C–O Bond Cleavage

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Catalytic Cleavage of Ether C–O Bonds by Pincer Iridium Complexes**

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In memory of Gregory L. Hillhouse

Abstract: *The development of efficient catalytic methods to cleave the relatively unreactive C–O bonds of ethers remains an important challenge in catalysis. Building on our group's recent work, we report the dehydroaryloxylation of aryl alkyl ethers using pincer iridium catalysts. This method represents a rare fully atom-economical method for ether C–O bond cleavage.*

The relative inertness of the C(alkyl)–O bond of aryl alkyl ethers both contributes to the stability of lignocellulosic biomass[1] and leads to its value as a protecting group for phenols.[2] In both cases, less-than-ideal conditions are required to break this unreactive bond. Many current processes for cleavage of the C–O bonds in lignin require the use of H_2, which presently invokes a non-renewable carbon-based input. Deprotection of alkyl (typically methyl) aryl ethers typically uses stoichiometric quantities of strong Lewis acids[2] (BBr_3, TMSI) or strong nucleophiles[3] (typically thiols or their salts) (Figure 1). Thus the development of systems that can effect the redox or atom-economic[4] catalytic cleavage of ether C–O bonds currently represents a major goal in the field of catalysis.

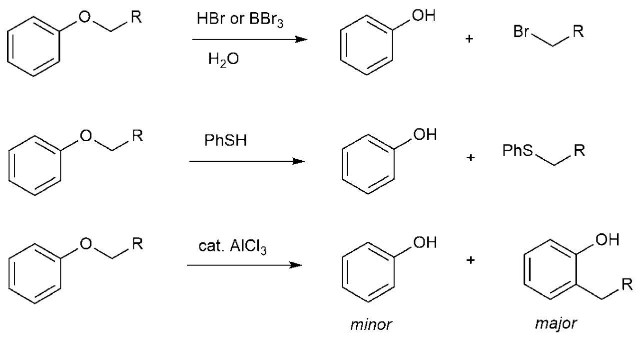

Figure 1. Classical methods for ether C–O bond cleavage.

Friedel–Crafts catalysts have classically been shown to rearrange phenol alkyl ethers to 2-(alkyl)phenols[5] (Figure 1). Although not a true net cleavage reaction, advances in acid catalysis have allowed this process to become synthetically useful for the production of *o*-alkylphenols.[6]

The use of H_2 represents the most widely studied catalytic method to cleave ethers. Most classical examples require pressures and temperatures higher than typically accessible under common laboratory condition to cleave alkyl ethers, with an important exception: the Pd-catalyzed hydrogenolysis of benzyl ethers is a standard transformation in organic synthesis.[7] More recently, some notable examples have advanced the scope of ether C–O bonds cleavable with H_2 under more accessible conditions. Hartwig and co-workers have developed Ni-based catalysts that selectively cleave the aryl C–O bond of ethers under only 1 atm H_2 (Figure 2).[8a,b] In studies by Marks and co-workers, cyclic alkyl ethers are catalytically cleaved using $Yb(OTf)_3$ through dehydroalkoxylation.[9] To overcome the endergonic ring opening, the initially generated alkenols were hydrogenated using palladium nanoparticles. Ellman and Bergman reported a Ru-catalyzed cleavage of alkyl aryl ethers, in which an adjacent alcohol group serves as the internal H_2 donor.[1d] Aside from that work, we are not aware of any reported method whereby the C–O bond of an ether can be cleaved catalytically in

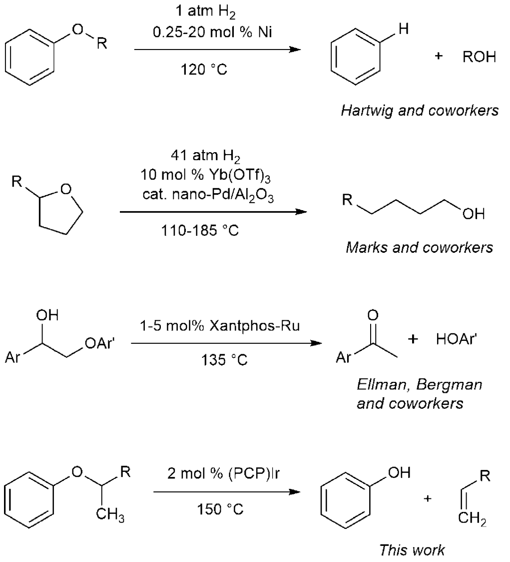

Figure 2. Recent advances in catalytic ether C–O bond cleavage.

