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Iridium-Catalysed Reductive Deoxygenation of Ketones with Formic Acid as Traceless Hydride Donor

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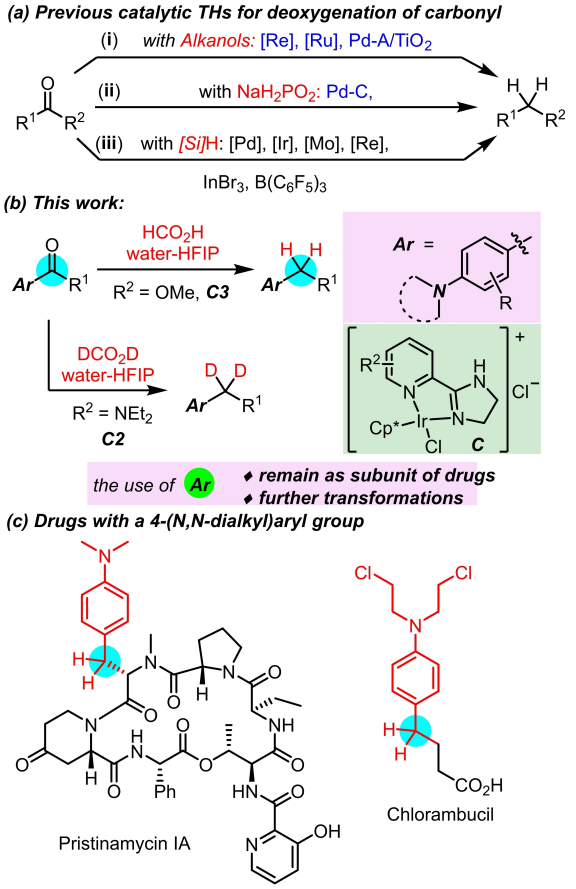
Abstract: An iridium-catalysed deoxygenation of ketones and aldehydes is achieved, with formic acid as hydride donor and water as co-solvent. At low catalyst loading, a number of 4-(*N*,*N*-disubstituted amino) aryl ketones are readily deoxygenated in excellent yields and chemoselectivity. Numerous functional groups, especially phenolic and alcoholic hydroxyls, secondary amine, carboxylic acid, and alkyl chloride, are well tolerable. Geminally dideuterated alkanes are obtained with up to 90% D incorporation, when DCO_2D and D_2O are used in place of their hydrogenative counterparts. The activating 4-(*N*,*N*-disubstituted amino)aryl groups have been demonstrated to undergo a variety of useful transformations. The deoxygenative deuterations have been used to prepare a deuterated drug molecule Chlorambucil-4,4-d_2.

Keywords: Iridium catalysis; transfer hydrogenation; deoxygenation; deuteration; ketones

Introduction

The reductive deoxygenation of carbonyl compounds to alkanes constitutes a fundamental yet highly valuable transformation in organic chemistry. The zinc-mediated Clemensen reduction under acidic conditions[1] and hydrazine-participated Wolff-Kishner reduction under basic conditions,[2] together with their various modified versions, are classical procedures to realize the deoxygenation, although they suffer from unsatisfactory tolerance with respect to base- or acid-sensitive substrates. The complementary two step carbonyl thioketalization with thiols and thioketal desulfurization with Raney-nickel (Mozingo reaction) under neutral conditions show good functional group tolerance but less satisfactory step- and atom economy.[3] Other stoichiometric reagents[1d,e] that directly convert aromatic ketones or aldehydes to the corresponding hydrocarbons include boranes,[4] borohydrides,[5] $LiAlH_4$–$AlCl_3$,[6] HI-red P,[7] Ni–Al alloy,[8] $P(OiPr)_3$,[9] Se–CO–H_2O,[10] Raney Ni,[11] and $(i\text{-BuClAl})_2O$.[12] To preclude hazardous reductants and reduce organic by-products, homogeneously or heterogeneously catalytic hydrogenations with high-pressure hydrogen gas (up to 60 bar) are developed.[1d,e,13] However, the safety issue caused by the high-pressure hydrogen gas always hangs like the sword of Damocles. Instead, transfer hydrogenations (THs), especially those in aqueous media,[14] due to the convenient handling and easy access of hydrogen donors, have received much attention and emerged as a safer and preferred tool in synthetic community.

In the TH carbonyl deoxygenation field, various hydrogen donors and different catalysts were developed (Scheme 1a).[15] Isopropanol,[15a] 3-pentanol,[15b] and ethanol[15c] were proved viable under the catalysis of Re, Ru, and Pd–A/TiO_2 (namely Pd/TiO_2 prepared from $Pd(OAc)_2$) for the deoxygenation of aromatic aldehydes or ketones in organic solvents (i, Scheme 1a). Interestingly, aromatic ketones were also deoxygenated by hypophosphites with heterogeneous Pd/C catalyst (ii, Scheme 1a).[16] The most popular



Scheme 1. Reported strategies for reductive deoxygenation of carbonyls and our work.

hydrogen donors were hydrosilanes. Dependent on the different structures of the hydrosilanes used, structurally diverse metal catalysts were adopted to realize the deoxygenation of aromatic carbonyls to methylenes under corresponding conditions (iii, Scheme 1a).[17] Particularly, Lu and Song's group developed a B$(C_6F_5)_3$-catalyzed strategy to selectively deoxygenate ether-substituted aliphatic carbonyl compounds using $(HMe_2SiCH_2)_2$ (iii, Scheme 1a).[17h] The ether substituent acted as a mandatory activating and directing group. In the above advances, harsh conditions were required, and organic waste was imperfectly generated in most cases. A novel procedure in environment-friendly solvent, with traceless hydrogen donor, by easy and convenient operations, producing no organic by-product, and in high chemoselectivity and conversion,[18] is still in high demand.

