ORGANIC CHEMISTRY







FRONTIERS

REVIEW

View Article Online View Journal | View Issue



Cite this: Org. Chem. Front., 2020, 7,

Recent progress in C(aryl)-C(alkyl) bond cleavage of alkylarenes

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Cleavage of the C(aryl)-C(alkyl) σ -bond is important both in academy and industry as it holds the potential to provide straightforward access to a variety of targets from readily available chemical feedstocks such like alkylarenes. However, C(aryl)-C(alkyl) bonds of alkylarenes remain intact under most conventional reaction conditions. In this review, we highlight the results of recent C(aryl)-C(alkyl) bond cleavages that have been induced by homogeneous transition metal reagents, by oxidative cleavages, and by rearrangement.

Received 3rd December 2019, Accepted 22nd February 2020 DOI: 10.1039/c9go01438a

rsc.li/frontiers-organic

Introduction 1.

Alkylarenes are products from the coal or petrochemical industries. Transformations of these chemicals by cleaving the C(aryl)-C(sp³) σ-bond provide straightforward access to a variety of feedstocks and therefore are important both in academy and industry. Toluene hydrodealkylation is one of the industrial application examples for C(aryl)-C(sp³) bond cleavage. Toluene and hydrogen are compressed to pressures between 20 and 60 atmospheres and are heated to temperatures between 500 and 600 degrees centigrade in the presence of a metal oxide catalyst leading to the formation of benzene via C(aryl)-C(sp³) σ-bond cleavage (Scheme 1, above). Another example is the cumene-phenol process (or the Hock process) which produces over nine million tonnes of phenol per year.² Oxidation of cumene under heating forms a cumene radical which bonds with an oxygen molecule to give cumene hydroperoxide. The hydroperoxide is then hydrolysed in an acidic medium (the Hock rearrangement) to give phenol and acetone (Scheme 1, below). Several modifications using a catalytic amount of N-hydroxyphthalimide or derivatives to perform this reaction under mild conditions are also known.3

Although over the past few decades, several strategies towards C-C bond cleavage,4 such as using a small ring system to release the ring strain,⁵ using the driving force of the aromaticity in a prearomatic system,6 or using a carbonyl group or a cyano group to activate,7 have been established, transformations directly from non-polar, unstrained, unactivated alkyl-

Replacing one of the phosphine ligands with a less steric hindered nitrogen ligand provided a lower activation barrier of the C-C insertion than of the C-H insertion and allowed the $C(aryl)-C(sp^3)$ insertion to take place even at -30 °C. Other transition metal complexes such as platinum, ruthenium, osmium and nickel complexes towards C(aryl)-C(sp³) bond cleavage have also been demonstrated using similar PCP systems.11

Recently, the combination of homogeneous transition metal reagents with the assistance of monodentate ligands has

Scheme 1 Hock rearrangement and hydrogenation of toluene.

arenes remain rare because of the inertness and thermo-

dynamic stability of the C(aryl)-C(sp3) bond in alkylarenes resulting from the high bond dissociation energy. Moreover, the C(aryl)-C(sp3) bonds in alkylarenes are surrounded by more C-H and C-C bonds and thus suffer from steric hindrances. In 1993, Milstein and co-workers reported the first example of insertion into an unstrained C(aryl)-C(sp³) σ-bond of a diphosphinoxylene in solution with the assistance of metal precoordination without using strain relief or aromatization as a driving force (Scheme 2, 1 to 4).8 The competing C-H activation process (1 to 2) was observed. Later, a catalytic version of this process was reported by using [{Rh(coe)₂Cl}₂] (coe = cyclooctene) either under H₂ pressure or with an excess of triethoxysilane with 4-106 turnovers.9

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Scheme 2 C(aryl)-C(sp³) bond cleavage by rhodium.

