Reductive Bond Cleavage

Selective Reductive Cleavage of Inert Aryl C−O Bonds by an Iron Catalyst**

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The transition-metal-catalyzed activation of aryl carbon–oxygen bonds is a challenging task for organic chemists because of the relatively high bond energies.[1] Although various effective catalysts have been developed for activating aryl C−O bonds to form carbon–carbon and carbon–heteroatom bonds,[2] the development of a non-toxic and inexpensive iron catalyst for this transformation remains a desirable, but challenging research goal from environmental and economic perspectives.[2a–c] Iron catalysts are effective for the activation of aryl carbon–oxygen bonds of aryl tosylates,[3] triflates,[3b] carboxylates,[4] sulfamates,[3a,5] and carbamates;[5] however, to the best of our knowledge, the iron-catalyzed activation of aryl carbon–oxygen bonds of aryl ethers has not been reported. Thus, the objective of this work was to develop an iron catalyst that enables the selective reductive cleavage of aryl carbon–oxygen bonds in aryl ethers. Such a reductive cleavage might become an important process for the selective fragmentation of lignin into smaller molecules, which can be further transformed into fuels or high-value chemicals.[6] Furthermore, this process might be valuable for organic synthesis, because it can expand the utility of alkoxy,[7] pivalate,[8] and aryl *O*-carbamate[9] substituents as removable directing groups, as these are frequently used to overcome the drawbacks of unselective arene functionalization.

The reductive cleavage of C−O bonds in aryl ethers often requires high temperatures, and occurs with poor selectivity.[10] Several highly selective homogeneous catalyst systems that are based on nickel compounds have been reported for the reductive cleavage of aryl C−O bonds.[7,11] These results have sparked growing research interest in this area over the past few years.[8,9,12] Hartwig and co-workers reported an effective heterogeneous catalyst system that was formed in situ from [Ni(cod)$_2$] or [Ni(CH$_2$TMS)$_2$(TMEDA)] (cod = 1,5-cyclooctadiene, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, TMS = trimethylsilyl).[13] Zhao, Lercher, and He reported another heterogeneous catalyst system (57 wt% Ni/SiO$_2$) that was obtained from Ni(NO$_3$)$_2$·6H$_2$O, SiO$_2$, and HNO$_3$.[14] During the preparation of this manuscript, a method with an expensive Rh catalyst was also described.[15] Herein, we report a highly selective iron-based catalytic system for the reductive cleavage of aryl C−O bonds that employs iron(III) acetylacetonate ([Fe(acac)$_3$]) as the catalyst precursor and LiAlH$_4$ as the reducing agent. The present catalyst system was further shown to be effective for the selective cleavage of the β-O-4 linkage of lignin model compounds under a hydrogen atmosphere in the absence of LiAlH$_4$.[16] Moreover, through the cleavage of inert aryl C−O bonds by the iron catalyst, a strategy has been developed for the synthesis of regioisomeric products that are unattainable through conventional functionalization of substituted benzene derivatives.[7–9,17]

The reductive cleavage of diphenyl ether was chosen as the model reaction to investigate the efficiency of various iron catalyst precursors. A reaction using FeCl$_3$ gave only small amounts of phenol and benzene as the products (see the Supporting Information, Table S2). A combination of FeCl$_3$ and a ligand, such as *N*,*N*′-dimethylethylenediamine, 2,2′-bipyridine, or triphenylphosphine, did not improve the reaction results (Table S2, entries 3–5), which suggests that bonded ligands are not advantageous. The use of other iron salts, including ferric citrate, ferrocene, and γ-Fe$_2$O$_3$, also led to only a small amount of conversion (Table S2, entries 6–8). Ferric acetylacetonate, however, was an efficient catalyst precursor for our reaction. As described below, when this catalyst is employed for such a reductive cleavage, the desired phenol and benzene products are obtained in high yields (Table 1, entry 1). After a suitable catalyst system had been identified, other critical reaction parameters, such as the use of additives, the catalyst amount, temperature, and tolerance to moisture, were optimized. Sodium *tert*-butoxide was found to be indispensable as an additive, because product formation was not observed in its absence. When the catalyst loading was reduced to 5 mol%, the product yield dropped significantly, even with a prolonged reaction time of 40 h. The reaction could proceed smoothly at temperatures of 100°C and 120°C, but the experimental results were not always reproducible. Therefore, we chose a reaction temperature of 140°C. Furthermore, the transformation must be performed under an inert atmosphere, because some of the reagents, including LiAlH$_4$ and *t*BuONa, were sensitive to moisture.