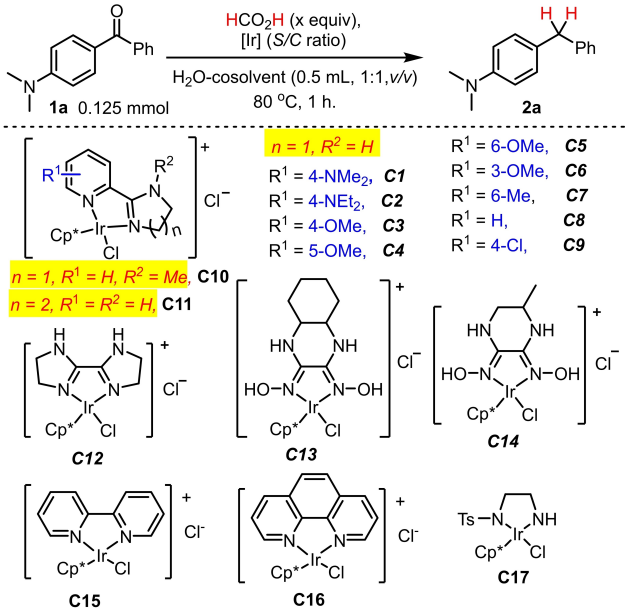
Recently, we have developed a new type of iridium catalysts and used them to realize highly efficient transfer hydrogenations of aldehydes, ketones, and carbocations.[19] Based on our background, we herein report the iridium-catalysed reductive deoxygenation of 4-(*N*,*N*-disubstituted amino)aryl ketones and aldehydes, with formic acid as a hydride donor in aqueous media (Scheme 1b). During the reactions, only carbon dioxide is generated as a by-product from formic acid, and this is why formic acid is called a traceless hydride donor. Unlike previous inert-gas-protected transfer hydrogenations for deoxygenating of ketones,[15–17] our reactions are performed without excluding air from the reaction vessels. Our protocol also establishes a convenient access to *geminally* dideuterated alkane when DCO_2D is used as the deuteride source (Scheme 1b). Although there existed several methods for deoxygenation of ketones and aldehydes to alkanes (Scheme 1a), very few of them have been turned to a deuterative version.[20] In our deoxygenations, all substrates contain a 4-(*N*,*N*-disubstituted amino)aryl as an activating group to facilitate the deoxygenation and to obtain good regioselectivity and chemoselectivity. Such kind of activating groups has been also used by other groups for aromatic C–H functionalization.[21] On one hand, such a functional group plays a necessary role in numerous drug molecules such as antineoplastic agent Chlorambucil (Leukeran) and cholecystokinin receptor agonist Pristinamycin IA (Scheme 1c). On the other hand, the recently developed trimethylarylamonium[22] and iminium[23] chemistry guarantees further transformations of the activating group and will lead to more useful products.

Results and Discussion

Reductive Deoxygenation of Ketones

We performed the optimization of reaction conditions using commercially available ketone **1a** (Table 1). Although our previous reduction of ketones[19b] and deoxygenation of alcohols[19c] proceeded readily in water in extremely low catalyst loading, the deoxygenation of ketone **1a** under the catalysis of **C3** at 5000 *S/C* molar ratio in only water did not occur (entry 1). Water-soluble co-solvent such as methanol, ethanol, isopropanol, acetonitrile, acetone, tetrahydrofuran, *N*,*N*-dimethylformamide, dimethyl sulfoxide, and hexamethylphosphoric triamide did not facilitate the deoxygenation. However, the addition of trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) gave desired product **2a** in 62% and 90% isolated yields, respectively (entries 2 and 3). It is probably the enhanced acidity, high hydrogen-bonding donor ability, and high ionizing power of fluorinated alkanols[24] that promote the deoxygenation. Next, HFIP was selected as the optimal co-solvent to perform catalyst screening at 5000 *S/C* ratio. Our previously developed pyrid-2-yl dihydroimidazole-type (**C1**–**C10**) and tetrahydropyrimidine-type (**C11**) catalysts were first evaluated (entries 4–12), and **C8** gave the highest 95% isolated yield (entry 10). Three ionic catalysts (**C12**–**C14**) developed by Li and co-workers were also tested,[25] but all displayed inferior activities as compared with **C8**

Table 1. Condition optimization for deoxygenation of ketones.