provided a powerful tool for the cleavage of C(aryl)-C(alkyl) σ-bonds in alkylarenes via a direct or stepwise C-C bond insertion pathway. Moreover, several strategies using oxidative cleavage or rearrangement as a driving force to cleave the inert C(aryl)-C(sp³) bonds of alkylarenes have also been demonstrated. In this mini-review, we will focus on the discussion of these recent publications and four parts will be included. In the first part, we will briefly summarize the cleavage of C(aryl)-C(sp³) bonds via a C(aryl)-C(sp³) insertion using homogeneous transition metal reagents in the presence of monodentate ligands. In the second part, we will discuss the cleavage of C(aryl)-C(alkyl) bonds of alkylarenes, except for methylarenes, through the combination of an oxidative amination and a rearrangement in the absence of any directing groups. In the third part, we will introduce the recent results in the cleavage of C(aryl)-C(methyl) bonds using tandem oxidation/decarboxylative transformations. Finally, miscellaneous C(aryl)-C(sp³) bond cleavage of alkylarenes via alkyl or aryl migrations will be highlighted.

Monodentate ligand chelationassisted C(aryl)-C(sp³) bond cleavage

Monodentate ligands such as N-heterocyclic carbenes (NHCs) could assist the C(aryl)-CH3 bond cleavage. Whittlesey and coworkers reported a cleavage of the C(aryl)-CH3 bond of 1,3dimesitylimidazol-2-ylidene (IMes) in the presence of Ru (PPh₃)₃(CO)H₂ (Scheme 3).¹² The methyl group on ruthenium

Scheme 3 Activation of the C(aryl)-CH₃ bond in N-heterocyclic carbene using ruthenium complexes.

complex 5 is eliminated with the hydride to release methane forming ruthenium complex 6 at the same time.

Using osmium-amido complex 7, Esteruelas and co-workers demonstrated that an isopropyl group of 1,3-bis(2,6-diisopropylphenyl)imidazolylidene could be activated and it involves a β-elimination, an imine dissociation, a C(arvl)-CH₃ bond activation, a reductive elimination, and ammonia coordination processes (Scheme 4). 13

Recently, Tobisu et al. demonstrated the iridium-mediated arylation of quinolones with 9. The cleavage of a nonpolar, unstrained C(aryl)-C(alkyl) bond on N-heterocyclic carbene iridium complex 11 was proposed to occur generating complex 12 that reacted with quinolones with the release of methanes. The subsequent reductive elimination of 13 forms complex 14, which would lead to the coupling product 10 (Scheme 5).14

Pyridyl or pyrazolyl groups were also demonstrated as nitrogen monodentate ligands for C(aryl)-C(allyl) bond cleavage. Kakiuchi and co-workers reported a transformation of allyl groups in allylbenzenes 15 into alkenyl groups 17 via a rhodium-catalysed C-C bond cleavage. 15 Pyridyl and pyrazolyl groups in allylbenzenes work as a directing group for the β-carbon elimination of alkyl rhodium complex 18 to form 19 (Scheme 6).

Scheme 4 Activation of the C(aryl)-iPr bond in N-heterocyclic carbene using an osmium complex.

Scheme 5 Iridium-mediated arylation of various heteroarenes by activation of the C(aryl)-alkyl bond in N-heterocyclic carbene complexes of

Scheme 6 Deallylative alkenylation of allylbenzene derivatives 15 with styrene derivatives 16

C(aryl)-C(sp³) bond cleavage via tandem oxidative amination/ rearrangement

3.1. Tandem oxidative amination/rearrangement mediated by DDO and azide

Nitrogen containing organic compounds such as amides and amines are important moieties in organic syntheses and in biological and pharmaceutical compounds. Recently, Jiao et al. developed a tandem oxidative substitution/rearrangement strategy to prepare amides or amines 23 from alkylarenes 20 via amination intermediates 21 and 22 (Scheme 7). Besides, the substituent on the α -methyl on the alkylarenes is necessary for these reactions, while methylbenzene derivatives are inert under these reaction conditions.

