Complimentary and personal copy for Mutoh Y, Ilies L.

www.thieme.com

Activation of Strong Bonds Enabled by Arene π-Coordination

Synthesis

2025

10.1055/a-2655-4268

Georg Thieme Verlag KG,
Oswald-Hesse-Straße 50,
70469 Stuttgart, Germany
ISSN 0039-7881

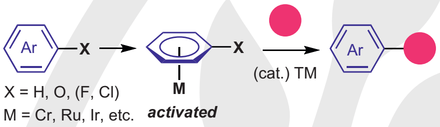
Thieme

Short Review

Activation of Strong Bonds Enabled by Arene π-Coordination

Yuichiro Mutoh, Laurean Ilies
Affiliation addresses are listed at the end of the article.

GRAPHICAL ABSTRACT



ABSTRACT

π-Coordination of an arene to a metal fragment decreases its electron density and has been often utilized to accelerate nucleophilic aromatic substitution, for example. By contrast, this strategy has only recently been applied to transition metal–catalyzed C–H bond functionalization. This short review summarizes the development of the field, with the hope to further stimulate interest in this methodology. Transition metal–catalyzed and –mediated C–H activation of arenes η^6-coordinated to chromium and other metals is mainly discussed; to highlight the potential of this strategy for organic synthesis, the activation of other strong bonds, with a focus on C–O bond activation, is also presented.

Keywords π-Coordination, η^6-Complex, Arene functionalization, C–H bond activation, C–O bond activation, C–Halogen bond activation

received March 31, 2025 | **accepted after revision** July 15, 2025 | **article published online** 2025
Bibliography Synthesis **DOI** 10.1055/a-2655-4268 **Art ID** SS-2025-03-0084-SR

Correspondence Dr. Yuichiro Mutoh and Dr. Laurean Ilies, Center for Sustainable Resource Science, RIKEN, 2-1 Hirosawa, Wako, Japan,
Emails: yuichiro.mutoh@riken.jp; laurean.ilies@riken.jp

*Part of the Special Issue Romanian Chemists in Synthesis

1 Introduction

Transition-metal–catalyzed C–H bond activation has become an important methodology in modern organic synthetic chemistry,[1] allowing direct functionalization of arenes for the straightforward construction of molecular complexity.[2] In order to activate the strong C–H bond (the bond dissociation energy [BDE] for the C–H bond in benzene: 113 kcal/mol)[3] and also to control the site selectivity, various strategies have been developed,[4] mostly relying on the modification of the substrate, such as the introduction of directing groups,[5] of bulky substituents, heteroatoms, etc. By contrast, the activation of simple arenes lacking such groups is more challenging[6] and typically requires highly active catalysts, often bearing engineered, sophisticated ligands.

η^6-Coordination of an arene to a metal fragment decreases the electron density on the arene and has been used for a long time in organic synthesis.[7] For example, the π-coordination strategy has been used to accelerate nucleophilic aromatic substitution[8] or to enhance transition metal–mediated or –catalyzed oxidative addition of aryl halides,[9] among many others. Moreover, the arene coordinated to the metal can undergo ligand exchange,[10] and therefore catalytic activation of a substrate through transient π-coordination becomes possible, as it was demonstrated, for example, in the nucleophilic aromatic substitution of fluoroarenes and congeners through catalytic η^6-coordination to ruthenium or rhodium.[8]

Considering this background, the π-coordination strategy is appealing as an enabler for the activation of simple arenes, because decreasing electron density is expected to accelerate transition metal–catalyzed C–H activation that proceeds through oxidative addition or concerted metalation–deprotonation (CMD). Moreover, in principle, catalytic η^6-coordination could also be possible through ligand exchange with an appropriate precursor.[10] However, this research field[11] is still in its infancy: the first reports on palladium-mediated[12] and -catalyzed[13] C–H functionalization of arenes coordinated to a chromium fragment were published in 2013; since then, the number of publications still remains limited.