Following the optimization of the catalyst and the associated reaction conditions, we evaluated the scope of

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this method for a large number of compounds. In some cases, the yields of isolated products were significantly lower than those obtained from gas-chromatographic analysis of the reaction mixture; this might be due to the loss of volatile products during purification by column chromatography. When diaryl ethers were employed as the substrates, only aryl C−O bonds were cleaved, and hydrogenation of the aryl rings hardly occurred (Table 1, entries 1–7). This complete selectivity for the cleavage of the C−O bonds over the hydrogenation of aryl π-bonds is in clear contrast to the hydrogenation of aryl ethers with heterogeneous catalysts,[18] which typically leads to a mixture of arenes, cycloalkanes, phenols, and cycloalkanols. Furthermore, we found that aryl hydroxy groups were tolerated (Table 1, entries 13 and 16), whereas aryl carbon–fluorine and carbon–chlorine bonds were cleaved under our reaction conditions (Table 1, entries 9 and 11). The desired products were not observed when diaryl ether substrates that bear carboxyl, nitryl, or ester groups were employed (data not shown).

The substrate that bears an electron-withdrawing fluorine substituent was less reactive than substrates bearing electron-donating alkyl or methoxy moieties. For example, the reductive cleavage of 4-fluorodiphenyl ether required a high temperature (180°C) to ensure the reaction to proceed smoothly (Table 1, entries 8 and 9). The bond-cleavage reaction did not occur with diaryl ethers bearing two fluorine substituents. Steric hindrance had a crucial effect on the reaction, and the cleavage of 2,6-dimethyldiphenyl ether hardly occurred at the sterically more-hindered C−O bond (Table 1, entry 7).

In the presence of both aryl and alkyl C−O bonds, reductive cleavage selectively occurred at the aryl C−O bonds, and only trace amounts of the products of alkyl C−O bond cleavage were observed (Table 1, entries 4, 10, 14–21). Phenyl methyl ether without any further substituents showed poor reactivity (Table 1, entry 14), whereas the cleavage of naphthalene derivatives always resulted in high product yields (Table 1, entries 19 and 21). However, in contrast to the results of previously reported reactions using nickel catalyst systems,[7,14] the introduction of methoxy or phenyl groups onto the aryl rings increased the reactivity of the aryl methyl ether (Table 1, entries 15–18). Our results therefore suggest that the iron-based catalyst developed in this work has additional unique features over the reported nickel-based catalysts.[7,14]

Having identified a catalyst for the reductive cleavage of simple aryl ethers, we tested the ability of this system to catalyze the cleavage of the β-O-4 linkage of lignin model compounds, which is the most abundant linkage in lignin.[6b,16] A dimeric lignin model compound that contained a β-O-4 linkage was smoothly converted into the desired products with high selectivity and without saturation of the aromatic rings (Table 1, entry 25). The reductive cleavage selectively occurred at the alkyl C−O bond. Considering that the use of LiAlH$_4$ would severely limit the application of this transformation to real-world biomass processing, we chose to replace LiAlH$_4$ with hydrogen gas as the hydrogen source. The experimental results suggest that aryl ethers were almost inactive under the conditions using H$_2$ as the reductant

