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Reductive Cleavage of Inert Aryl C-O Bonds to Arenes

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Reductive cleavage of the aryl C-O bonds in various phenolic compounds and aryl ethers was achieved using LiAlH₄ combined with KOtBu and without any other catalysts or additives, solely producing arenes in high yields.

Reductive cleavage of the aryl C-O bonds in aromatics including phenols and aryl ethers to form arenes is challenging because of the high strength and stability of the C-O linkage. However, this process is important for the production of deoxygenated fuels and chemicals from oxygen-rich lignin and coal compounds. Moreover, phenolic hydroxyl and aryloxy substituents are often used as synthetic intermediates in aromatic substitution, thus a general method for reductive cleavage of inert aromatic C-O bonds would expand the utility of these kinds of chemicals as removable directing groups, and can influence synthetic transformation of aromatics.

The cleavage of C-O bonds in aryl ethers has been studied, producing arenes and phenols or alcohols.¹ The reported processes generally suffer from their inherent drawbacks such as requiring high temperature, needs of alkali metals² or electrocatalytic hydrolysis³, and poor selectivity to arenes. Recently, Ni⁴ and Fe⁵ catalysts have been reported for the hydrogenolysis of aryl C-O in aryl ethers, producing arenes and phenolic compounds. In contrast to the deoxygenation transformation of aryl ethers, the deoxygenation of phenols is difficult to directly cleave phenolic hydroxy groups from the aromatic rings. The traditional deoxygenation of phenols undergoes two steps: esterification of phenolic hydroxyl group to corresponding sulfonate, dimethyl thiocarbamate, aryl ether, 5-phenyltetrazolyl ether, and phosphate ether, and deoxygenation of the resultant intermediates catalyzed by metal-based catalysts. Recently, the cleavage of C-O bonds in phenols has been realized via the hydrogenolysis catalyzed by metal

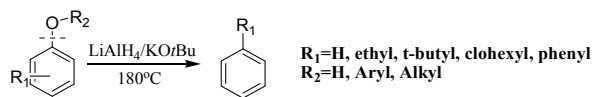
catalysts under acidic conditions; however, the aryl ring was hydrogenated to form cyclohexanes.⁷ The reductive cleavage of aromatic C-O bonds in phenolic compounds to arenes under relatively mild conditions is challenging and has not been reported.

LiAlH₄ is a strong reducing agent (or hydride donor), which has been widely applied in organic synthesis, and showed powerful reduction ability.⁸ KOtBu as an organic base can initiate radicals and promote some organic reactions.⁹ Herein, we discovered that the combination of LiAlH₄ with KOtBu was very active to cleave the aryl C-O bonds in various aromatic compounds including phenols, alkyl aryl ethers and diary ethers, without using any other catalysts or additives (Scheme 1). The corresponding arenes were produced very selectively without concurrent aromatic ring hydrogenation, and good to excellent yields of arenes were achieved.

Initially, the reductive cleavage of C-O in phenol was investigated under different conditions (Table 1, entries 1-4 and Table S1). It was found that phenol could be selectively converted to benzene with LiAlH₄ as a hydride source in the presence of KOtBu in the temperature range of 140-180°C, and the benzene yield increased with temperature, reaching up to 80% at 180°C (Table 1, entries 1-4). The other hydrides (e.g., KBH₄, NaBH₄, diisobutylaluminum hydride DIBALH, NaH) and organic/inorganic bases (e.g., KOH, DBU, NaOEt, LiOtBu, NaOtBu) were also examined for the phenol reduction (see Supporting Information, Table S1). It was indicated that the combination of LiAlH₄ and KOtBu showed the best performance for the effective cleavage of the phenolic hydroxyl group from phenol, solely producing benzene. Notably, the amounts of LiAlH₄ and KOtBu were important factors to influence the product yield. With the amounts of LiAlH₄ and KOtBu at 5 and 2.5 equiv. to phenol, respectively, the product yield reached 80% (see Table S1). In addition, the dependences of the phenol conversion and benzene yield on reaction time were investigated.