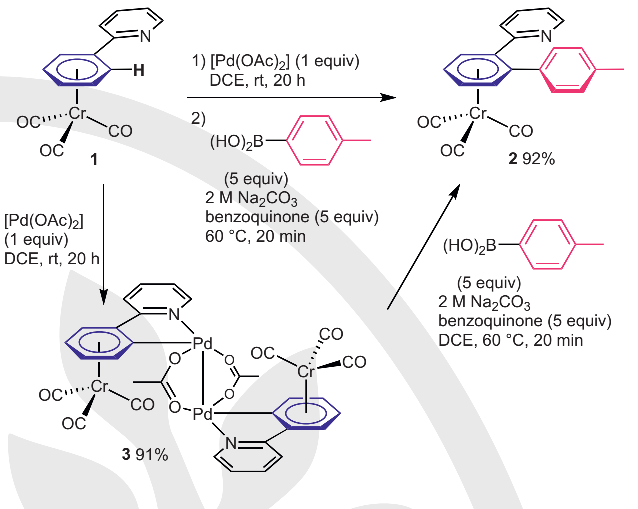
This short review describes the state-of-the-art to date, with the hope to further stimulate the interest of the community in this methodology. Transition metal–catalyzed and –mediated

C–H activation of arenes η^6-coordinated to chromium will be mainly discussed, together with coordination to other metals such as ruthenium, iridium, or nickel. Chromium η^6-complexes have been the preferred choice to date, because they are well investigated, easy to make, and bench stable.[7,14] In this review, "π-coordination" refers mostly to the η^6-coordination mode, with one example of η^4/η^3-coordination in **Scheme 10**. We selected examples where the authors explicitly mention the involvement of a key metal η^6–complex (or η^4/η^3) intermediate, even if in some cases the effect of complexation on the cleavage step is not discussed in detail. A main approach has been the increase of reactivity of an arene substrate through η^6-coordination, mainly toward palladium/silver-catalyzed CMD-type C–H cleavage; very recently, an example of acceleration of iridium-catalyzed C–H activation that proceeds through oxidative addition was reported.[15] In the context of this review, we define "C–H activation" as the cleavage of a C–H bond that involves (catalytic) formation of a C–metal bond. Thus, while according to this definition, not a C–H activation reaction, but the borylation of arenes through a proposed nucleophilic aromatic substitution mechanism and the oxidation of arenes through π-coordination will also be briefly presented as an interesting mode of activation. Finally, functionalization of other strong bonds, with a focus on C–O bond activation, will also be briefly highlighted, with the intent to offer a perspective into the potential of this strategy for organic synthesis. The functionalization of C–halogen (F and Cl) bonds will be just briefly mentioned, because they have been previously reviewed.[8,9]

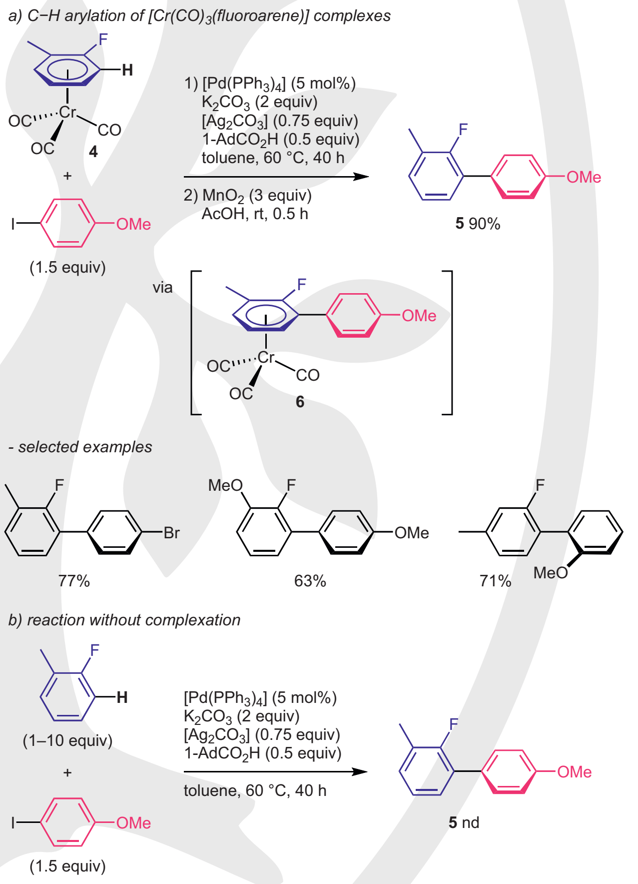
2 C–H Bond Functionalization Enabled by η^6-Coordination to Chromium

In 2013, Fuchter described the enhancement of stoichiometric palladation of *N*-arylpyridines by coordination to a chromium fragment (**1**), followed by functionalization of the resulting palladacycle **3** with aryl boronic acids (**Scheme 1**).[12] The authors rationalized the reactivity through the known increase in acidity of the C–H bond of the arene by π-coordination,[7] but control experiments were not described. The palladacycle intermediate **3** was isolated and characterized, and its stepwise and one-pot reaction with aryl boronic acids was optimized to give complex **2** in high yield. While the reaction requires a pyridine directing group and a stoichiometric amount of palladium, this report is a conceptual demonstration for the activation of a C–H bond through η^6-coordination to a chromium fragment.

