol^{-1} for Knölker's complex, whereas there is no barrier with **Fe1** for the transition state leading to the enolate intermediate (Scheme 4). The enolates are also more stable than the corresponding enol by at least 41.9 kcal mol^{-1}. The base is not innocent in this alkylation process.

Having established an efficient procedure, we delineated the scope of the reaction by varying the benzyl alcohols (Table 2) under the optimized reaction conditions:

(i) conditions A, "thermal activation": 2 mol% **Fe2**, 10 mol% cesium carbonate, 1 equivalent of ketone, 1.3 equivalents of primary alcohol in toluene for 16 h at 90°C;

(ii) or conditions B, "photolytic activation": 2 mol% **Fe1**, 10 mol% cesium carbonate, 1 equivalent of ketone, 1.3 equivalents of primary alcohol in toluene at room temperature under UV-A light for 2 h, then at 90°C for 16 h.

In all these reactions, both conditions (thermal activation or photoactivation) could be used without any important modification of the chemical yield, but, owing to the easiest implementation, the thermal activation with complex **Fe2** was chosen. Some remaining starting material could accompany the alkylated ketone, but neither reduction of the para-methoxyacetophenone nor the unsaturated ketone was observed. Such results are in sharp contrast with those of the previously reported alkylation procedure in the presence of Knölker's complex.[10] Electron-donating or electron-withdrawing group could be tolerated, and ketones were isolated in yields ranging from 40 to 70% (Table 2, entries 1–6). More interestingly, heteroaromatic alcohols, such as 2- or 3-pyridylmethanol (entries 7, 8), 2-thiophenyl or 2-furanylmethanol (entries 9, 10) performed well in these conditions and the corresponding alkylated ketones were isolated in 41–97% yield. Their coordinating abilities do not inhibit the catalytic activities. Finally, as suggested by DFT calculations and by the initial screening of the reaction

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Table 2. Alkylation of (hetero)aromatic ketones with various benzylic alcohols.
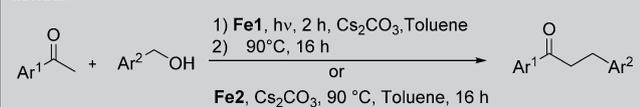
Entry[a]		Conv. [Yield][b] [%]
1	R = 4-OCH₃	89 [70]
2	R = 4-Br	80 [63]
3	R = 4-CH₃	64 [40]
4[c]	R = 2-OCH₃	62 [44]
5	R = 2-Br	64 [59]
6		94 [60]
7		50 [41]
8		78 [70]
9	Y = O	100 [97]
10	Y = S	100 [86]
11	R = 4-CH₃	100 [98]
12	R = H	100 [94]
13	R = 4-Br	98 [90]
14	R = 4-F	92 [72]
15	R = 4-CF₃	97 [76]
16	R = 4-CN	100 [78]
17	R = 2-CH₃	100 [87]
18	R = 2-Br	100 [70]
19	X = O	100 [77]
20	X = S	100 [99]
21	X = NH	77 [61]
22		100 [75]
23	Y = O	88 [80]
24	Y = S	86 [74]

[a] General conditions: carbonyl derivative (1 mmol), alcohol (1.2 mmol), complex **Fe2** (2 mol%), Cs₂CO₃ (10 mol%) in toluene (2 mL) at 90 °C for 16 h. [b] Conversion was determined by ¹H NMR analysis of the crude mixture; yield was based on the purified product. [c] With CsOH (10 mol%) as base. [d] At 110 °C for 24 h.

conditions, the use of **Fe5** instead of **Fe2** in this alkylation led to similar results (Supporting Information, Table S2, entries 3, 4).

We also studied variations of the substitution on the ketone (Table 2, entries 11–24). Electron donating or withdrawing substituents on the aryl ketone were tolerated. The alkylated derivatives were isolated in good to excellent yields (70–98%). Heteroaromatic ketones such as thiophenyl-, furanylmethyl ketone could be used in the presence of benzyl alcohol as alkylating agent, without lowering the chemical yields (Table 1, entries 19, 20, 22). To demonstrate the versatility of this protocol and increase the potential in synthesis, unprotected pyrrole was used. Under the previously optimized reaction conditions, the alkylated derivatives were obtained selectively, and no alkylated amine was produced (Table 2, entries 21, 23, 24).