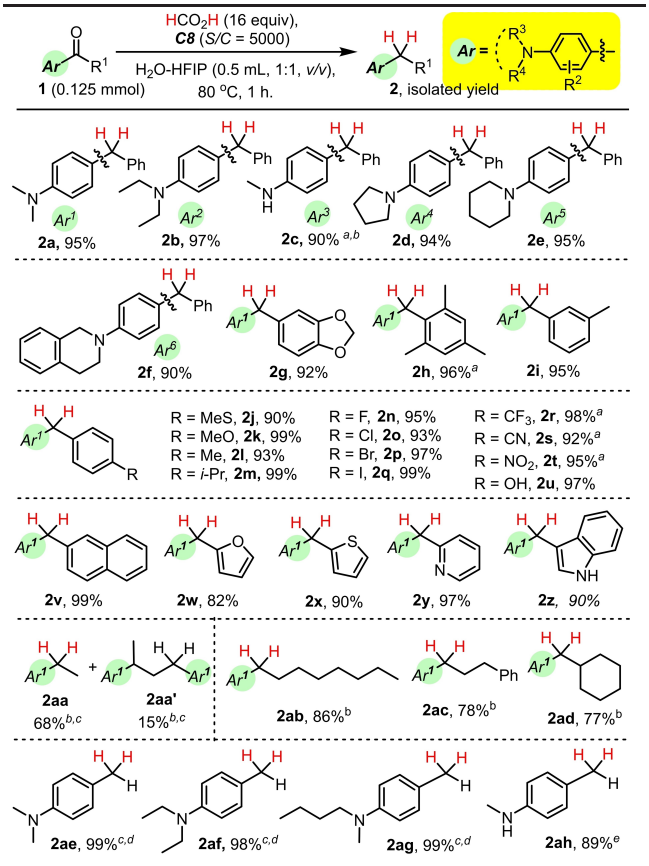
entry	[Ir]	*cosolvent*	*S/C*	*x*	Yield (%)[a]
1	**C3**	none	5 000	16	trace
2	**C3**	TFE	5 000	16	62
3	**C3**	HFIP	5 000	16	90
4	**C1**	HFIP	5 000	16	78
5	**C2**	HFIP	5 000	16	75
6	**C4**	HFIP	5 000	16	82
7	**C5**	HFIP	5 000	16	70
8	**C6**	HFIP	5 000	16	37
9	**C7**	HFIP	5 000	16	74
10	***C8***	***HFIP***	***5 000***	***16***	***95***
11	**C9**	HFIP	5 000	16	43
12	**C10**	HFIP	5 000	16	89
13	**C11**	HFIP	5 000	16	80
14	**C12**	HFIP	5 000	16	74
15	**C13**	HFIP	5 000	16	19
16	**C14**	HFIP	5 000	16	15
17	**C15**	HFIP	5 000	16	trace
18	**C16**	HFIP	5 000	16	trace
19	**C17**	HFIP	5 000	16	0
20	**C8**	HFIP	5 000	12	79
21	**C8**	HFIP	10000	16	57
22[b]	**C8**	HFIP	10000	16	97
23	None	HFIP		16	0

[a] Isolated yields after column chromatography.
[b] For 8 h.

(entries 14–16), although they show catalytic activities toward reduction of ketoens.[25c] When catalysts **C15** and **C16** were used, TLC only showed trace amount of product (entries 17 and 18). Nonionic catalyst **C17**, which was proved very efficient in transfer hydrogenation of aldehydes under neutral conditions with sodium formate,[26] showed no activity in deoxygenating **1a** (entry 19). Thus, **C8** turned out to be the most active catalyst. Decreasing the formic acid amount to 12 equivalents (entry 20), or reducing the catalyst amount by half (entry 21), caused less satisfactory results. However, prolonging the reaction time was beneficial to the reaction (entry 22). In the presence of $[Ir(cod)Cl]_2$ or $[IrCp^*Cl_2]_2$ at 1000 *S/C* ratio, or in the absence of a catalyst (entry 23), no reaction occurred. Overall, the conditions listed in entry 10 were selected as the optimal.

A number of ketone substrates were tested under the optimal conditions, and excellent yields and chemoselectivity were obtained (Table 2). All the chemicals were handled directly in the air, and no inert-gas protection was needed. In most cases, complete conversions of substrates were observed by TLC. First, we tested the substituted amino group in the *para*-position of the aryl. Obviously, *N*,*N*-dialkyl (**2a** and **2b**), *N*-monoalkyl (**2c**), or *N*,*N*-(1,n-alkylene) amino groups (**2d** and **2e**) or their analogues (**2f**) were very efficient in effecting the deoxygenation of the

Table 2. Deoxygenation of ketones.



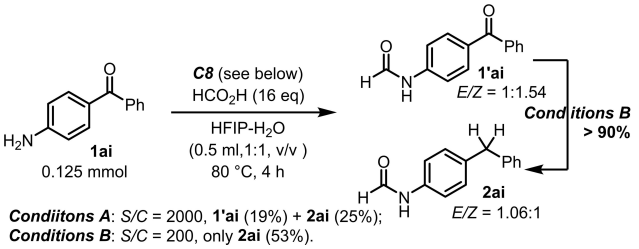
[a] For 4 h.
[b] *S/C* = 2000.
[c] On 0.25 mmol scale.
[d] *S/C* = 20000 in only water.
[e] *S/C* = 5000 in HFIP-water.

corresponding ketones. In contrast, the *N*,*N*-diphenyl or *N*-methyl-*N*-phenyl amino groups only gave complex mixtures, possibly due to their weaker electron-donating abilities. Subsequently, ketones with 4-dimethylaminophenyl group (G^1) were exposed to the optimal conditions to test substrate scope and functional tolerance. 3,4-Methylenedioxyphenyl (**2 g**), 2,4,6-trimethylphenyl (**2 h**), and 3-methylphenyl (**2 i**) ketones, regardless of the substituted positions and numbers of substituents, all selectively underwent the deoxygenation and gave desired products in excellent yields. Methylthio, methoxy, methyl, and isopropyl groups were well tolerated (**2 i**-**2 m**). These groups allow further manipulation of the products. For example, methyl thioethers could undergo fluorium-initiated demethylative cyanation to give thiocyanates.[27] Halogen atoms were also well compatible (**2 n**–**2 q**), in contrast with previous deoxygenation of aromatic ketones in which the required harsh conditions could not tolerate C_{Ar}–Cl bonds.[8c,17b] Other more electrophilic functional groups (**2 r**–**2 t**) such as trifluoromethyl, cyano, and nitro,[28] remained intact during the reductive deoxygenation, although the cyano and nitro were susceptible to reduction.[16a] Notably, also well tolerated were phenolic (**2 u**) hydroxyls. Moreover, ketones with fused and heterocyclic aryls (**2 v**–**2 z**) also demonstrated excellent conversion and chemoselectivity. The present transfer hydrogenation protocol for deoxygenation was also applicable to the deoxygenation of alkyl aryl ketones (**2 aa**–**2 ad**), provided that the catalyst loading was improved (*S*/*C* = 2000), because under the standard conditions (*S*/*C* = 5000) alkenes products resulting from ketone reduction and alcohol elimination appeared. Specially, in the reaction of ketone **1 aa**, a dimeric product **2aa'** was isolated in 15% yield. The deoxygenation of aldehydes was also investigated, and it was much easier. For example, at *S*/*C* = 20000 in only water, aldehyde **2 ae**–**2 ah** were converted to the corresponding 4-toluidine derivatives in quantitative yields.