(Table 1, entries 2, 5, 20, and 23), whereas the β-O-4 linkage of a series of lignin model compounds was smoothly cleaved to give phenols in high yields (Table 2) and acetophenone derivatives in low yields (Table S4). In fact, the acetophenone product could be further converted into organic products under the reaction conditions (see Scheme S1), which might explain why a high yield of acetophenone could not be obtained. Some unknown organic products were also observed, but our attempts to identify these products were not successful. In line with previous work related to the cleavage of lignin-related β-O-4 linkages,[16a] a small amount of 2-phenoxyacetophenone, which is an intermediate of the dehydrogenation of the benzylic alcohol moiety of the substrate, was also detected (Scheme S2); this intermediate could then undergo cleavage of the ether bond to yield acetophenone and phenol (Scheme S3). However, we are not sure whether the primary mechanistic pathway involves the formation of 2-phenoxyacetophenone followed by hydrogenative cleavage of the ether bond,[16a] because the C−O cleavage reaction possibly occurs under experimental conditions where the hydroxy group in the substrate was replaced by a methoxy group to block the formation of 2-phenoxyacetophenone as an intermediate. Although the cleavage of the ether bond also occurred in the absence of hydrogen gas, the desired product was obtained in a lower yield (Table 2, entry 2), which prompted us to perform the cleavage reactions under hydrogen atmosphere. As shown in Table 2, several functional groups, including methoxy, fluoro, bromo, nitryl, and amido groups, were tolerated (Table 2, entries 5–9), whereas the presence of aryl hydroxy groups significantly hindered the reaction (Table 2, entry 10).

The [Fe(acac)$_3$] catalyst precursor was further used to address another challenge in organic synthesis; in this case, a methoxy group was employed as a removable directing group to synthesize rare regioisomeric products that are difficult to obtain from the direct functionalization of substituted benzene derivatives.[7,17] As shown in Scheme 1,
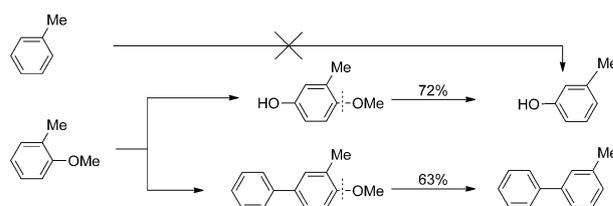
Scheme 1. Synthesis of the regioisomeric products that are unattainable from conventional toluene functionalization (for the reaction conditions, see the Supporting Information, Scheme S4).

the *meta*-substituted products are often unattainable from a reaction of toluene, because the methyl group is an *ortho/para*-directing substituent. However, when applying our strategy, the *meta*-substituted products prevail, and two *meta*-substituted toluene derivatives were obtained from 3-methylanisole in moderate yield (Scheme 1). Although our method has obvious limitations, the previously unattainable regioisomeric products can be synthesized from the functionalization of substituted benzenes with this strategy.[7–9,17]

Table 1: Arene products of the iron-catalyzed reductive cleavage of C—O bonds.[a]

$$\text{R'}{-}\text{O}{-}\text{R} \xrightarrow[\text{tBuONa, toluene, 140 °C, 24 h}]{\text{LiAlH}_4,\ [\text{Fe(acac)}_3]\ (20\ \text{mol\%})} \text{R'}{-}\text{H} \ + \ \text{HO}{-}\text{R}$$