The first catalytic C–H activation enhanced by η^6-coordination to chromium was reported by Larrosa and coworkers in 2013.[13] They hypothesized that π-coordination would increase the acidity of the C–H bond, resulting in an acceleration of the palladium-catalyzed C–H cleavage step, known to proceed through a concerted metalation–deprotonation (CMD) mechanism.[16] According to this hypothesis, a fluoroarene η^6-coordinated to a chromium fragment (**4**) was efficiently arylated with iodoarenes in the presence of a catalytic amount of Pd(0)[17] and a substoichiometric amount of silver at 60 °C (**Scheme 2a**). The reaction also proceeded regioselectively to give the *ortho*-arylated product **5** as a single isomer. Notably, control experiments showed that C–H arylation does not proceed at all in the absence of π-coordination under the same reaction conditions, even when an excess (up to 10 equiv) of fluoroarene was used (**Scheme 2b**). The biaryl product was obtained as a chromium complex, and the authors developed a MnO$_2$/AcOH system for fast and practical in situ decomplexation.



Scheme 1 Stoichiometric C–H arylation of 2-phenylpyridine in a chromium complex. DCE = 1,2-dichloroethane.



Scheme 2 C–H Arylation of [Cr(CO)$_3$(fluoroarene)] complexes. Ad = adamantyl. nd = not detected.

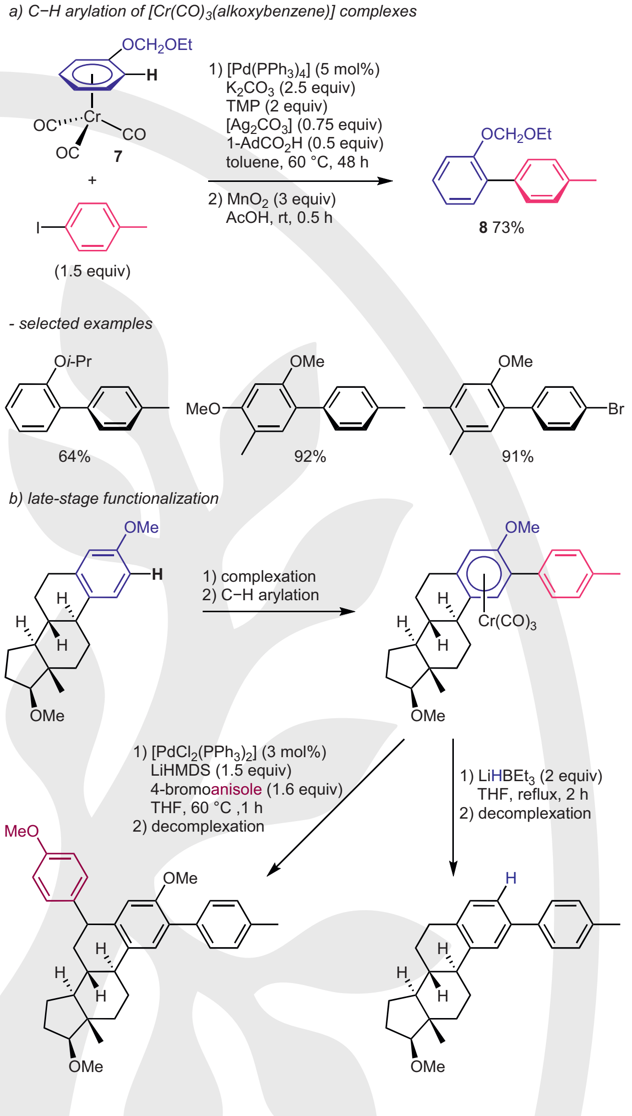
Substrates bearing functionalities sensitive to oxidative conditions could be thermally decomplexed in DMSO at 80 °C, or under visible light irradiation. The reaction proceeds under relatively mild reaction conditions, and therefore various functional groups were tolerated. For example, the reaction tolerates Cl and Br substituents, which allows for orthogonal functionalization. Simple benzene could also be arylated upon coordination to chromium, albeit harsher conditions (100 °C, 40 h) were needed, and the yield was lower (42% after decomplexation).

A kinetic isotope effect (KIE) of 2.1 was measured for parallel reactions, and the authors proposed that the C–H cleavage step is a turnover-limiting step. The authors investigated the origins of reactivity enhancement by DFT calculations, to find that C–H activation proceeds indeed via a concerted metalation–deprotonation transition state and that η^6-coordination to chromium lowers the energy of the transition state (TS) by 5.7 kcal/mol. A distortion-interaction analysis revealed that π-coordination decreases the energy cost necessary for distorting the C–H bond of the arene in the CMD TS. However, as detailed below (**Schemes 5** and **6**), later studies revealed a crucial role of silver, which was proposed to activate the C–H bond, rather than palladium.