In 2011, Jiao and co-workers reported a transformation of benzyl hydrocarbons 24 into the corresponding amides 28 using a tandem iron-catalyzed oxidative substitution/rearrangement reaction (Scheme 8).16 In wet protonic acid, iron-assisted oxidative addition with TMSN₃ in the presence of DDO formed 25 which subsequently undergoes a highly chemoselective Beckmann rearrangement followed by hydrolysis resulting in the formation of amide 28. Six- and seven-membered rings could also be converted into the corresponding lactams in good yields. However, in the case of the reaction of fluorene, phenanthridine was produced suggesting that the desired lactam undergoes dehydration.

On the other hand, on using a copper catalyst in the presence of dry acetonitrile, the oxidative substitution of 29 or electron-rich alkylarenes could also lead to Beckmann-type aryl migration from the carbon atom to the nitrogen atom to gene-

R¹ = aryl, styryl, R² = aryl, alklyl (not including methyl)

Scheme 7 Transformation of alkylarenes into amides or amines via a tandem oxidative substitution/rearrangement reaction.

Scheme 8 Transformation of the benzyl hydrocarbons 24 amides 28.

rate intermediate 34; the following nucleophilic addition and cyclization with another azide finally lead to the desired tetrazole product 31 or 32 in good yields (Scheme 9). 17

Later, Jiao et al. developed an iron-catalyzed cleavage of unactivated C(aryl)-C(alkyl) bonds on diarylmethanes or alkylarenes 20 using stable long chain alkyl azides to form arylamines 35 and aldehyde 36 (Scheme 10).18 Intermediate 21, generated from the nucleophilic attack of 37 by organic azide, is proposed, and it undergoes a Schmidt-type rearrangement involving the release of nitrogen and the trans-aryl group migration and leads to the formation of iminium 38. When a mixture of alkyl benzenes was subjected to the standard reaction conditions, a single N-alkylaniline was obtained in a moderate yield demonstrating the potential for applying this method to the conversion of a crude mixture of benzyl hydrocarbons from the oil and coal industry. Moreover, a commercially available polystyrene sample and waste polystyrene foam were both used to test the potential of this method in the degradation of polymers and they performed well, giving N-nonylaniline 40 in 17% yield.

Scheme 9 Transformation of 29 into tetrazoles 31 and 32

Scheme 10 Direct synthesis of arylamines through C(aryl)–C(sp³) bond cleavage.

The same group also reported an electrochemical C-C amination of alkylarenes 41 for the synthesis of anilines 43 using graphite plates as electrodes in an undivided cell without any external catalyst or oxidant (Scheme 11).¹⁹ The substrate is first oxidized on the anode generating a radical cation which is deprotonated to give a benzyl radical. The benzyl radical further undergoes oxidation forming an intermediate cation which could be nucleophilically attacked by organic azide 42 producing the Schmidt-type intermediate. This method is efficient for a variety of alkylarenes except for substrates with strong electron-withdrawing groups.

Using NaN₃, DDQ and TFA, anilines **49** could be prepared from the corresponding alkylarenes **45** or benzyl alcohols under mild conditions *via* a dealkylating C–C amination (Scheme 12).^{20a} Alkyl groups such as ethyl, i-propyl, benzyl, cyclohexyl, and *n*-butyl could be selectively cleaved and replaced by amine. Secondary benzyl alcohols could also be converted into the corresponding substituted anilines. A Schmidt-type rearrangement pathway including intermediates **46–48** was proposed. Utilization of oxygen as an alternative environmentally benign oxidant is also developed. To demonstrate the utility of this method the depolymerization of lignin was also studied by using model compounds obtaining the desired products in moderate yields.

Using organic azide, DDQ and TFA, the allylic C(aryl)-C (alkyl) bond of **50** could be cleaved under metal-free conditions *via* a 1,2-aryl or alkyl migration producing the corres-

Scheme 11 Electrochemically oxidative $C(sp^2)-C(sp^3)$ bond cleavage of alkylarenes for aniline synthesis.