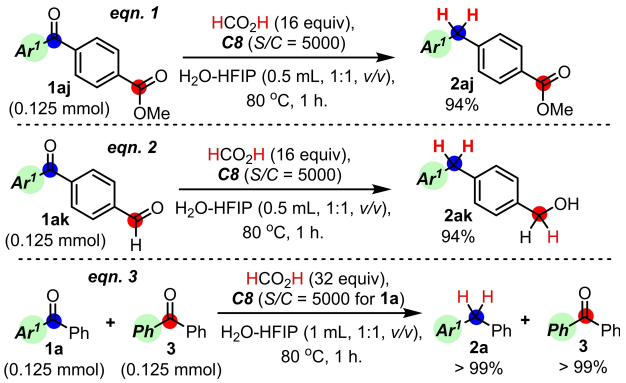
The influence of a free NH_2 group of a directing group was investigated (Scheme 2). Under standard conditions (*S*/*C* = 5000), no deoxygenation prodcut (**2 ai**) was detected by TLC. At *S*/*C* = 2000 (*Conditions A*), formylation product **1'ai** and deoxygenation product **2 ai** were isolated in 19% and 25% yields, respectively. Further imporving the catalyst amount (*S*/*C* = 200, *Conditons B*) led to exclusive deoxygenation product **2 ai** in 53% isolated yield. We also submitted **1' ai** to *Conditions B*, and suprisingly found that it was completely consumed, and the deoxygenation product **2 ai** was generated in more than 90% ^{1}H NMR yield. These results indicated that free 4-aminopheny and 4-formadylphenyl were able to serve as activating groups under higher catalyst loading.

The chemoselectivity over different types of carbonyls were studied by competition experiments (Scheme 3, eqns. 1 and 2). When ketoester **1 aj** was submitted to the standard conditons, only the ketone carbonyl was deoxygenated, while the ester carbonyl remained intact (eqn. 1). Under the same conditions, the ketone carbonyl of ketoaldehyde **1 ak** were deoxygenated, while the aldehyde moiety was reduced to hydroxyl, showing high tolerance of the benzyl hydroxyl. It should be noted that in quite a lot of deoxygenation conditions, the benzyl hydroxyl could not survive.[13,15–17]

Notably, the *para*-(*N*,*N*-dialkyllamino)aryl group of ketones are pivotal as activating and directing group for the dexoygenation. Other less donating substituents, for example, methylenedioxy, methythio, and methoxy, could not promote the deoxygenation under these conditions. Intermolecular competition experiments were performed to show the importance of such an activating group (Scheme 3, eqn. 3). When **1 a** and diphenyl ketone (**3**) were simultaneously submitted to the identical conditions, complete deoxygenation of **1 a** was observed by TLC, while **3** kept intact. These results revealed that the *para*-(*N*,*N*-dialkyllamino)aryl group rendered the carbonyl deoxygenations regioselective and might be useful in further organic syntheses.



Scheme 2. Investigation of directing group with a free NH_2 group.



Scheme 3. Inter- and intramolecular control experiments on carbonyl selectivity.

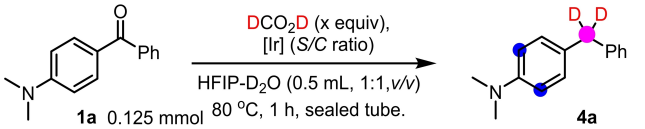
Deuterative Deoxygenation of Ketones

Deuterium-labelled compounds have found indispensable applications, for example, as isotope tracing and kinetic isotope effect probes in mechanistic studies,[29] as internal standards in life-science sample analyses,[30] and as optical polymer fibers in materials science.[31] Particularly in pharmaceutical field, the incorporation of deuterium in medicinal molecules can enhance their metabolism and pharmacokinetic properties.[32a] A variety of synthesized deuterated pharmaceutical candidates are in clinical trials,[32b] and the year of 2017 saw the first marketed deuterated drug-Austedo.[32c] Thus, the selective introduction of deuterium atom(s) in organic compounds, especially the construction of a C(sp^3)–D bond, attracts much attention in synthetic community.[32] In this context, we decided to modify our reductive deoxygenation into a deuterative version by replacing formic acid and water with formic acid-d_2 and deuterium oxide.