One year later, the same group reported the palladium-catalyzed arylation of anisoles using the π-coordination strategy.[18] Under similar conditions with the reaction of fluoroarenes, chromium anisole complex **7** could be arylated with aryl iodides to obtain biraryl derivative **8** after oxidative decomplexation with MnO_2/AcOH (**Scheme 3a**). The reaction proceeded regioselectively at the *ortho* C–H site, even when using a sterically hindered isopropyl ether. Electron-rich arenes are typically less reactive under the CMD conditions; however, the π-coordination strategy enabled even the reaction of arenes containing two methoxy groups. As a synthetic application, a steroid derivative was selectively arylated *ortho* to a methoxy group after π-complexation, and the resulting compound could be further functionalized (**Scheme 3b**).

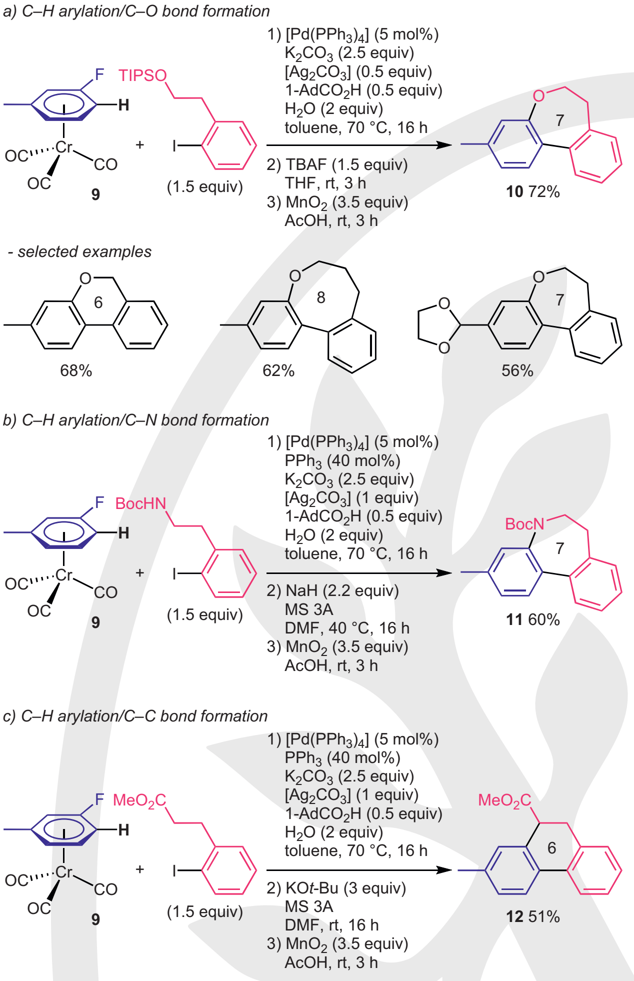
A competition experiment showed that the anisole coordinated to chromium is 4.7 times more reactive than 1,3,5-trifluorobenzene; taking into account that anisole is about 10^4 times less reactive than 1,3,5-trifluorobenzene under standard CMD conditions,[16a,17] the impact of π-coordination on reactivity is impressive. A KIE value of 2.0 was measured, similar to the one obtained for the reaction of fluoroarenes,[13] suggesting that a similar reaction mechanism is operating.

The Larrosa group utilized the palladium-catalyzed *ortho*-arylation of chromium fluoroarene complexes for the synthesis of medium-sized cyclic compounds,[19] which are challenging targets in organic synthesis.[20] The palladium-catalyzed reaction of chromium fluoroarene complex **9** with a 2-substituted iodoarene, followed by one-pot cyclization and demetallation, gave the oxygen- and nitrogen-containing medium-sized rings **10**–**12** in good overall yields (**Scheme 4**). These reactions are a clever example of using two advantages of π-coordination: enhancement of palladium-catalyzed C–H *ortho*-arylation of fluoroarenes, and acceleration of the intramolecular nucleophilic aromatic substitution of the resulting fluoroarene chromium complexes.