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Scheme 1. Selective cleavage of aryl C-O bonds to arenes

Table 1. Reduction cleavage of C-O bonds in phenolic compounds by LiAlH₄ in the presence of KOtBu.^[a]

Entry	Substrate	Temp./°C	Product	Yield (%) ^[b]
1		140		11
2		140		14 ^[c]
3		160		25
4		180		80
5		180		91
6		180		74
7 ^[d]		160		81/72 ^[e]
8 ^[c]		160		97/85 ^[e]
9		180		79/64 ^[e]
10		180		76/65 ^[e]
11		180		58
12		180		54/99 ^[f]

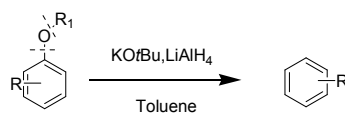
^[a]Conditions: substrate (1 mmol), LiAlH₄ (5 mmol), KOtBu (2.5 mmol), toluene (5 mL), 180°C, 24h. ^[b]GC yield. ^[c]140°C, 36 h. ^[d]160°C, 24 h. ^[e]isolated yield. ^[f]LiAlH₄ (10 mmol), KOtBu (5 mmol), toluene (8 mL).

Interestingly, phenol was not detected as the reaction proceeded only for 2h, however, the benzene yield was very low. To explore the reason, the reaction solution was acidified by HCl (1 mol/L), and analyzed by GC. Phenol was detected in the acidified solution, indicating that phenol was first converted to intermediate in the reaction system, which further converted to benzene under the experimental conditions. As expected, the benzene yield increased with the reaction time, reaching 80% at 24h. Further prolonging the time to 32h, the yield of benzene was increased slightly to 82% (see Figure S1).

Having identified the activity of the LiAlH₄/KOtBu system, we applied it in the reductive cleavage of aryl C-O bonds in other

phenolic compounds with different substituents. It was found that all the tested phenols could be exclusively converted to the corresponding arenes (Table 1, entries 5-12). Depending on the nature of the substituents, the tested substrates showed different activity compared to phenol. Both 2- and 4-ethyl phenols were reduced to ethyl benzene, affording product yields of 91% and 74%, respectively (Table 1, entries 5-6); the C-O cleavage in 2- and 4-hydroxydiphenyl produced biphenyl, affording the product yields of 97% and 81%, respectively (Table 1, entries 7-8). The above findings indicate that the combination of LiAlH₄ and KOtBu was powerful enough for the cleavage of phenolic hydroxyl group, without the hydrogenation of arene ring. Although both the ortho- and para-substituted substrates could be deoxygenated to generate the same products, the yields of products from para-substituted substrates were lower than those from ortho-substituted substrates, suggesting that the ortho- substitution made the C-O cleavage more easily than para- substitution. 1,2,3,4-Tetrahydro-1-naphthol was reduced to tetrahydronaphthalene without the hydrogenation of aryl ring (Table 1, entry 10). Besides the substitution position, the substituents also affected the activity of a substrate. For example, 4-tert-butylphenol showed lower activity than 4-ethyl phenol, producing tert-butylbenzene in a yield of 58% under the same conditions (Table 1, entries 6 vs 11). Notably, the C-O cleavage in phenolic compounds with two hydroxyl groups also proceeded very well. For instance, catechol was successfully transformed to benzene, and the yield of benzene was 54% under the same conditions. Excitingly, as the amount of LiAlH₄ increased to 10 equiv. of catechol, e.g., keeping 5 equiv. to C-O bond in catechol, the yield of benzene reached to 99% (Table 1, entry 12). This suggests that for the multiple phenolic hydroxyl-containing substrates the LiAlH₄ amount should be kept at a comparable ratio to the phenolic hydroxyl group instead of the substrate in order to get a high product yield. All the above results also indicate the low reactivity of LiAlH₄ toward hydrogenation of aromatic rings, which prevents competitive formation of cycloalkanes in the reactions.