Finally, owing to the reactivity of **Fe2** compared to other iron complexes, we extended this work to alkyl compounds. Alkylation of aryl ketones with primary alkyl alcohols such as 2-phenyl ethanol led to the corresponding ketones in moderate yields (45–70%, Table 3, entries 1–3). Higher yields were obtained by changing the base (70% yield with CsOH vs. 49% with Cs₂CO₃). Dialkylation of cyclohexanone was also possible with **Fe2**, whereas Knölker's complexes led only to the reduction of the starting alkyl ketones in these conditions.[10] The corresponding dialkylated ketones were isolated in 55–72% yield (entries 4–7). Finally, alkylation of aliphatic ketones in the same conditions provided the corresponding monoalkylated products in good isolated yields (87–98%, entries 8–10).
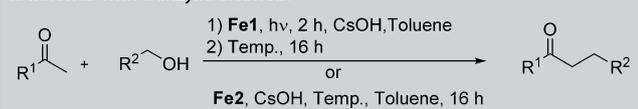
Conclusions

Based on in silico predictions and experimental approaches, we have designed several iron complexes that displayed good activities in the C—C bond formation by a hydrogen autotransfer process between ketones and alcohols. Both aliphatic and aromatic ketones and alcohols could be engaged. Alkylated ketones were isolated in good to excellent yields in mild reaction conditions. These iron-based frustrated Lewis pairs also extended the scope of substrates. Our data highlight the crucial role of the base both in the dehydrogenation step and in the reduction of the alkene. These iron complexes now become competitive with noble metals.

Experimental Section

Synthesis of (1,4-dimethyl-5,7-diphenyl-1,2,3,4-tetrahydro-6*H*-cyclopenta[*b*]pyrazin-6-one) iron tricarbonyl complex[13] [**Fe1**]: In a 100 mL dried Schlenk tube under an argon atmosphere, the cyclopentadienone ligand (2.52 mmol, 800 mg, 1 equiv.) and **Fe2**(CO)₉ (5.06 mmol, 1.84 g, 2 equiv.) were introduced in dry and degassed toluene (10 mL). The reaction mixture was stirred under reflux overnight. The resulting mixture was cooled down to room temperature and purified on neutral alumina oxide column chromatography surrounded by a pad of Celite (eluent: CH₂Cl₂ to CH₂Cl₂/CH₃OH [98:2]). Precipitation on a mixture of pentane/Et₂O and filtration under vacuum gave the pure complex as a yellow powder (560 mg, 49%).

Table 3. Alkylation of aromatic ketones with aliphatic alcohols or aliphatic ketones with benzylic alcohols.

$$ R^1\text{C(O)CH}_3 + R^2\text{CH}_2\text{OH} \xrightarrow[\text{or}\quad \text{Fe2, CsOH, Temp., Toluene, 16 h}]{\text{1) Fe1, h}\nu,\ 2\ h,\ \text{CsOH, Toluene} \quad 2)\ \text{Temp., 16 h}} R^1\text{C(O)CH}_2\text{CH}_2 R^2 $$

Entry[a]		Temp. [°C]	Yield [%][b]
1		110	70
2[c]			49
3		110	45
4		90	55
5		90	72
6		90	66
7		90	45
8		90	98
9		90	87
10		90	98

[a] General conditions: carbonyl derivative (1 mmol), alcohol (1.2 mmol), complex **Fe2** (2 mol%), CsOH (10 mol%) in toluene (2 mL) for 16 h. [b] Yield was based on the purified product. [c] With Cs_2CO_3 (10 mol%) as base.

General procedure for ligand exchange

In a flame-dried Schlenk tube under an argon atmosphere, iron complex **Fe1** (1 equiv.) and the corresponding phosphine or phosphite (1.06 equiv.) were introduced in freshly distilled and degassed xylenes (mixture of isomers) ($c = 0.03$ M). The reaction mixture was heated under reflux overnight and then the solvent was removed under vacuum to furnish the crude product.