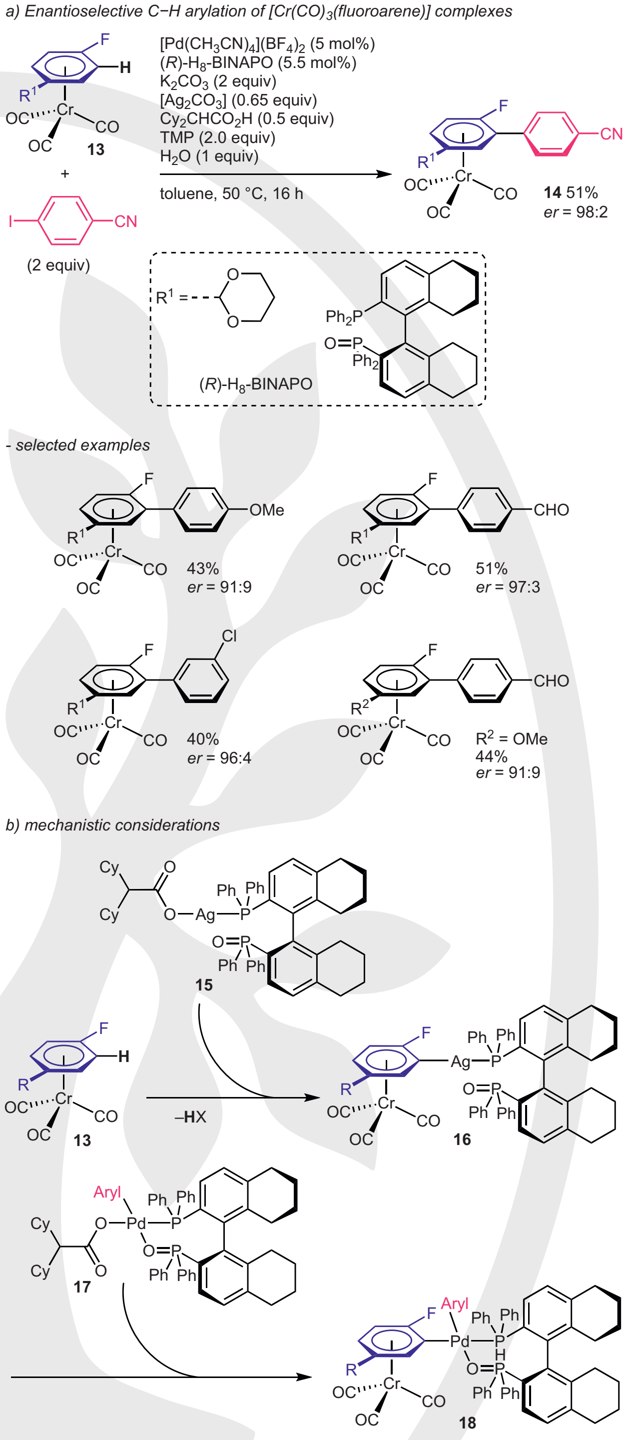


Scheme 3 *Ortho*-selective C–H arylation of $[Cr(CO)_3(alkoxybenzene)]$ complexes. TMP = 2,2,6,6-tetramethylpiperidine. Ad = adamantyl.

The group of Larrosa also developed an asymmetric palladium-catalyzed arylation of fluoroarene chromium complexes, with applications to the synthesis of planar-chiral phosphine ligands.[21] Thus, fluoroarene chromium complex **13** was arylated with 4-iodobenzonitrile in the presence of a catalytic amount of a palladium salt, chiral phosphine ligand (*R*)-H_8-BINAPO, and the additives previously optimized for these reactions: a substoichiometric amount of a silver salt, potassium carbonate, a carboxylic acid, and TMP. Under these conditions, chiral biaryl chromium complex **14** was obtained in moderate yield and high enantioselectivity (**Scheme 5a**). The key to success was the choice of the chiral phosphine ligand, a hemilabile ligand rarely used in asymmetric catalysis,[22] which has both a strong and a weak donor atom and therefore can behave as a bi- or monodentate ligand. Under these reaction conditions, the authors could synthesize a variety of chiral *ortho*-fluorobiaryl compounds with typically moderate yields, high enantioselectivity, and good functional group tolerance. The *ortho* fluorine group on the biaryl product was used as a synthetic handle for further functionalization: after converting it to the corresponding phosphine through nucleophilic aromatic substitution, chiral mono- and diphosphines could be synthesized.