Further optimization of the deoxygenative dideuteration conditions was performed in HFIP–D_2O mixed solvents with DCO_2D (Table 3). Screening of the catalysts at 5000 *S/C* ratio (entries 1–11) gave ***C2*** as the most active one (entry 2). Especially, the result with ***C8*** in entry 7, Table 3 was quite different from that in entry 8, Table 1, indicating obvious kinetic isotope effect. In other words, the deoxygenative dideuteration of ketones was more difficult. Prolonging reaction time (entries 12 and 13) or increasing the catalyst loading gave higher yields (entries 14). When H_2O was used instead of D_2O (entry 15), or HCO_2H was used instead of DCO_2D (entry 16), the ratios of mono- and undeuterated products increased a lot. Decreasing the amount of DCO_2D to 8 equiv. demanded further increase of the catalyst loading to 200 *S/C* ratio (entries 18–20). We also found that reducing the solvent by half did not affect the result (entry 21). Without catalyst, no deoxygenative deuteration took place. Thus, the conditions in entry 21 were selected as the optimal. Notably, in the above optimizations, (1) undeuterated, monodeuterated, and dideuterated products were observed in most cases (entries 1–9, 12–15, and 17–21), (2) and electrophilic deuteration of the electron-rich 4-(*N,N*-dimethylamino) phenyl rings of **4a** occurred to varying degrees (see crude ^{1}H NMR spectra in the Supporting Information).

Several ketones were submitted to the optimal conditions (Table 4). In most cases, the products were isolated in 40–99% yields, containing the corresponding dideuteration products in 70–92% molar fractions. Electron-donating methylenedioxy (**4g**), weakly electron-accepting fluorine (**4n**), bromine (**4p**), and idodine (**4q**) atoms, as well as strongly electron-withdrawing trifluoromehtyl (**4r**) and methoxycabronyl (**4k**), all gave desired dideuterated products in moderate to excellent yields. Well compatible

Table 3. Optimization of the conditions.[a]



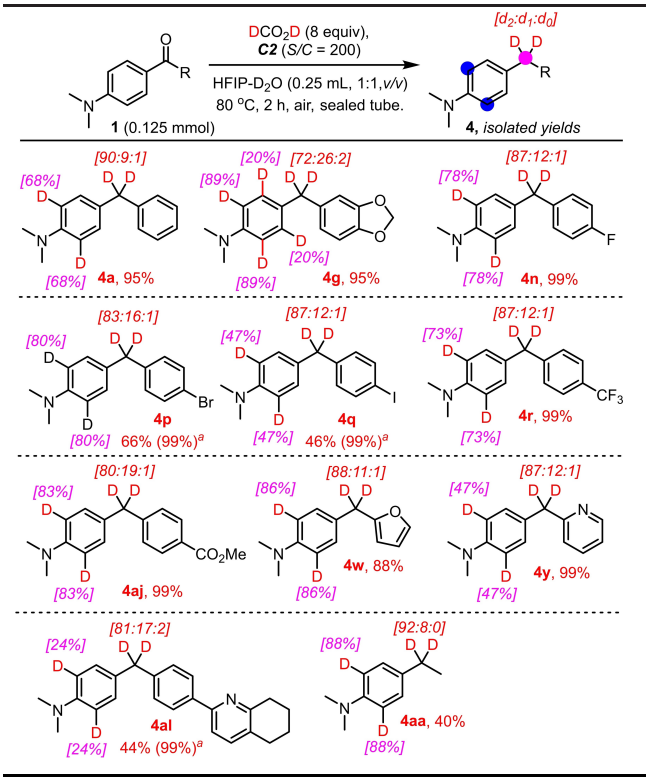
1a 0.125 mmol **4a**

entry	[Ir]	*S/C*	*x*	Yield (%)[b]	*[d_2:d_1:d_0]*[c]
1	**C1**	5 000	16	5	87:12:1
2	**C2**	**5 000**	**16**	**34**	**89:10:1**
3	**C3**	5 000	16	20	89:10:1
4	**C4**	5 000	16	21	94:6:0
5	**C5**	5 000	16	4	84:13:1
6	**C6**	5 000	16	10	86:13:1
7	**C8**	5 000	16	19	88:11:1
8	**C9**	5 000	16	7	98:2:0
9	**C12**	5 000	16	8	92:8:0
10	**C13**	5 000	16	0	–
11	**C14**	5 000	16	0	–
12[d]	**C2**	5 000	16	50	88:11:1
13[e]	**C2**	5 000	16	68	86:13:1
14	**C2**	1 000	16	75	89:10:1
15[f]	**C2**	1 000	16	78	58:35:7
16[g]	**C2**	1 000	16	99	0:10:90
17[d]	**C2**	**1 000**	**16**	**99**	**85:13:2**
18[d]	**C2**	1, 000	8	51	90:9:1
19	**C2**	200	8	84	90:9:1
20[h]	**C2**	200	8	95	85:14:1
21[h,i]	**C2**	**200**	**8**	**99**	**90:9:1**

[a] Reactions in entries 1–13 were performed under nitrogen atmosphere, while the rest without exclusion of air.
[b] Yields calculated from the crude ^{1}H NMR spectra.
[c] Molar ratios of dideuterated (d_2), monodeuterated (d_1), and undeuterated (d_0) products, and the ratios were calculated by the crude ^{1}H NMR spectra (see ESI).
[d] Reaction for 2 4 h.
[e] Reaction for 8 h.
[f] H_2O was used instead of D_2O.
[g] HCO_2H was used instead of DCO_2D.
[h] Reaction for 2 h.
[i] 0.25 mL of solvent was used.

were also heteroaryls such as pyridyl- and furyl-containing groups (**4w**, **4y**, and **4al**). Moreover, alkyl ketones were also good substrates to selectively undergo the deoxygenative dideuteration (**4aa**). The 4-(*N,N*-dimethylamino)phenyl was crucial to the site-selective deoxygenation. However, we herein found that the dimethylamino group also acted as a good directing group to guide aromatic electrophilic deuteration at its *ortho*-positions, and the deuterium incorporation reached as high as 89% (**4g**). Such an observation is in high accordance with Werner's and Lautens's reports on electrophilic deuteration of electron-rich arenes.[21c,d]

Table 4. Deoxygenative dideuteration of ketones.