Entry	Substrate	Product **1**	Yield [%][b]	Yield (GC) [%]	Product **2**	Yield (GC) [%]
1	*diphenyl ether*	*phenol*	81	100	*benzene*	97
2[c]			–	trace		trace
3	*di(4-methylphenyl) ether*	*4-methylphenol*	88	99	*toluene*	98
4	*bis(4-methoxyphenyl) ether*	*4-methoxyphenol*	51	57	*4-methoxybenzene*	76
5[c]			–	3		4
6	*bis(2-methylphenyl) ether*	*2-methylphenol*	62	66	*toluene*	83
7	*2,2',6-trimethyldiphenyl ether*	*2,6-dimethylphenol*	–	98	*toluene*	95
8	*4-fluorophenyl phenyl ether*	*phenol*	–	trace	*benzene*	trace
9[d]			75	79		78
10	*4-methoxyphenyl phenyl ether*	*phenol*	–	92	*benzene*	78
11[d]	*4-chlorophenyl phenyl ether*	*phenol*	–	81	*benzene*	69
12	*4-aminophenyl phenyl ether*	*phenol*	–	35	*aniline*	26
13	*4-(phenoxy)-2-methylphenol*	*2-methylphenol*	–	63	*phenol*	57
14	*anisole*	*phenol*	–	trace	*benzene*	trace
15	*1,3-dimethoxybenzene*	*3-methoxy...*	–	63	–	–
16	*4-methoxyphenol*	*phenol*	53	68	–	–
17[e]	*4-methoxybiphenyl*	*biphenyl*	–	84	–	–
18[e]	*4-isopropoxybiphenyl*	*biphenyl*	–	48	–	–
19	*1-methoxynaphthalene*	*naphthalene*	–	95	–	–
20[c]			–	3	–	–
21	*2-methoxynaphthalene*	*naphthalene*	–	94	–	–
22	*2-ethylbenzofuran*	*2-ethylphenol*	73	88	–	–
23[c]			–	trace	–	–
24	*dibenzofuran*	*2-phenylphenol*	80	–	–	–
25	*2-phenoxy-1-phenylethanol*	*phenol*	69	83	*1-phenylethanol*	41
26	*(2-phenoxyethyl)benzene*	*2-phenylethanol*	–	trace	*phenol*	7

[a] Reaction conditions: substrate (0.2 mmol), LiAlH$_4$ (0.5 mmol), [Fe(acac)$_3$] (0.04 mmol), toluene (1.5 mL), tBuONa (0.5 mmol), 140 °C, 24 h.
[b] Yields of isolated products, as averages of three experiments conducted in parallel. [c] H$_2$ atmosphere (5 MPa), no LiAlH$_4$. [d] 180 °C. [e] Substrate (0.1 mmol).

The catalytically active species may consist of heterogeneous iron clusters or particles from the reduction of the [Fe(acac)$_3$] catalyst precursor, because metal catalysts can be reduced to lower oxidation states by the reducing agents employed.[13] Indeed, a certain amount of dark clusters or particles was observed in the reaction system (Supporting

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Table 2: Phenolic products of the bond cleavage of the β-O-4 linkage of lignin model compounds.[a]

Entry	Substrate	Product	Yield [%][b]	Yield (GC) [%]
1			76	81
2[c]			–	69
3			65	72
4			–	63
5			64	73
6			–	74
7			–	71
8			59	–
9			–	67
10			–	6

[a] Reaction conditions: substrate (0.2 mmol), [Fe(acac)$_3$] (0.04 mmol), toluene (2 mL), tBuONa (0.5 mmol), 140 °C, 24 h, H$_2$ (1 atm). [b] Yields of isolated products, as averages of three experiments conducted in parallel. [c] Without hydrogen gas.

Information, Figures S1 and S2). TEM analysis of an aliquot of a reaction mixture revealed the presence of heterogeneous clusters (Figure S3 and S4). Composition analysis of these clusters indicated that they contain iron (Figure S5).

To gain preliminary insights into the composition of the active Fe catalyst, we conducted the reactions in the presence of mercury. Mercury is a poison for heterogeneous catalysts,[13,11,19] but typically has only little effect on the activity of homogeneous catalysts. As expected, the presence of an excess amount of mercury had a significant effect on the activity of the iron catalyst (Scheme S5), which suggests that a heterogeneous species possibly serves as the active catalyst. This hypothesis was further confirmed by additional experimental results: After a heterogeneous species was removed from a reaction that had proceeded for 20 min or 1 h by filtration, the homogeneous system obtained displayed no catalytic activity (Scheme S6). The structure and composition of this uniquely effective iron catalyst and the mechanism induced by such catalyst for the target reaction are subjects of our ongoing research.