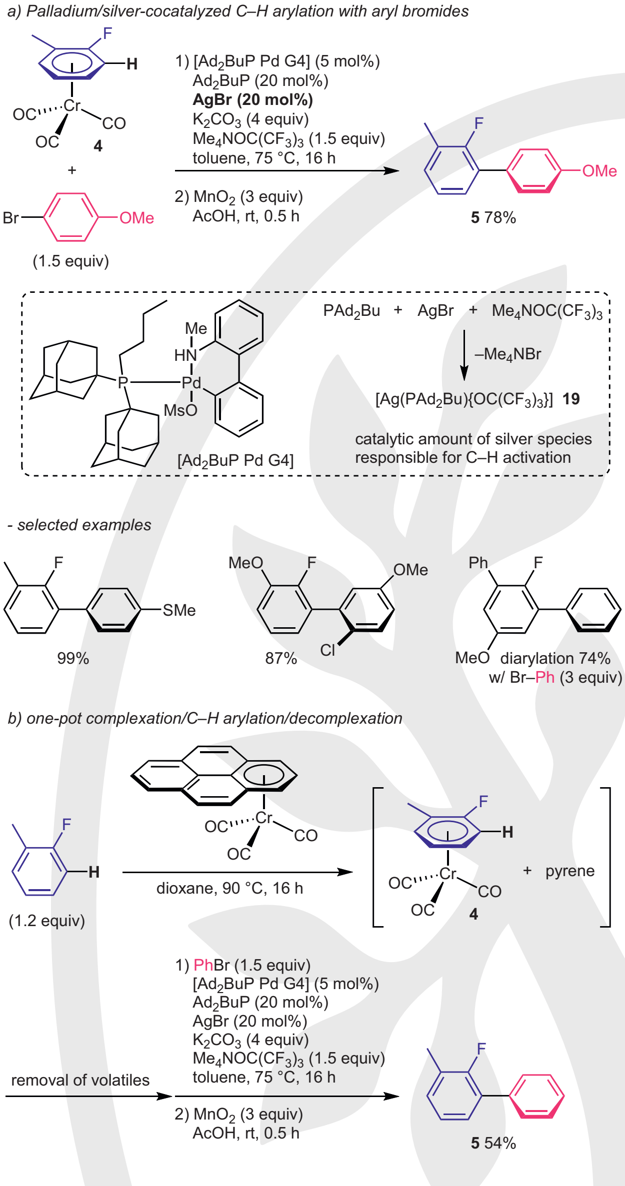
Scheme 4 One-pot C–H arylation–S_NAr cyclization to synthesize a medium-sized ring structure. Ad = adamantyl. MS = molecular sieves.



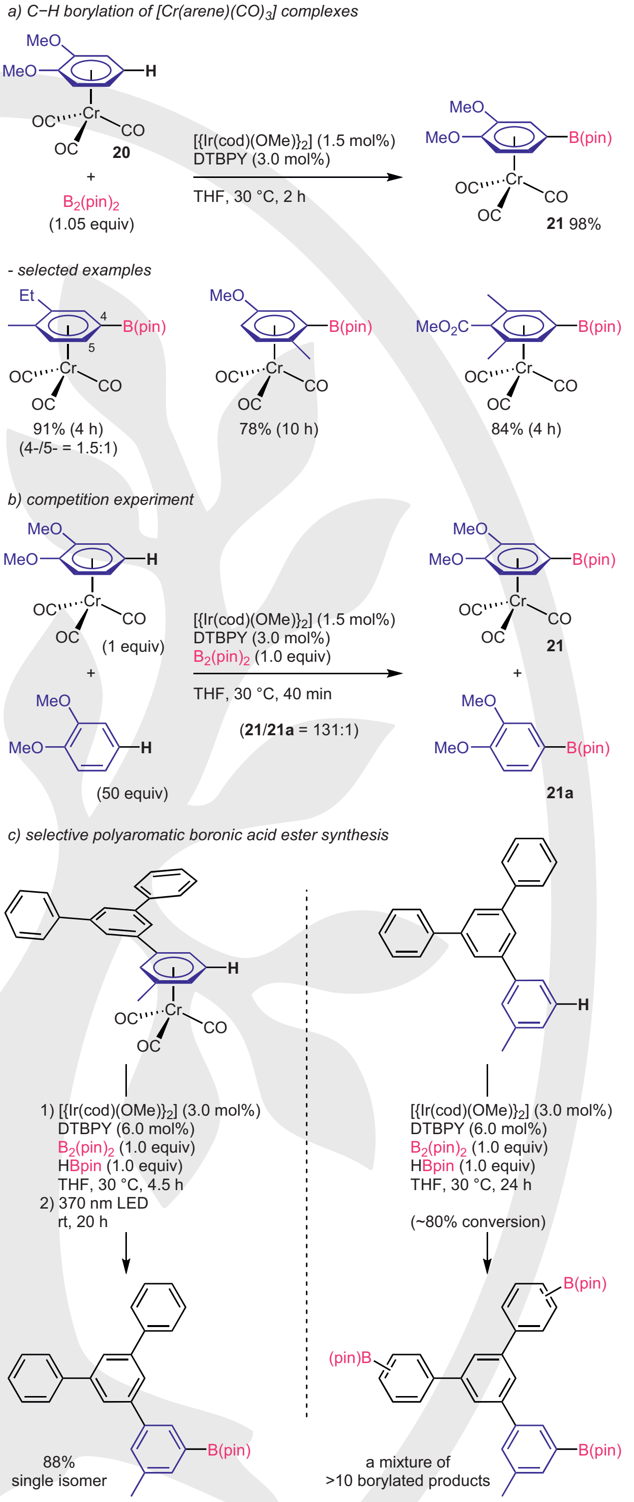
Scheme 5 Enantioselective C–H arylation of $[Cr(CO)_3(fluoroarene)]$ complexes. TMP = 2,2,6,6-tetramethylpiperidine.