Scheme 12 Transformation of alkylbenzene derivatives 45 into anilines 49 through site-directed C(aryl)–C(sp³) bond cleavage.

ponding E-cinnamyl aldehydes 57 regio- and stereoselectively (Scheme 13). Alkyl azides work as a traceless reagent in this transformation by generating an azido cation intermediate 52 and finally turning into alkyl amines. In this transformation, E products are obtained in all cases, regardless of the geometry of the starting olefins.

Zhang *et al.* also developed an oxidative amination/ rearrangement of 1,3-diarylpropenes 58 or diarylmethanes 63 utilizing hydroxylamine as a nucleophile in the presence of DDQ and an acid (PPA or AlCl₃). The initial single-electron transfer process between 58 and DDQ produces benzyl cation 59 followed by the attack of hydroxylamine giving rise to 60. Oxidation of 60 by DDQ affords ketoximes 61, which convert into the corresponding amides 62 and 64 *via* a Beckmann rearrangement in the presence of an acid with 38–96% yields and 4.4/1–1.1/1 regioselectivities (Scheme 14).²²

Scheme 13 Transformation of 50 into cinnamyl aldehydes 57 through selective allylic C–C bond cleavage.

Scheme 14 Transformation of 1,3-diarylpropenes 58 and diarylmethanes 63 into amides via oxidative amination/rearrangement.

3.2. One-pot oxygenation/amination/rearrangement using nitromethane

Recently, Jiao and co-workers reported an activation of nitromethane that utilizes triflic anhydride, formic acid, and acetic acid, and this method provides a nitrogen donor instead of azides for the amination of ketones or aldehydes. When they subjected ethylbenzenes 65 to the classic oxidation conditions using the Co/NHPI/O2 system, the corresponding ketones 66 were generated in situ, and the following addition of triflic anhydride, formic acid, and acetic acid afforded 67. Hydrolysis of 67 gave rise to the corresponding dealkylated amides 68. When cumene 69 and cyclohexylbenzene 71, important feedstock materials, were subjected to the protocol, secondary amides 70 and 72 were obtained through oxidative β -scission of alkyl chains. Reactions with substituted methylarenes were also investigated but they provided primary benzamides without C(aryl)-C(alkyl) bond cleavage (Scheme 15).²³

Cleavage of the C(aryl)–CH₃ bond via tandem oxidation/decarboxylative transformations

Using amination/rearrangement strategies, great success has been achieved in the scission of the C(aryl)-C(alkyl) bond in ethylarenes, cumene, cyclohexylbenzenes, etc., but demethylative C(aryl)-CH3 bond cleavage of inert methylarenes has been less reported.

Kim and co-workers reported a one-pot demethylative coupling reaction between inert methylarenes 73 and benzenes using substoichiometric silver nitrate in the presence of an excess amount of the potassium persulfate oxidant under heating. Observations of benzyl hydrogen sulfate, benzaldehyde, and benzoic acid by GC analysis, control experiments, and detection of carbon dioxide by GC-MS analysis suggest that this process involves a radical oxidation of methyl-

Scheme 15 Preparation of amides via a one-pot oxygenation/amination/rearrangement of alkylarenes using nitromethane.

arenes 73 to substituted benzoic acids 74 and a following decarboxylative coupling with benzenes. A two-electron oxidative transfer Ag(I)/Ag(III) system for the generation of the free radical SO4. is proposed based on the studies by XANES and EXAFS analyses (Scheme 16).24

Recently, we have developed a site-selective C(aryl)-CH₃ bond cleavage/borylation reaction²⁵ by using a sequential tandem strategy (Scheme 17).26 Methyl groups of a variety of arenes 73 and biologically active natural products could be

Scheme 16 Demethylative coupling between methylarenes 73 and benzenes

Scheme 17 Sequential radical demethylative C(aryl)-C(CH₃) bond cleavage and borylation.

selectively cleaved and replaced by boryl groups under directing group-free and transition metal-free conditions. An N-hydroxyphthalimide-ester 77 was isolated from the first step of the standard conditions. It was proposed to be the key intermediate which converted into the corresponding boronate 78^{25a} through a decarboxylative borylation (Scheme 17).