In conclusion, we have reported an iron-based catalytic system for the selective reductive cleavage of aryl C–O bonds with iron (III) acetylacetonate as the catalyst precursor. Unlike the previously reported nickel catalyst systems,[7,14] the present iron catalyst is inexpensive and unique in its high effectiveness for the cleavage of aryl C–O bonds of aryl methyl ethers. The iron-catalyzed cleavage reactions described herein must be performed under an inert atmosphere, because some of the reagents used, namely LiAlH$_4$ and tBuONa, were sensitive to moisture. Preliminary mechanistic investigations suggest that a heterogeneous species possibly serves as the active catalyst. The present method for the cleavage of aryl C–O bonds is applicable to the synthesis of several rare regioisomeric products that are unattainable from the conventional functionalization of substituted benzenes. This method was also effective for the selective cleavage of the β-O-4 linkage of lignin model compounds under an atmosphere of hydrogen (1 atm) in the absence of LiAlH$_4$. Therefore, this process might become suitable for the selective conversion of lignin into small molecules that can be further upgraded into fuels or high-value chemicals.[6] Further mechanistic studies are underway in our laboratory.

[1] a) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359; b) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651.

[2] For recent reviews, see: a) T. Mesganaw, N. K. Garg, *Org. Process Res. Dev.* **2013**, *17*, 29; b) F.-S. Han, *Chem. Soc. Rev.* **2013**, *42*, 5270; c) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417; d) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg, V. Percec, *Chem. Rev.* **2011**, *111*, 1346.

[3] a) T. Agrawal, S. P. Cook, *Org. Lett.* **2013**, *15*, 96; b) A. Fürstner, A. Leitner, *Angew. Chem.* **2002**, *114*, 632; *Angew. Chem. Int. Ed.* **2002**, *41*, 609.

[4] B.-J. Li, L. Xu, Z.-H. Wu, B.-T. Guan, C.-L. Sun, B.-Q. Wang, Z.-J. Shi, *J. Am. Chem. Soc.* **2009**, *131*, 14656.

[5] A. L. Silberstein, S. D. Ramgren, N. K. Garg, *Org. Lett.* **2012**, *14*, 3796.

[6] a) P. Azadi, O. R. Inderwildi, R. Farnood, D. A. King, *Renew. Sust. Energ. Rev.* **2013**, *21*, 506; b) J. Zakzeski, P. C. A. Bruijnincx, A. L. Jongerius, B. M. Weckhuysen, *Chem. Rev.* **2010**, *110*, 3552.

[7] P. Álvarez-Bercedo, R. Martin, *J. Am. Chem. Soc.* **2010**, *132*, 17352.

[8] M. Tobisu, K. Yamakawa, T. Shimasaki, N. Chatani, *Chem. Commun.* **2011**, *47*, 2946.

[9] T. Mesganaw, N. F. F. Nathel, N. K. Garg, *Org. Lett.* **2012**, *14*, 2918.

[10] For recent reports, see: a) R. Olcese, M. M. Bettahar, B. Malaman, J. Ghanbaja, L. Tibavizco, D. Petitjean, A. Dufour, *Appl. Catal. B* **2013**, *129*, 528; b) S.-K. Wu, P.-C. Lai, Y.-C. Lin, H.-P. Wan, H.-T. Lee, Y.-H. Chang, *ACS Sustainable Chem. Eng.* **2013**, *1*, 349; c) M. V. Bykova, S. G. Zavarukhin, L. I. Trusov, V. A. Yakovlev, *Kinet. Catal.* **2013**, *54*, 40; d) R. N. Olcese, J. Francois, M. M. Bettahar, D. Petitjean, A. Dufour, *Energy Fuels* **2013**, *27*, 975; e) I. T. Ghampson, C. Sepúlveda, R. Garcia, L. R. Radovic, J. L. G. Fierro, W. J. DeSisto, N. Escalona, *Appl. Catal.*

A **2012**, *439–440*, 111; f) X. Wang, R. Rinaldi, *ChemSusChem* **2012**, *5*, 1455.

