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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.

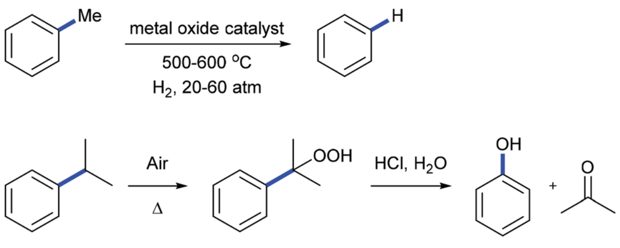
1. Introduction

Alkylarenes are products from the coal or petrochemical industries. Transformations of these chemicals by cleaving the C(aryl)–C(sp^3) 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(sp^3) 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(sp^3) σ-bond cleavage (Scheme 1, above).[1] 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 alkylarenes remain rare because of the inertness and thermodynamic stability of the C(aryl)–C(sp^3) bond in alkylarenes resulting from the high bond dissociation energy. Moreover, the C(aryl)–C(sp^3) 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(sp^3) 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 H_2 pressure or with an excess of triethoxysilane with 4–106 turnovers.[9]

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.[10] Other transition metal complexes such as platinum, ruthenium, osmium and nickel complexes towards C(aryl)–C(sp^3) 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.

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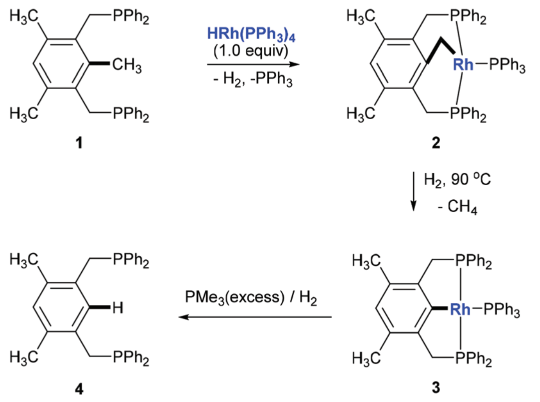


Scheme 2 C(aryl)–C(sp^3) bond cleavage by rhodium.

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(sp^3) 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(sp^3) bonds *via* a C(aryl)–C(sp^3) 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(sp^3) bond cleavage of alkylarenes *via* alkyl or aryl migrations will be highlighted.

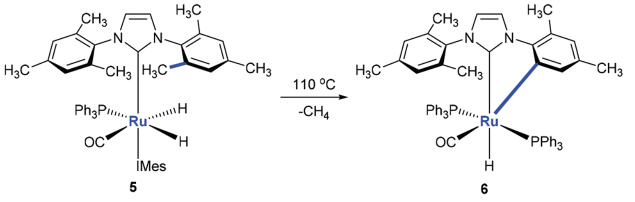
2. Monodentate ligand chelation-assisted C(aryl)–C(sp^3) bond cleavage

Monodentate ligands such as N-heterocyclic carbenes (NHCs) could assist the C(aryl)–CH_3 bond cleavage. Whittlesey and co-workers reported a cleavage of the C(aryl)–CH_3 bond of 1,3-dimesitylimidazol-2-ylidene (IMes) in the presence of Ru$(PPh_3)_3(CO)H_2$ (Scheme 3).[12] The methyl group on ruthenium complex **5** is eliminated with the hydride to release methane forming ruthenium complex **6** at the same time.

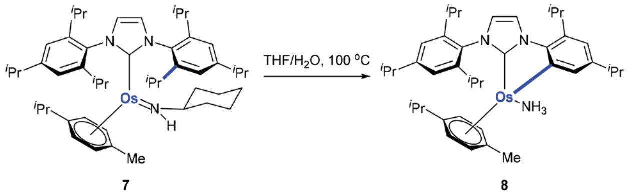
Using osmium-amido complex **7**, Esteruelas and co-workers demonstrated that an isopropyl group of 1,3-bis(2,6-diisopropylphenyl)imidazolylidene could be activated and it involves a β-elimination, an imine dissociation, a C(aryl)–CH_3 bond activation, a reductive elimination, and ammonia coordination 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]