The authors also conducted a detailed mechanistic study, including H/D exchange experiments, and synthesis and characterization of potential silver and palladium intermediates. From these experiments and previous knowledge,[23] they proposed a bimetallic catalytic cycle, where the iodoarene oxidatively adds to a Pd(0) complex, then ligand exchange gives arylpalladium **17**, while the C–H bond in the fluoroarene chromium complex **13** is cleaved by silver carboxylate **15** to give intermediate **16**, which then transmetalates with **17** to afford **18** (**Scheme 5b**). Two possible enantio-determining steps were proposed: enantioselective C–H activation followed by a fast reaction with **17**, or a fast reversible C–H activation, followed by an enantioselectivity-determining transmetalation with **17**.

One year later, the same group further studied the involvement of silver in the C–H activation step and developed a reaction catalytic in both palladium and silver.[24] The model reaction was the same arylation of fluoroarene chromium complexes **4**, but this time with less reactive bromoarenes (**Scheme 6a**). To overcome the slower oxidative addition of aryl bromides and to make the reaction catalytic in silver, two key modifications were made: an ammonium salt, $NMe_4OC(CF_3)_3$, was used as a halide abstractor to regenerate the silver active species, and a Buchwald-type palladium precursor was used. Under these conditions, the reaction showed a large scope, and good to excellent yields were achieved, with tolerance of various functional groups. Moreover, the authors developed a one-pot two-step protocol to directly use fluoroarenes as the substrate, upon ligand exchange with a pyrene



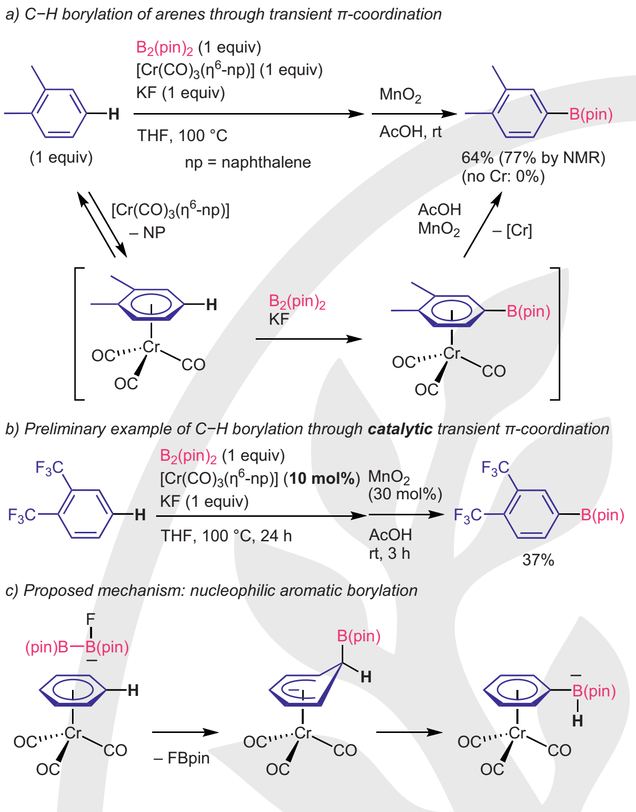
Scheme 6 Palladium/silver-cocatalyzed C–H arylation of [Cr(CO)$_3$(fluoroarene)] complexes with bromoarenes.