Synthesis of (1,4-dimethyl-5,7-diphenyl-1,2,3,4-tetrahydro-6H-cyclopenta[b]pyrazin-6-one) triphenylphosphine dicarbonyl iron complex [**Fe2**]: Following the general procedure, starting from complex **Fe1** (0.44 mmol, 200 mg) and triphenylphosphine (0.47 mmol,

122 mg), complex **Fe2** was obtained as an orange powder (144 mg, 48%) after purification by flash column chromatography on neutral aluminum oxide topped with a pad of Celite (eluent: pentane/AcOEt [90:10] to [70:30]). X-ray-quality crystals were grown by slow diffusion of pentane in dichloromethane (vide infra). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.82 (d, $J = 7.0$ Hz, 4H), 7.39 (s, 2H), 7.34–7.20 (m, 9H), 7.16 (t, $J = 7.0$ Hz, 4H), 7.07–7.03 (m, 6H), 3.49 (s, 4H), 2.59 (s, 6H) ppm. ^{13}C NMR (CDCl$_3$, 100 MHz) $\delta = 216.9$, 160.9, 133.9, 133.8, 133.3, 133.2, 130.8, 128.9, 127.5, 127.4, 125.9, 108.6, 71.3, 47.1, 40.2 ppm. ^{31}P NMR (CDCl$_3$, 162 MHz) $\delta = 50.68$ ppm. IR (neat) $\tilde{v} = 3058$, 2925, 1969, 1902, 1603, 1573, 1542, 1498, 1484, 1470, 1434, 1417, 1380, 1354, 1332, 1251, 1175, 1089, 1029, 930, 846, 762, 750, 740, 693 cm^{-1}. HRMS $[M+H]^+$ calculated for C$_{41}$H$_{36}$N$_2$O$_3$PFe: 691.1813; found: 691.1812.

Synthesis of (1,4-dimethyl-5,7-diphenyl-1,2,3,4-tetrahydro-6H-cyclopenta[b]pyrazin-6-one) trimethyl phosphite dicarbonyl iron complex [**Fe3**]: Following the general procedure, starting from complex **Fe1** (0.22 mmol, 100 mg) and trimethyl phosphite (0.23 mmol, 27.5 μL), complex **Fe3** was obtained as a yellow powder (63 mg, 52%) after purification by flash column chromatography on neutral aluminum oxide topped with a pad of Celite (eluent: CH$_2$Cl$_2$/MeOH [100:0] to [98:2]). X-ray-quality crystals were grown by slow diffusion of pentane in dichloromethane (see below). ^{1}H NMR (CDCl$_3$, 400 MHz) $\delta = 7.84$ (d, $J = 7.3$ Hz, 4H), 7.33 (t, $J = 7.3$ Hz, 4H), 7.28–7.26 (m, 2H), 3.44 (d, $J = 10.8$ Hz, 9H), 3.38–3.28 (m, 2H), 3.11–3.03 (m, 2H), 3.29 ppm (s, 6H). ^{13}C NMR (CDCl$_3$, 100 MHz) $\delta = 214.9$, 214.7, 163.1, 134.1, 132.1, 127.7, 126.9, 110.2, 69.8, 52.5, 49.1, 41.3 ppm. ^{31}P NMR (CDCl$_3$, 160 MHz) $\delta = 164.8$ ppm. IR (neat) $\tilde{v} = 2951$, 2851, 1989, 1938, 1909, 1603, 1593, 1540, 1497, 1444, 1419, 1380, 1355, 1177, 1059, 1020, 782, 739, 698 cm^{-1}. HRMS $[M+H]^+$ calculated for C$_{26}$H$_{30}$FeN$_2$O$_6$P: 553.1191; found: 553.1199.

Synthesis of (1,4-dimethyl-5,7-diphenyl-1,2,3,4-tetrahydro-6H-cyclopenta[b]pyrazin-6-one) tributylphosphine dicarbonyl iron complex [**Fe4**]: Following the general procedure, starting from complex **Fe1** (0.44 mmol, 200 mg) and tributylphosphine (0.47 mmol, 116 μL), complex **Fe4** was obtained as an orange powder (219 mg, 79%) after purification by flash column chromatography on neutral aluminum oxide topped with a pad of Celite (eluent: pentane/AcOEt [100:0] to [9:1]). X-ray-quality crystals were grown by slow diffusion of pentane in dichloromethane (see below). ^{1}H NMR (CDCl$_3$, 400 MHz) $\delta = 8.15$ (d, $J = 7.4$ Hz, 4H), 7.33–7.25 (m, 4H), 7.20 (t, $J = 7.4$ Hz, 2H), 3.42–3.35 (m, 2H), 3.31–3.24 (m, 2H), 2.49 (s, 6H), 1.43–1.37 (m, 6H), 1.06–0.86 (m, 12H), 0.68 ppm (t, $J = 7.1$ Hz, 9H). ^{13}C NMR (CDCl$_3$, 100 MHz) $\delta = 217.3$, 217.2, 157.8, 135.1, 130.5, 127.5, 126.3, 107.9, 70.5, 47.5, 40.8, 29.7, 25.2, 25.2, 24.3, 24.2, 23.6, 23.4, 13.6 ppm. ^{31}P NMR (CDCl$_3$, 162 MHz) $\delta = 32.24$ ppm. IR (neat) $\tilde{v} = 2957$, 2929, 2858, 2324, 2111, 1965, 1910, 1599, 1580, 1532, 1498, 1464, 1442, 1417, 1380, 1355, 1336, 1263, 1215, 1176, 1041, 1030, 913, 763, 742, 714, 698 cm^{-1}. HRMS $[M+H]^+$ calculated for C$_{35}$H$_{48}$FeN$_2$O$_3$P: 631.2752; found: 631.2761.