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a fully atom-economic fashion, that is, without the use of additional reagents (including H_2). We report here the first such example, an iridium-catalyzed dehydroaryloxylation of alkyl aryl ethers.

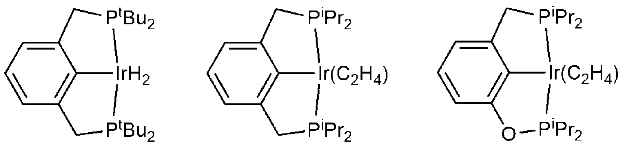
Recently, our group and that of Hartwig independently developed methods for the formation of ether C–O bonds through iridium-catalyzed olefin hydroaryloxylation.[10] In our system, iridium complexes of PCP-type pincers catalyze the O–H addition of phenols across olefins at 150 °C. The reaction is understood to proceed through formation of a six-coordinate (pincer)Ir(H)(OAr)(olefin), insertion of the olefin into the Ir–OAr bond, and then C–H reductive elimination. In the course of our investigation of the reaction mechanism, we observed that the catalysts could also effect the "back-reaction", that is, ether dehydroaryloxylation. We had previously reported that (^{tBu}PCP)Ir and EtOPh or *i*PrOPh underwent such a reaction in a stoichiometric fashion to give (^{tBu}PCP)Ir(H)(OPh) and the corresponding free olefin.[11] However, heating a 500 mM solution of (3,5-Me$_2$C$_6$H$_3$)O-*i*Pr in the presence of 2 mol % (^{tBu}PCP)IrH$_2$/TBE[12] results in negligible catalytic activity (4 % conversion to (3,5-Me$_2$C$_6$H$_3$)OH after 16 h at 150 °C). As is the case in the hydroaryloxylation reaction, the use of less sterically congested (^{iPr}PCP)Ir[13] and (^{iPr}PCOP)Ir[14] precursors is found to lead to much higher conversions (88 % and 92 % respectively; Table 1, entries 2 and 3b) under identical conditions. No organic products other than the phenol and olefin are detected during the reaction. In particular, the dehydroaryloxylation process does not suffer from a competing Friedel–Crafts alkylation reaction between the olefin and the phenol.

The scope of the dehydroaryloxylation by (^{iPr}PCOP)Ir, as initially determined, is shown in Table 1, entries 3–10. Reactions were conducted in glass ampules sealed under vacuum to facilitate the loss of gaseous olefins from the liquid phase.[15] In most cases, more than 70 % conversion was obtained with 2 mol % catalyst within 16–48 h at 150 °C. In the case of *p*-methoxyphenyl isopropyl ether, no cleavage of the methyl C–O bond is observed (entry 5). (3,5-Me$_2$C$_6$H$_3$)O-2-Bu undergoes 99 % conversion after an extended period (240 h; entry 4d), along with the detection of a mixture of butenes. Thus, despite a slower initial rate when compared with the corresponding aryl isopropyl ether (41 % versus 72 % after 4 h), the 2-butyl ether reaction also eventually proceeds to full conversion (entries 4c,d).

While we have not yet conducted extensive optimization of reaction conditions, we note that the reaction proceeds at a much faster rate at 200 °C. In the case of (3,5-Me$_2$C$_6$H$_3$)O*i*Pr, 97 % conversion is observed after only 1 hour (entry 11), corresponding to an average TOF of 0.81 min^{-1}. The higher reaction temperature allows for the conversion of an aryl *n*-octyl ether (entries 13a, b), a substrate that was found to react only slowly at 150 °C (entry 10).[16]

Table 1: Optimization and scope of the dehydroaryloxylation.[a]

$$\underset{500\text{ mM}}{\text{ArO-R}} \xrightarrow[\substack{150\ ^\circ\text{C or }200\ ^\circ\text{C}\\ p\text{-xylene}}]{2\text{ mol \% } \mathbf{A}, \mathbf{B} \text{ or } \mathbf{C}} \text{ArOH} + \text{olefin}$$