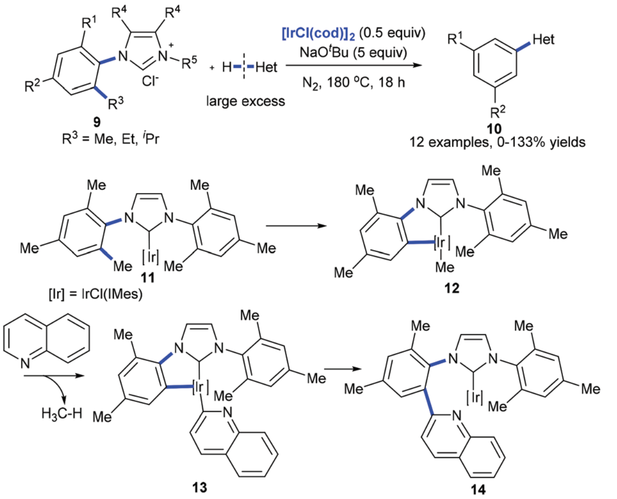
Pyridyl or pyrazolyl groups were also demonstrated as nitrogen monodentate ligands for C(aryl)–C(allyl) bond cleavage. Kakiuchi and co-workers reported a transformation of allyl groups in allylbenzenes **15** into alkenyl groups **17** *via* a rhodium-catalysed C–C bond cleavage.[15] Pyridyl and pyrazolyl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



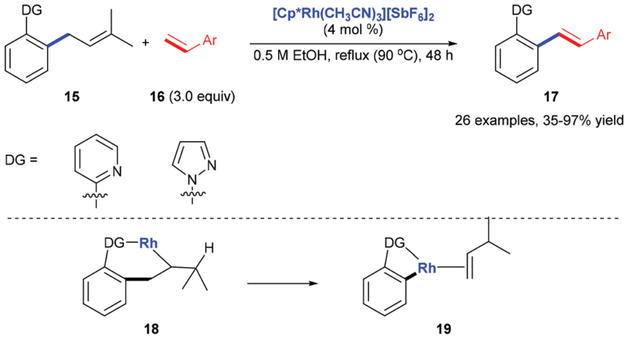
Scheme 3 Activation of the C(aryl)–CH_3 bond in N-heterocyclic carbene using ruthenium complexes.



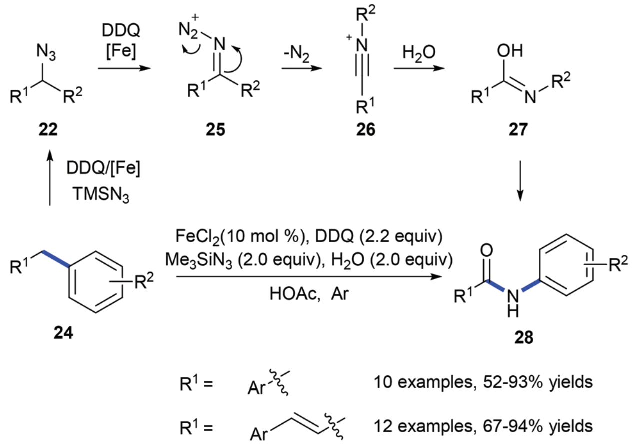
Scheme 4 Activation of the C(aryl)–^{i}Pr bond in N-heterocyclic carbene using an osmium complex.



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



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



Scheme 8 Transformation of the benzyl hydrocarbons **24** into amides **28**.

3. C(aryl)–C(sp^3) bond cleavage *via* tandem oxidative amination/rearrangement

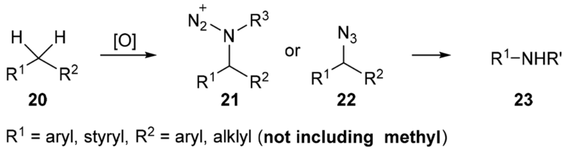
3.1. Tandem oxidative amination/rearrangement mediated by DDQ and azide

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.

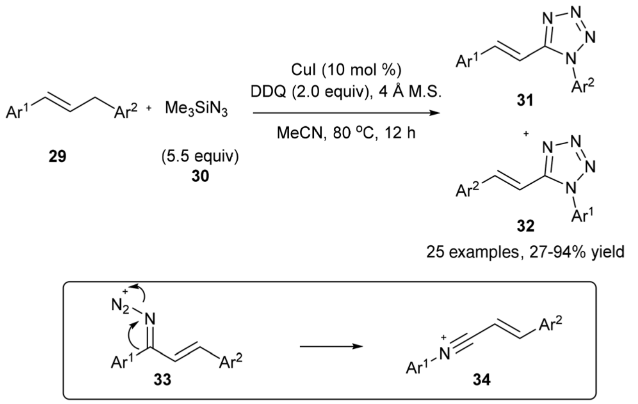
In 2011, Jiao and co-workers reported a transformation of benzyl hydrocarbons **24** into the corresponding amides **28** using a tandem iron-catalyzed oxidative substitution/rearrangement reaction (Scheme 8).[16] In wet protonic acid, iron-assisted oxidative addition with TMSN$_3$ in the presence of DDQ 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 generate 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]