Aryl alkyl ethers are a class of important compounds widely existing in lignin. The cleavage of C-O in aryl alkyl ethers has been achieved by complicated catalytic systems, producing mixture of arenes and phenols/alcohols.¹⁰ In this work, we found that the combination of LiAlH₄ and KOtBu was also very active for the reductive cleavage of aryl C-O bonds in aryl alkyl ethers, yielding arenes and alkane instead of phenols or alcohols (Table 2). The cleavage of C-O in anisole led to benzene in yield up to 86% at 180°C, and methane was detected in the gas phase (Table 2, entry 1; Figure S2). The cleavage of C-O bonds in both 2- and 4-methoxybiphenyl produced biphenyl, and a higher yield of biphenyl was obtained from the ortho-substituted substrate (Table 2, entries 6,7), also suggesting that the ortho substitution made the aryl C-O bond in aryl alkyl ethers more easily to be cleaved. Compared to the case of anisole reduction, it appeared that the phenyl group linked to the aryl ring increased the reactivity of the aryl ethers, resulting in higher product yield. The cleavage of C-O bonds in aryl methyl ethers with two methoxy groups (e.g., 1,2- and 1,3-dimethoxy benzenes) produced benzene in yields of 92% and 85%, respectively (Table 2, entries 8,9).

Table 2. Reductive cleavage of C-O bonds in aryl ethers by LiAlH₄ with KOtBu.^[a]

Entry	Ethers	Product and yield (%) ^[b]	Entry	Ethers	Product and yield (%) ^[b]
1		86	11		82
2		92	12		91/81 ^[c]
3		76	13		82
4		70	14		60
5		81/70 ^[c]	15		62
6		88 ^[d] /71 ^[c]	16		38/77 ^[e] /95 ^[f]
7		99 ^[d] /89 ^[c]	17		94 ^[e] 74 ^[e]
8		92 ^[e]	18		68 ^[e] 80 ^[e]
9		85 ^[e]	19 ^[e]		82 29 14
10		74 ^[e]	20		64 ^[e]

Conditions : ^[a] substrate (1 mmol), LiAlH₄(5 mmol), KOtBu (2.5 mmol), toluene (5 mL), 180 °C, 24 h. ^[b] GC yield. ^[c]isolated yield. ^[d]substrate (1 mmol), LiAlH₄(10 mmol), KOtBu (5 mmol), toluene (8 mL) , 160 °C, 24 h. ^[e] substrate (1 mmol),LiAlH₄ (10 mmol), KOtBu (5 mmol), toluene (8 mL), 180 °C, 24 h. ^[f] substrate (1 mmol),LiAlH₄ (15 mmol), KOtBu (7.5 mmol), toluene (10 mL) , 180 °C, 24 h.

The cleavage of C-O bonds in the aryl compounds with various aryl C-O bond linkages was also investigated. To our delight, both phenolic hydroxyl and aryl methoxyl groups could be removed simultaneously from the same aryl ring via the C-O cleavage, producing the corresponding arenes in good to excellent yields. For example, 4-ethylguaiaicol that is considered as a primary monomer to constitute lignin was completely deoxygenated to ethylbenzene in a yield 74% by LiAlH₄/KOtBu (Table 2, entry 10). This is the first reaction system with the ability for the direct deoxygenation of aryl alkyl ethers and phenols. The aryl C-O-C bonds are the most

representative linkage of phenolic dimers and trimer in lignin, and dibenzofuran (β-5 linkage), diphenyl ether (4-O-5 linkage) and 2-phenoxy-1-phenethanol (β-O-4 linkage) are the most representative lignin model compounds. The reductive C-O-C cleavage in these compounds was examined via LiAlH₄ combined with KOtBu (Table 2, entries 11-20). The conversion of benzofuran resulted in ethylbenzene in a yield of 82%, and the cleavage of C-O-C in dibenzofuran produced diphenyl in a yield up to 91% (Table 2, entry 12). As for reduction of diphenyl ether, benzene was obtained as the sole product in a yield of 82% (Table 2, entry 13). Similarly, the