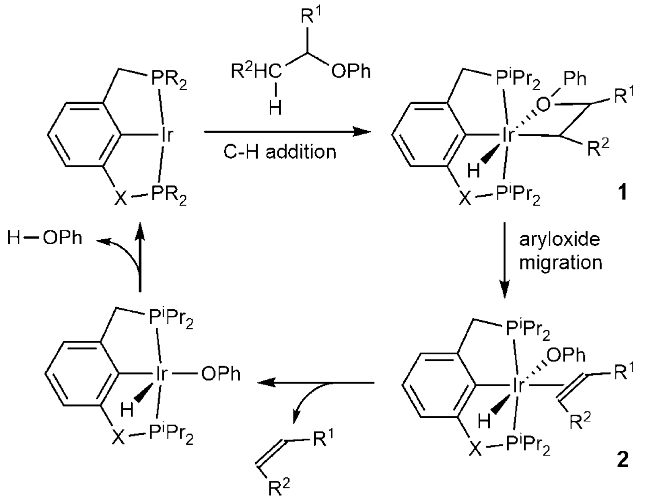


(^{tBu}PCP)IrH$_2$ **A** (^{iPr}PCP)Ir(C$_2$H$_4$) **B** (^{iPr}PCOP)Ir(C$_2$H$_4$) **C**

Entry	*T* [°C]	Ar	R	Cat.	*t* [h]	Conv. [%]
1	150	3,5-Me$_2$C$_6$H$_3$	*i*Pr	A[b]	16	4
2	150	3,5-Me$_2$C$_6$H$_3$	*i*Pr	B	16	88
3a	150	3,5-Me$_2$C$_6$H$_3$	*i*Pr	C	4	72
3b	150	3,5-Me$_2$C$_6$H$_3$	*i*Pr	C	16	92
3c	150	3,5-Me$_2$C$_6$H$_3$	*i*Pr	C	48	97 (83)[c]
4a	150	3,5-Me$_2$C$_6$H$_3$	2-Bu	C	4	41
4b	150	3,5-Me$_2$C$_6$H$_3$	2-Bu	C	20	77
4c	150	3,5-Me$_2$C$_6$H$_3$	2-Bu	C	48	85
4d	150	3,5-Me$_2$C$_6$H$_3$	2-Bu	C	240	99
5	150	4-MeOC$_6$H$_4$	*i*Pr	C	44	62 (55)[c]
6	150	4-FC$_6$H$_4$	*i*Pr	C	36	76 (52)[c]
7a	150	2-naphthyl	*i*Pr	C	16	80
7b	150	2-naphthyl	*i*Pr	C	48	88 (72)[c]
8	150	Ph	*i*Pr	C	48	78 (63)[c]
9	150	4-MeC$_6$H$_4$	*i*Pr	C	48	90
10	150	3,5-Me$_2$C$_6$H$_3$	*n*-Oct	C	48	23
11	200	3,5-Me$_2$C$_6$H$_3$	*i*Pr	C	1	97
12a	200	Ph	*i*Pr	C	16	55
12b	200	Ph	*i*Pr	C	48	55
13a	200	3,5-Me$_2$C$_6$H$_3$	*n*-Oct	C	16	57
13b	200	3,5-Me$_2$C$_6$H$_3$	*n*-Oct	C	240	68
13c	200	3,5-Me$_2$C$_6$H$_3$	*n*-Oct	B	16	52
13d	200	3,5-Me$_2$C$_6$H$_3$	*n*-Oct	B	240	72
14a	200	3,5-Me$_2$C$_6$H$_3$	*n*Bu	C	4	66
14b	200	3,5-Me$_2$C$_6$H$_3$	*n*Bu	C	48	69
15a	200	3,5-Me$_2$C$_6$H$_3$	2-Bu	C	1	64
15b	200	3,5-Me$_2$C$_6$H$_3$	2-Bu	C	16	96

[a] 2 mol % catalyst (500 mM ether and 10 mM catalyst). Reactions were carried out in glass ampules sealed under vacuum (0.01 Torr), headspace/solvent volume = 50, on a 0.05 mmol scale and were monitored by GC using C$_6$Me$_6$ as an internal standard. [b] 1.0 equiv *tert*-butylethylene added to dehydrogenate (^{tBu}PCP)IrH$_2$. [c] The yield of isolated products on a 0.25 mmol scale is indicated in parentheses.