Synthesis of (1,4-dimethyl-5,7-diphenyl-1,2,3,4-tetrahydro-6H-cyclopenta[b]pyrazin-6-one) tris(p-tolylphosphine) dicarbonyl iron complex [**Fe5**]: Following the general procedure, starting from complex **Fe1** (0.44 mmol, 200 mg) and tris(p-tolyl)phosphine (0.47 mmol, 141 mg), complex **Fe5** was obtained as an orange powder (190 mg, 59%) after purification by flash column chromatography on neutral aluminum oxide topped with a pad of Celite (eluent: pentane/AcOEt [90:10] to [70:30]). X-ray-quality crystals were grown by slow diffusion of pentane in dichloromethane (see below).
^{1}H NMR (CDCl$_3$, 400 MHz) $\delta = 7.66$ (d, $J = 7.4$ Hz, 4H), 7.15–7.02 (m, 8H), 6.99 (t, $J = 7.4$ Hz, 4H), 6.71 (d, $J = 7.4$ Hz, 6H), 3.36–3.31 (m,

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General procedure: [Fe1]-catalyzed alkylation of ketones

In a 15-mL flame-dried Schlenk tube equipped with a stirring bar, the desired ketone (1 equiv.), alcohol (1.3 equiv.), iron complex **Fe1** (2 mol %) and Cs$_2$CO$_3$ (10 mol %) and toluene ($C = 1$ M) were poured in under an argon atmosphere. The mixture was rapidly stirred at room temperature under UV-A light for 2 h and then placed into a preheated oil bath at 90 °C and stirred overnight. The mixture was cooled down to room temperature and then diluted with ethyl acetate and washed with brine solution. The organic layers were dried over MgSO$_4$ and concentrated under reduced pressure. The conversion was determined by ^{1}H NMR spectroscopy, and then, the residue was purified by flash chromatography on silica gel to afford the desired product.

General procedure: [Fe2]-catalyzed alkylation of ketones

In a 15-mL flame-dried Schlenk tube equipped with a stirring bar, the desired ketone (1 equiv.), alcohol (1.3 equiv.), iron complex **Fe2** (2 mol %) and Cs$_2$CO$_3$ (10 mol %) and toluene ($C = 1$ M) were poured in under an argon atmosphere. The mixture was rapidly stirred at room temperature for 2 min and then placed into a preheated oil bath at 90 °C and stirred overnight. The mixture was cooled down to room temperature and then diluted with ethyl acetate and washed with brine solution. The organic layers were dried over MgSO$_4$ and concentrated under reduced pressure. The conversion was determined by ^{1}H NMR spectroscopy, and then, the residue was purified by flash chromatography on silica gel to afford the desired product.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

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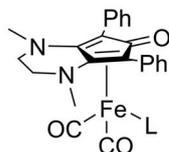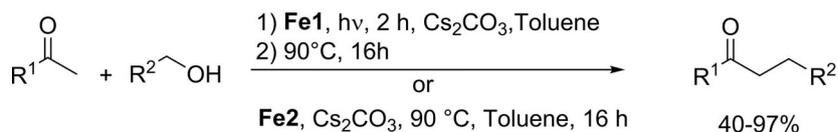
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💻 **Alkylation of Ketones Catalyzed by Bifunctional Iron Complexes: From Mechanistic Understanding to Application**

Fe1: L= CO
Fe2: L= PPh₃

40-97%

DFT analysis
Alkyl or aryl ketones
Alkyl or aryl alcohols

Borrow hydrogen for iron complexes: A cyclopentadienone iron dicarbonyl complex is applied in the alkylation of ketones with various aliphatic and aromatic ketones and alcohols through the borrowing hydrogen strategy in mild reaction conditions. DFT calculations and experimental works highlight the role of this transition metal Lewis pair and the base.

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