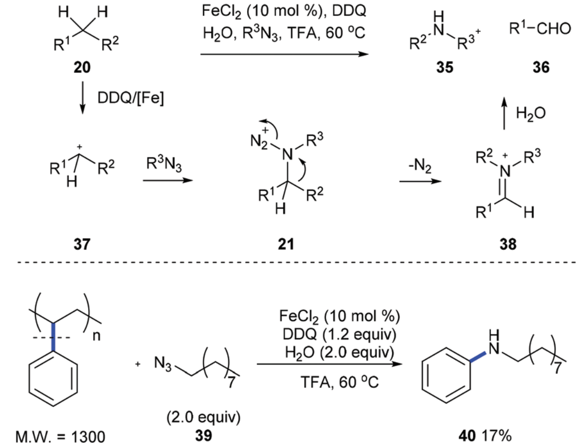
Later, Jiao *et al.* developed an iron-catalyzed cleavage of unactivated C(aryl)–C(alkyl) bonds on diarylmethanes or alkylarenes **20** using stable long chain alkyl azides to form arylamines **35** and aldehyde **36** (Scheme 10).[18] Intermediate **21**, generated from the nucleophilic attack of **37** 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.



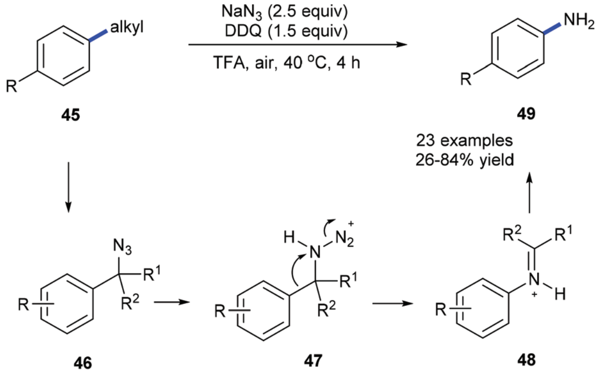
Scheme 7 Transformation of alkylarenes into amides or amines *via* a tandem oxidative substitution/rearrangement reaction.



Scheme 9 Transformation of **29** into tetrazoles **31** and **32**.



Scheme 10 Direct synthesis of arylamines through C(aryl)–C(sp^3) bond cleavage.



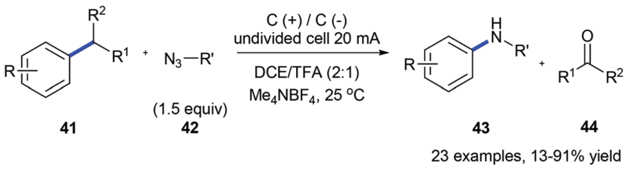
Scheme 12 Transformation of alkylbenzene derivatives **45** into anilines **49** through site-directed C(aryl)–C(sp^3) bond cleavage.

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.

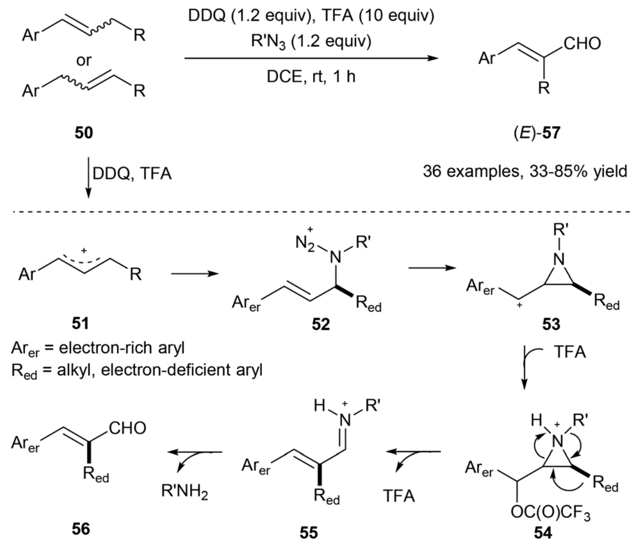
Using NaN_3, DDQ and TFA, anilines **49** could be prepared from the corresponding alkylarenes **45** or benzyl alcohols under mild conditions *via* a dealkylating C–C amination (Scheme 12).[20a] Alkyl groups such as ethyl, i-propyl, benzyl, cyclohexyl, and *n*-butyl could be selectively cleaved and 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 corresponding *E*-cinnamyl aldehydes **57** regio- and stereoselectively (Scheme 13).[21] 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.