The mechanism of the dehydroaryloxylation reaction is proposed to occur through the same set of steps as does the stoichiometric variant with (^{tBu}PCP)Ir and EtOPh or *i*PrOPh studied previously by our group[11b] (Scheme 1). The initial step is the addition of a C–H bond to yield **1**, followed by aryloxide migration to form the six-coordinate intermediate **2**. Loss of the olefin and phenol from **2** regenerates the active (pincer)Ir species and completes the catalytic cycle. The apparent relative reactivity levels observed for the ethers investigated (Table 1) are consistent with aryloxide migration being the rate-determining step, assuming that the transition state would have some character of both species **1** and **2**. Primary alkyl transition metal complexes are generally thermodynamically favored over secondary alkyls;[17] thus R^2 = H would be favored over R^2 = alkyl, accounting for the much greater reactivity of *i*PrOAr and 2-BuOAr compared with *n*BuOAr and *n*-OctOAr. The binding of propene would be less sterically demanding than the binding of 1-butene, contributing to a greater reactivity for *i*PrOAr versus 2-

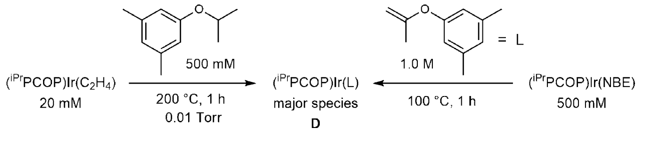


Scheme 1. Proposed mechanism for the dehydroaryloxylation.

BuOAr. *i*PrOAr would also enjoy a statistical advantage of a factor of two, having two methyl groups bound to the α-carbon (this point is equally applicable if C–H addition or β-aryloxide elimination is rate-determining).

The dehydroaryloxylations do not appear to be limited by thermodynamic factors under our reaction conditions. Thus even at 150 °C the reaction of 2-BuOAr and *i*PrOAr can proceed essentially to completion (Table 1, entries 3c and 4d); the equilibrium would of course be shifted significantly further right by higher temperature. In these cases with gaseous olefin product the equilibrium has been favored by employing a high ratio (50:1) of head space to solution volume. Note that at equilibrium *n*BuOAr and 2-BuOAr would achieve the same distribution of products (in fact, no interconversion between these two ethers is observed) and that the less reactive ether, *n*BuOAr, (see entry 14) is thermodynamically higher in energy.[18] Thus the relatively low reactivity of *n*BuOAr (and by extrapolation, *n*-OctOAr) is not a thermodynamic effect.

Pincer complexes **A**–**C** are known to be thermally robust in the context of alkane dehydrogenation; nevertheless, we sought to determine the nature of the iridium-containing species present after completion of reactions run at 200 °C.[19] The conditions of entry 11 were approximated inside an NMR tube sealed under vacuum (500 mM ether, 20 mM **C**; Scheme 2). After 1 hour at 200 °C, the major organometallic product identifiable in the ^{31}P NMR spectrum, **D**,[20] was distinct from **C**, (^{iPr}PCOP)Ir(propene), or (^{iPr}PCOP)Ir(H)(OAr). We hypothesized that as the reaction proceeds, the increasing concentration of propene (a hydrogen acceptor) could favor the dehydrogenation of the isopropoxy group by (^{iPr}PCOP)Ir. The resulting vinyl ether might strongly bind to the three-coordinate Ir center to give species **D**.



Scheme 2. Evidence of a vinyl ether addition product as the major iridium-containing species present after completion of reactions run at 200 °C.

To test this hypothesis, we prepared 2-(3,5-dimethylphenoxy)propene independently and treated it with a solution of the labile olefin complex (^{iPr}PCOP)Ir(NBE).[20] The ^{31}P NMR spectrum corresponding to the unknown **D** was observed,[20] confirming that **D** is a product of addition of (^{iPr}PCOP)Ir(vinyl ether). This result indicates that the catalyst remains homogenous throughout the reaction.

In conclusion, we report a unique process whereby the C–O bonds of ethers are catalytically cleaved by (PCP)Ir-type catalysts with complete atom-economy. This dehydroaryloxylation reaction proceeds in moderate to excellent conversion for a variety of substituted alkyl aryl ethers. Efforts are currently underway to increase the catalytic efficiency and functional group tolerance of this transformation.

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[19] We also carried out the reaction in entry 11 in the presence of Hg. 74 % conversion was observed after 1 hour. The measurable, but not major decrease in activity may reflect the reactive nature of free Hg atoms in solution (“dissolved vapor”) generated at high temperature. This preliminary evidence against catalysis by Ir nanoparticles has been supported by a kinetic analysis not yet submitted for publication. We thank a reviewer for this suggestion.

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