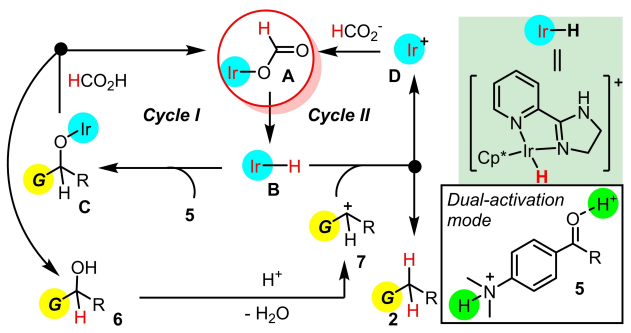


[a] Yields in the parentheses were based on recovered starting materials.

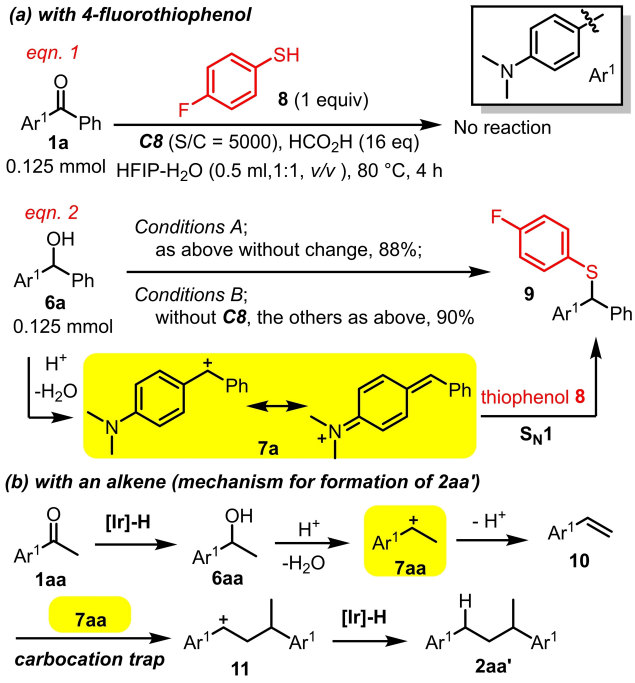
Mechanistic Studies

Based on our previous work on ketone reduction[19b] and alkanol deoxygenation,[19c] a plausible mechanism for carbonyl deoxygenation is proposed (Scheme 4). The key intermediate reducing reagent is iridium hydride **B**, which is generated by β-elimination of iridium formate **A**.[19b,c] The mechanism consists of two catalytic cycles. In *Cycle I*, the dually activated ketone (**5**) by proton is reduced by iridium hydride (**B**) under acidic conditions to alkanol **6**. In *Cycle II*, the carbocation (**7**) generated by acidic treatment of **6**, receives a hydride from **B** to form the deoxygenated product **2**. Notably, cations **7** are stabilized by both de activating group and fluorinated alkanol HFIP. The easy generation and good stability of the cabocations guarantee the deoxygenation. For dialkyl ketones, only reduction to alkanols were observed,[19b] and deoxygenation did not occur. This is because the dialkyl carbocations are quite unstable and difficult to form. The deoxygenation of alkanols **6** was proved to occur very fast in our previous work. For example, even at 1000000 *S/C* ratio, the deoxygenation of **6a** still gave **2a** in 87% yield.[19c] Therefore, we suggest that the rate-determining step for the carbonyl deoxygenation be the reduction of ketone **1** with iridium hydride **B**. Our previous work demonstrated that the reduction of ketone occurred not so fast and was very electronically and sterically sensitive.[19b]

We also attempted to trap the above proposed carbocation **7**. Addition of nucleophilic 4-fluorothiophenol (**8**) to the reaction of **1a** under standard conditions completely prevented the reaction to occur, probably due to the catalyst poisoning caused by **8** (*eqn. 1*, Scheme 5a). Next, we directly use alkanols **6a**, a verified key intermediate in the ketone deoxygenation, to perform the cabocation trapping. With or without the catalyst, thioether **9** was isolated in 88% or 90% isolated yield (*eqn. 2*, Scheme 5a). The formation of **9** can be regarded as an interception of carbocation **7a** via an S_N1 reaction. In addition, the formation of byproduct **2aa'** was well explained by a sequence of trapping of carbocation **7aa** with alkene **10** and



Scheme 4. Mechanism for deoxygenation of ketones.



Scheme 5. Trapping of the proposed carbocations.

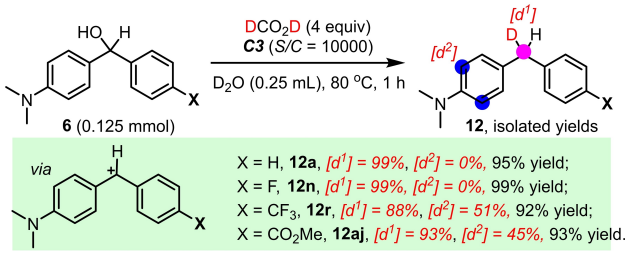
transfer hydridation of the resultant carbocation **11** with iridium hydride (Scheme 5b).