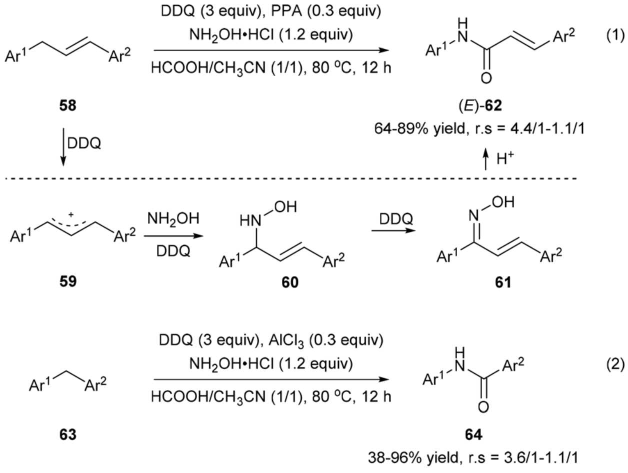
Zhang *et al.* also developed an oxidative amination/rearrangement of 1,3-diarylpropenes **58** or diarylmethanes **63** utilizing hydroxylamine as a nucleophile in the presence of DDQ and an acid (PPA or $AlCl_3$). The initial single-electron transfer process between **58** and DDQ produces benzyl cation **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]



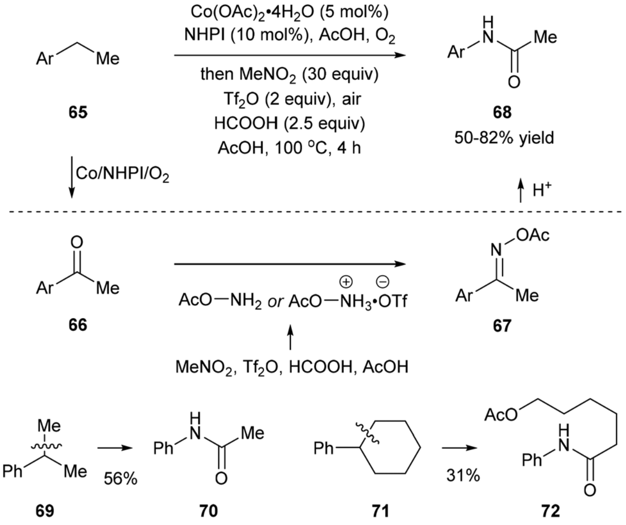
Scheme 11 Electrochemically oxidative C(sp^2)–C(sp^3) bond cleavage of alkylarenes for aniline synthesis.



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.



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

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

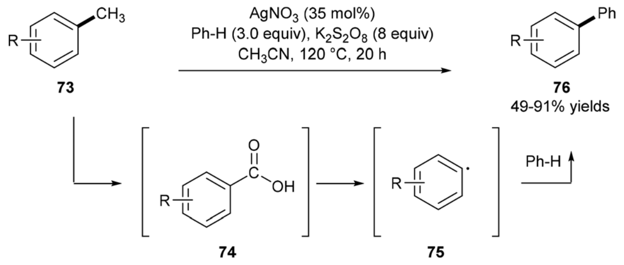
Recently, Jiao and co-workers reported an activation of nitromethane that utilizes triflic anhydride, formic acid, and acetic acid, and this method provides a nitrogen donor instead of azides for the amination of ketones or aldehydes. When they subjected ethylbenzenes **65** to the classic oxidation conditions using the Co/NHPI/O$_2$ 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]

4. Cleavage of the C(aryl)–CH$_3$ bond *via* tandem oxidation/decarboxylative transformations

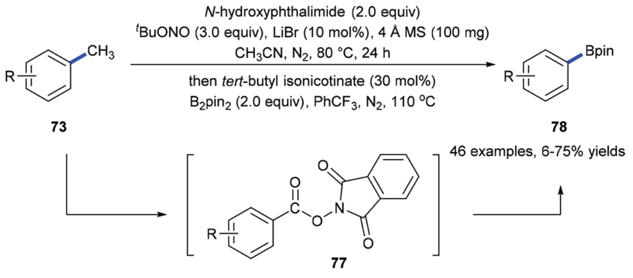
Using amination/rearrangement strategies, great success has been achieved in the scission of the C(aryl)–C(alkyl) bond in ethylarenes, cumene, cyclohexylbenzenes, *etc.*, but demethylative C(aryl)–CH$_3$ bond cleavage of inert methylarenes has been less reported.

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 methylarenes **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 SO$_4^{\bullet-}$ is proposed based on the studies by XANES and EXAFS analyses (Scheme 16).[24]

Recently, we have developed a site-selective C(aryl)–CH$_3$ bond cleavage/borylation reaction[25] 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(CH$_3$) bond cleavage and borylation.