cleavage of C-O-C in di-4-ethyl-phenyl ether and di-4-tert-butylphenyl ether resulted in ethylbenzene and tert-butylbenzene, respectively (Table 2, entries 14, 15). As for di-2-methoxyphenyl ether that contains two aryl methoxyl groups and an aryl C-O-C linkage, all the three aryl C-O bonds could be cleaved, producing benzene in a yield of 38% under the experimental conditions. When the amounts of LiAlH_4 and KOtBu were increased to 10 and 5 equiv., respectively, a benzene yield of 74% was achieved; further increasing the amounts of LiAlH_4 and KOtBu to 15 and 7.5 equiv., respectively, the benzene yield reached 95% (Table 2, entry 16). 2-Phenoxy-1-phenethanol was transformed to benzene and ethyl benzene under the experimental conditions (Table 2, entry 17). The formation of ethylbenzene suggests that the alkyl hydroxyl group could be removed under the experimental conditions, probably via the dehydration and subsequent hydrogenation of the corresponding intermediate. Similarly, keeping the amounts of LiAlH_4 and KOtBu to C-O bonds in the substrate at 5 and 2.5 equiv., respectively, higher products yields (benzene 94%, ethyl benzene 74%) could be achieved. 2-(2-Methoxyphenoxy)-1-phenethanol and 2-phenoxy-1-phenylpropanol-1,3-diol are lignin model compounds with more complicated structures, which were also nearly completely deoxygenated (Table 2, entries 18, 19). As for 1,4-diphenoxybenzene, which is a trimmer in lignin model compounds, the two C-O-C linkages were broken, further being deoxygenated to benzene (64%) (Table 2, entry 20). The above findings indicate that all the aryl C-O bonds in phenols, aryl ethers and diaryl ethers could be cleaved to form corresponding arenes via the reduction by LiAlH_4 in the presence of KOtBu .

The reaction system of LiAlH_4 and KOtBu was simple and very effective for the cleavage of various aryl C-O bonds. As known, LiAlH_4 is a commonly used reducing agent, which can generate active H in reaction process, and also can accelerate single electron transfer in C-S bond cleavage.¹¹ KOtBu is a strong base, which can initiate radicals.¹² The reactions performed in the above experiments might be under a radical mechanism. To get some evidences for the reaction mechanism, TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) as a radical scavenger was added to the reaction system of phenol. It was found that TEMPO influenced the reaction significantly. For example, a very low benzene yield of 3.2% was obtained as 1 equiv. of TEMPO was added, and no product was detectable as the amount of TEMPO was increased to 2.5 equiv. under the comparable other conditions (see Table S2). Moreover, the reaction mixture was EPR active (see Figure S3), indicating the existence of radicals during the reactions. As TEMPO was added to the reaction system of anisole, similar results were obtained. In addition, in the reaction solution of anisole methane was generated. All these findings indicate that the reduction of anisole also proceeded through a radical mechanism. Based on the above results, a tentative mechanism for deoxygenation of phenols and aryl ethers in the $\text{LiAlH}_4/\text{KOtBu}$ reaction system was proposed and shown in Scheme S1.

In summary, selective cleavage of various aryl C-O bonds in aromatic compounds to arenes was achieved using LiAlH_4 as a reducing agent in the presence of KOtBu . The $\text{LiAlH}_4/\text{KOtBu}$ combination system not only possesses the ability to simultaneously deoxygenate the aryl C-O containing aromatics to benzene analogous, but also has the powerful ability to

depolymerize the common aryl C-O-C linkage in lignin compounds to arenes. In these reactions, the desired products are obtained in good to excellent yields and the aromatic rings are not hydrogenated. Particularly, the transformation of phenols to arenes was achieved for the first time below 200 °C. Although the reaction mechanism of these interesting reactions needs to be further studied, the results from this work have demonstrated that the reductive cleavage of aromatic C-O bonds is under a radical mechanism. This work opens a novel and simple way to produce arenes from aryl C-O containing compounds, which may have promising applications in the production of aromatics from lignin compounds.

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