Next, to gain more detailed insight into the mechanism of deoxygenative dideuteration of ketones, we performed the deoxygenative monodeuteration of alkanols **6** (Scheme 6), in light of the similar reaction rates of the deoxygenations of **6** and **6**-d_1 (secondary kinetic isotope effect).[19c] At lower catalyst loading ($S/C = 10000$) and with less amount of DCO_2D (4 equiv.) in only D_2O, selected diarylmethanols (**6a**, **6n**, **6r**, and **6aj**) were converted to desired products in 92–95% isolated yields and up to 88–99% desired deuterium incorporations. Additionally, electrophilic deuteration was also observed when electron-withdrawing groups such as trifluoromethyl (**12r**) and methoxycarbonyl (**12aj**) were present.

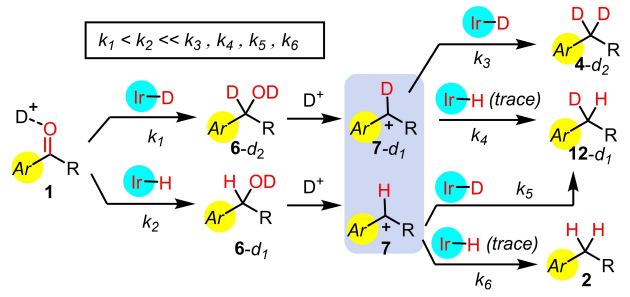
The plausible mechanism for the iridium-catalysed deoxygenative deuteration of ketones was shown in Scheme 7. Similarly, the first step involves the transfer deuteration of **1** with iridium deuteride, which was generated from DCO_2D and iridium chloride ***C2***, to deliver α-monodeuterated alkanol (**6**-d_2). In the second step, transfer deuteration of the carbocation **7**-d_1 gave desired dideuterated product **4**-d_2. Formic acid-d_2 served as both deuteride donor and acidic promotor.[34] In both steps, competitive transfer hydrogenation with iridium hydride was contaminated, causing incomplete deuterium incorporations that gave rise to corresponding alkanol **6**-d_1 and monodeuterated alkane **12**-d_1. The iridium hydride probably came from trace amount of HCO_2D in commercial DCO_2D (98% D). Transfer deuteration of ketones is much slower than the transfer hydrogenation ($k_1 < k_2$) (entry 8, Table 1 vs entry 7, Table 3), whereas the rates of transfer deuteration and hydrogenation of carbocations **7** and **7**-d_1 are comparable (98% D in DCO_2D contributed 99:1 D/H ratio in **12n**). Thus, it is the competition between transfer deuteration and transfer hydrogenation of ketones that mainly causes the relatively low ratios of alkane-d_2 products in the overall deoxygenation (Table 4). For example, the trace amount (2%) of HCO_2D contributed to 8–28% H incorporation in the deoxygenative dideuteration of ketones (for example, **4g**, **4ad**).

Gram-Scale Synthesis, Product Derivations, and Synthetic Applications

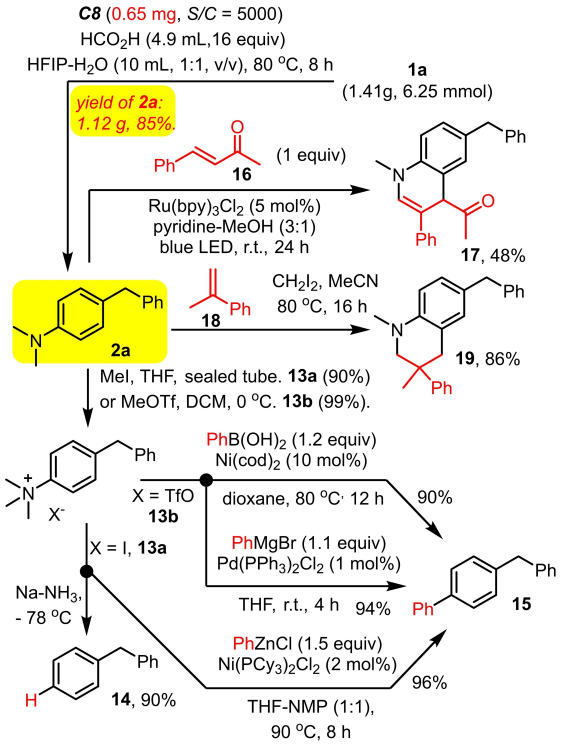
A gram-scale deoxygenation was also performed. In the presence of only 0.65 mg catalyst, 1.41 g of ketone **1a** was facilely converted to desired product **2a** in 85% isolated yield (Scheme 8, top). In our hydrogenative and deuterative deoxygenations of ketones, a 4-(*N*,*N*-disubstituted amino) aryl is necessary to activate the carbonyl and to direct a good regioselectivity. Such a group can be easily functionalized and thus allows transformation to other useful molecules. As indicated in Scheme 8, methylation of **2a** with methyl iodide or methyl triflate led to ammonium salt **13a** or **13b**. Treatment of **13a** with Na–NH_3(l) gave deamination product **14** in 90% yield. Cross-couplings



Scheme 6. Deoxygenative monodeuteration of alkanols.



Scheme 7. Mechanism for deoxygenative deuteration of ketones and alkanols.