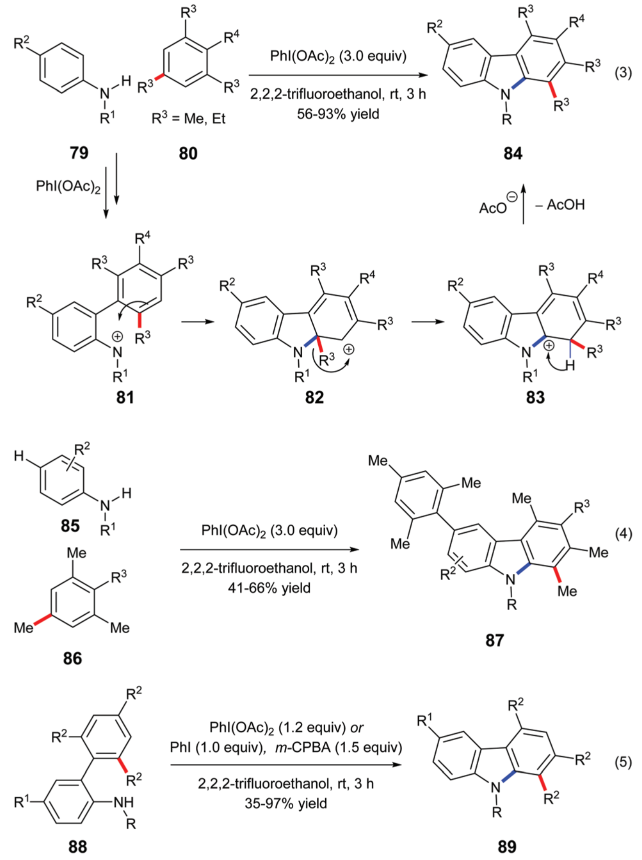
selectively cleaved and replaced by boryl groups under directing group-free and transition metal-free conditions. An *N*-hydroxyphthalimide-ester **77** was isolated from the first step of the standard conditions. It was proposed to be the key intermediate which converted into the corresponding boronate **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.

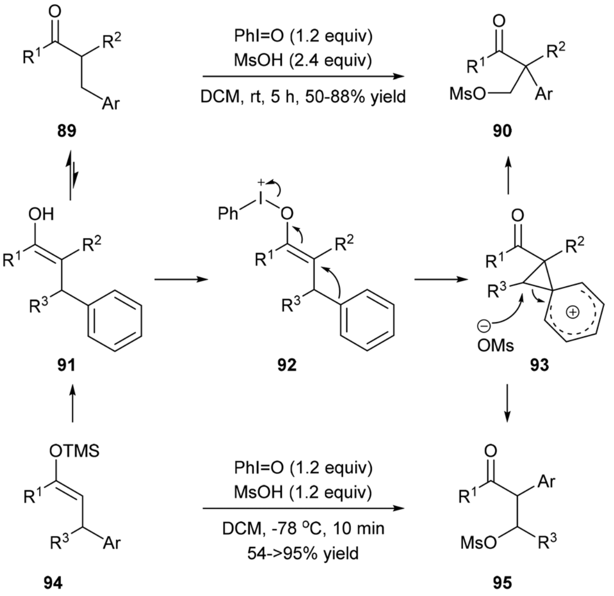
5.1 Hypervalent iodine(III)-mediated rearrangement

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 **82** which underwent alkyl migration forming a more stable cationic intermediate **83** (Scheme 18, eqn (3)).[27a] 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]

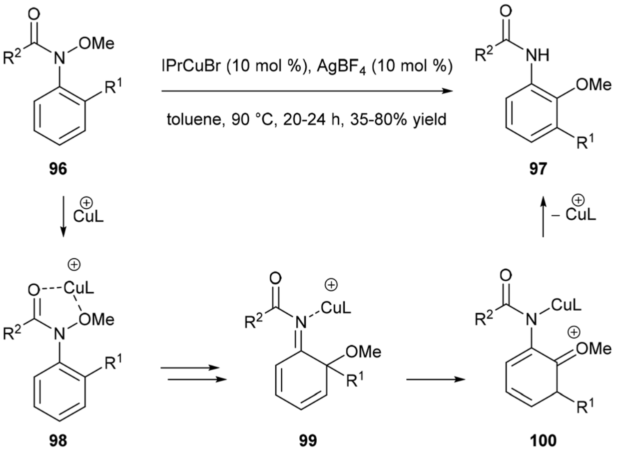


Scheme 18 PhI(OAc)$_2$ prompted alkyl migration.

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 electron-donating 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]

6. Summary and outlook

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.

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