5. Miscellaneous C(aryl)–C(alkyl) bond cleavage *via* alkyl or aryl migrations

Miscellaneous C(aryl)–C(alkyl) bond cleavage of alkylarenes involving alkyl or aryl migrations has been reported by using a hypervalent iodine(III) reagent or a cationic N-heterocyclic carbene copper catalyst giving the corresponding product in good yields.

5.1 Hypervalent iodine(III)-mediated rearrangement

Mal *et al.* reported a one-pot carbazole synthesis *via* an intermolecular annulation between aryl sulfonamides **79** and substituted mesitylenes or 1,3,5-triethylbenzene **80**. The hypervalent iodine(III) reagent PhI(OAc)₂ prompted the formation of nitrenium ion **81** from sulphonamide, and the following electrophilic aromatic substitution led to carbenium intermediate

Scheme 18 PhI(OAc)₂ prompted alkyl migration.

82 which underwent alkyl migration forming a more stable cationic intermediate **83** (Scheme 18, eqn (3)). When *N*-sulfonylanilides **85** with hydrogen at the *para*-position to the sulphonamide group were subjected to the standard conditions, *para*-arylated carbazoles **87** were obtained (Scheme 18, eqn (4)). An intramolecular reaction of **88** has also been reported by the same research group (Scheme 18, eqn (5)). ^{27b}

Maulide and co-workers found that a hypervalent iodine(III) reagent could induce a C(aryl)–C(alkyl) bond cleavage α -arylation of dicarbonyl compounds **89** that possess an aryl group in the β -position of ketones or ketone-derived silyl enol ethers **94** that feature an aryl group in the allylic position (Scheme 19). They proposed that a fragmentation of enolonium **92** could be triggered by a nucleophilic attack of the neighbouring arene to generate phenonium intermediate **93**.

Scheme 19 Hypervalent iodine(III) induced aryl migration.

Scheme 20 Copper catalysed domino rearrangement of *N*-methoxyanilines **96**.

Ring opening of 93 by weakly nucleophilic triflate accounts for the formation of the C(aryl)-C(alkyl) bond cleavage products **90** and **95**.²⁸

5.2 Copper-catalysed domino rearrangement

Nakamura and co-workers reported a catalytic domino rearrangement of N-methoxyanilines 96 that bear an electrondonating alkyl group (Scheme 20). The cationic copper catalyst was found to participate in the [1,3]-migration of the methoxy group from 98 to 99 and the [1,2]-migration of the alkyl group from the ortho to the meta position (from 99 to 100). This provides a method for the preparation of multisubstituted 2-aminophenol derivatives 97 from readily accessible N-methoxyanilines 96.29

Summary and outlook 6.

The C(aryl)-C(alkyl) σ-bond in alkylarenes is one of the least reactive functional groups; however, its cleavage could be realized by elaborating the reaction system. In this mini-review, we have highlighted the advances in the cleavage of C(aryl)-C (alkyl) σ-bonds of alkylarenes using a transition-metal insertion in the presence of directing groups, a tandem oxidative amination/rearrangement, tandem oxidation/decarboxylative transformations, and alkyl or aryl migrations. The development of new strategies towards C(aryl)-C(alkyl) bond cleaving functionalization may lead to the invention of new selective and efficient processes for the utilization of alkylarenes which are available or chemical raw materials from the coal and petrochemical industries.

Conflicts of interest

There are no conflicts to declare.

Note from RSC Publishing

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Acknowledgements

We thank the National Natural Science Foundation of China (21602001, 21922109, 21672196, and 21831007), the Start-Up Funding from Nanjing Tech University (39837134), and the Fundamental Research Funds for the Central Universities of China (WK2060190086) for financial support.

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