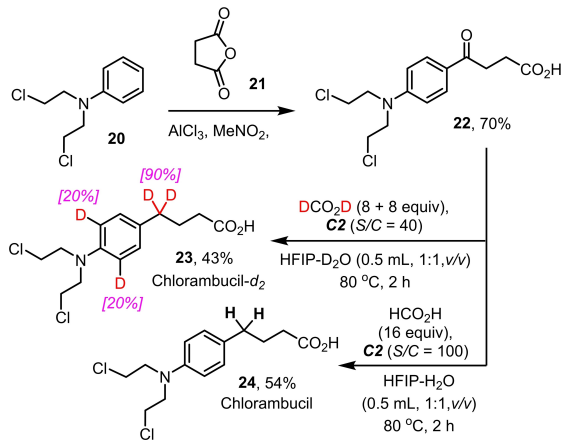
Scheme 8. Product derivations and synthetic applications.

of **13b** with phenyl boric acid, phenyl magnesium bromide, or phenyl zinc chloride, all gave desired product **15** in excellent yields. In addition, direct manipulations to azacycles of the activating group were also accessible. For example, Pandey's group reported the conversion of **2a** into 1,4-dihydroquinoline **17** through photocatalytic generation of amonomethyl radical and subsequent addition and cyclization with enone **16**.[23b] Wang's group synthesized tetrahydroquinoline **19** through aryl iminium formation by treating with methylene diiodide and subsequent [4+2] cycloaddition with olefin **18**.[23c]

The 4-(*N*,*N*-disubstituted amino) aryl also emerges as an important structural subunit in some medicines such as Chlorambucil (Leukeran), which is marketed and widely used in clinic for treating various forms of cancer. With our iridium-catalysed dideuteration protocol, chlorambucil (**24**) and its 4,4-d_2 counterpart (**23**) were successfully synthesized (Scheme 9). Friedel-Crafts acylation of *N*,*N*-bis(2-chloroethyl)aniline (**20**) with succinic anhydride (**21**) gave ketone **22** in 70% yield. Submission of **22** to our deoxygenation and dideuteration delivered **24** and **23** in 54% and 43% yields, respectively. Moreover, it also demonstrated the good tolerance of chloroalkyl and carboxylic groups, especially the former, which was intolerable in many reductive conditions for deoxygenations.[1–13,15–17]

Conclusion

We have developed an iridium-catalysed deoxygenation of ketones and aldehydes. Formic acid is used as hydrogen source and water is used as co-solvent. At 5000 *S/C* ratio, a number of 4-(*N*,*N*-disubstituted amino) aryl ketones are readily deoxygenated in excellent yields and chemoselectivity. Numerous functional groups, such as halogen atoms, ester, cyano, nitro, phenolic and alcoholic hydroxyls, heteroaryls, secondary amine, carboxylic acids, and especially alkyl chloride are well tolerable. Such a deoxygenation protocol also enables the preparation of geminally dideuterated alkane, by simply using DCO_2D as deuteride donor and D_2O as co-solvent. High deuterium incorporation at the target sites is obtained (up to 90% for dideuteration). The proposed mechanism involves the transfer hydrogenation of ketones to alkanols and deoxygenation of alkanols via transfer hydrogenation of the generated carbocations. Notably, the deuterative deoxygenation of ketones is much slower than the hydrogenative counterpart. The activating 4-(*N*,*N*-disubstituted amino)aryl group have been demonstrated to undergo a variety of useful transformations such as cross-coupling and transannulation reactions to synthesize azacyclic and multi-aromatic structures. A synthetic application of the deoxygenative deuterations has also been achieved to prepare the deuterated drug molecule Chlorambucil-4,4-d_2.



Scheme 9. Synthesis of Chlorambucil-4,4-d_2.

Experimental Section

General Procedure for Deoxygenation of Ketones 1.

To a 5-mL tube was sequentially added ketone **1** (0.125 mmol), and 125 μL of ***C8*** catalyst solution (0.0005 mmol/mL for *S/C* = 2000; 0.0002 mmol/mL for *S/C* = 5000; 0.00005 mmol/mL for *S/C* = 20000) in water, 125 μL of deionized water, 250 μL of HFIP (in most cases) or water (only for **1ai**, **1aj**, and **1ak**), and HCO_2H (76 μL, 2 mmol, 16 equiv.). The tube was sealed with a rubber septum that was connected with an empty balloon. The resultant reaction mixture was immersed in a preheated 80 °C heating-mantle and was stirred for 2 h. Upon cooling to room temperature, diluting with saturated sodium bicarbonate solution (5 mL), extracting with ethyl acetate (5 mL × 3), drying over Na_2SO_4, concentration of the organic phase under reduced pressure, and purification by column chromatography on silica gel with PE and EA as eluent afforded desired products **2**.

General Procedure for Deoxygenative Dideuteration of Ketones 1.

To a 5-mL reaction tube was sequentially added ketone **1** (0.125 mmol), 125 μL of the ***C2*** catalyst solution (0.005 mmol/mL for *S/C* = 200) in D_2O, 125 μL of HFIP, and 38 μL of formic acid-d_2 (DCO_2D, 1 mmol, 8 equiv.). The tube was sealed with a rubber septum that was connected with an empty balloon. The resultant reaction mixture was immersed in a preheated 80 °C heating-mantle and was stirred for 2 h. Upon cooling to room temperature, diluting with saturated sodium bicarbonate solution (5 mL), extracting with ethyl acetate (5 mL × 3), drying over Na_2SO_4, concentration of the organic phase under reduced pressure, and purification by column chromatography on silica gel with PE and EA as eluent afforded desired products **4**.

For more details of experimental procedures, analytical data, and NMR spectra, see the Supporting Information.

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FULL PAPER

Iridium-Catalysed Reductive Deoxygenation of Ketones with Formic Acid as Traceless Hydride Donor

Adv. Synth. Catal. **2020**, *362*, 1 – 11

Z. Yang, X. Zhu, S. Yang, W. Cheng, X. Zhang*, Z. Yang*