[11] A. G. Sergeev, J. F. Hartwig, *Science* **2011**, *332*, 439.

[12] a) P. Kelley, S. Lin, G. Edouard, M. W. Day, T. Agapie, *J. Am. Chem. Soc.* **2012**, *134*, 5480; b) J. Cornella, E. Gómez-Bengoa, R. Martin, *J. Am. Chem. Soc.* **2013**, *135*, 1997; c) A. Fedorov, A. A. Toutov, N. A. Swisher, R. H. Grubbs, *Chem. Sci.* **2013**, *4*, 1640.

[13] A. G. Sergeev, J. D. Webb, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 20226.

[14] J. Y. He, C. Zhao, J. A. Lercher, *J. Am. Chem. Soc.* **2012**, *134*, 20768.

[15] M. Chatterjee, T. Ishizaka, A. Suzuki, H. Kawanami, *Chem. Commun.* **2013**, *49*, 4567.

[16] a) J. M. Nichols, L. M. Bishop, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2010**, *132*, 12554; b) Q. Song, F. Wang, J. Xu, *Chem. Commun.* **2012**, *48*, 7019; c) T. H. Parsell, B. C. Owen, I. Klein, T. M. Jarrell, C. L. Marcum, L. J. Haupert, L. M. Amundson, H. I. Kenttämaa, F. Ribeiro, J. T. Miller, M. M. Abu-Omar, *Chem. Sci.* **2013**, *4*, 806; d) Q. Song, J. Y. Cai, J. J. Zhang, W. Q. Yu, F. Wang, J. Xu, *Chin. J. Catal.* **2013**, *34*, 651.

[17] a) C. W. Liskey, X. B. Liao, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 11389; b) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890; c) H. Y. Chen, S. Schlecht, T. C. Semple, J. F. Hartwig, *Science* **2000**, *287*, 1995; d) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 390; e) T. M. Boller, J. M. Murphy, M. Hapke, T. Ishiyama, N. Miyaura, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 14263; f) J. Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka, M. R. Smith, *Science* **2002**, *295*, 305.

[18] a) J. C. Serrano-Ruiz, J. A. Dumesic, *Energy Environ. Sci.* **2011**, *4*, 83; b) E. Furimsky, *Appl. Catal. A* **2000**, *199*, 147; c) M. K. Huuska, *Polyhedron* **1986**, *5*, 233; d) S. Utoh, T. Hirata, H. Oda, C. Yokokawa, *Fuel Process. Technol.* **1986**, *14*, 221; e) E. M. Van Duzee, H. Adkins, *J. Am. Chem. Soc.* **1935**, *57*, 147; f) G. Stork, *J. Org. Chem.* **1947**, *69*, 576.

[19] a) J. A. Widegren, R. G. Finke, *J. Mol. Catal. A* **2003**, *198*, 317; b) R. H. Crabtree, *Chem. Rev.* **2012**, *112*, 1536.
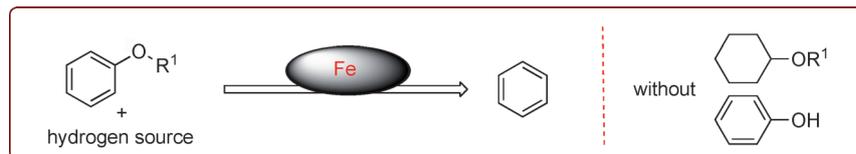
Communications

Reductive Bond Cleavage

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Selective Reductive Cleavage of Inert Aryl
C—O Bonds by an Iron Catalyst

Breaking point: An effective reductive cleavage of inert aryl C—O bonds with an inexpensive iron catalyst has been developed. During this process, the reduction of the arene rings was not observed. This catalytic system also enabled the selective cleavage of the β-O-4 linkage of lignin model compounds under an atmosphere of hydrogen, thus offering an opportunity for the depolymerization of lignin.