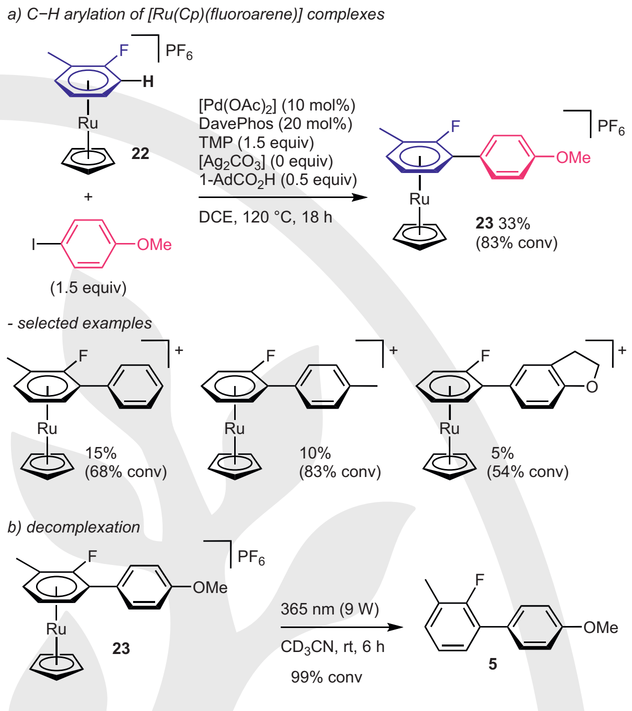
Scheme 7 C–H borylation of [Cr(η^6-arene)(CO)$_3$] complexes. DTBPY = 4,4′-di-*tert*-butyl-2,2′-bipyridyl.

chromium complex[25] (**Scheme 6b**). The bimetallic catalytic cycle was probed mechanistically through H/D exchange experiments, characterization of [(PBuAd$_2$)AgOC(CF$_3$)$_3$] (**19**), reaction progress kinetic analysis, and variable-time normalization analysis to determine kinetic orders, to conclude that a phosphine-ligated Ag(I) alkoxide (**19**) cleaves the C–H bond of the fluoroarene coordinated to chromium (**4**), then the resulting arylsilver species transmetalates with an arylpalladium bromide formed by oxidative addition of the aryl bromide to palladium, to regenerate silver and produce a diarylpalladium complex, which then gives **5** upon reductive elimination.

Very recently, Bunescu and coauthors reported that π-coordination accelerates iridium-catalyzed C–H borylation (**Scheme 7**).[15] Thus, chromium η^6–arene complex **20** reacted in the presence of an iridium catalyst and a bipyridine ligand under mild conditions with high yield (**Scheme 7a**). As oxidative addition is considered to be the turnover-limiting step, electron-rich arenes typically react slower; a control experiment showed that π-coordination strongly accelerates the reaction of 1,2-dimethoxybenzene (**Scheme 7b**). Moreover, the reaction of polyaromatic compounds proceeded



Scheme 8 C–H borylation of arenes through transient **π**-coordination.



Scheme 9 C–H arylation of [Ru(Cp)(fluoroarene)] (Cp = $C_5H_5^-$) complexes. DavePhos = 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl. TMP = 2,2,6,6-tetramethylpiperidine, Ad = adamantyl, DCE = 1,2-dichloroethane.

selectively at the ring coordinated to chromium; in the absence of π-coordination, the polyaromatic compound gave a mixture of isomers (**Scheme 7c**).

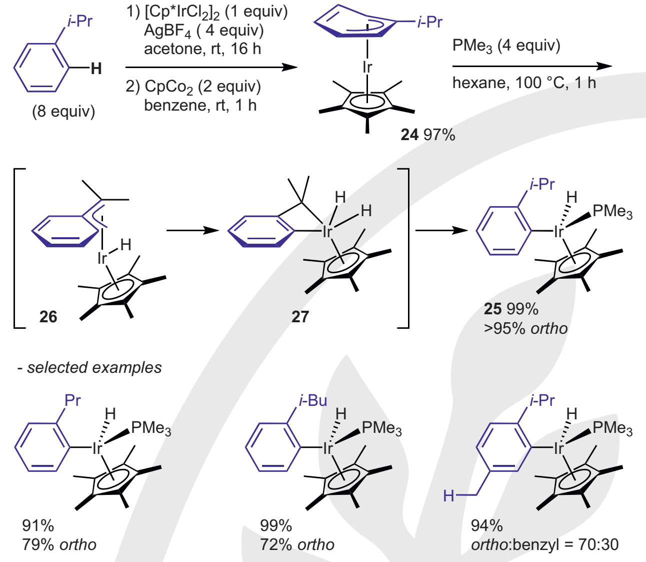
Also very recently, our group reported the borylation of simple arenes through transient π-coordination (**Scheme 8**).[26] For example, 1 equiv of *ortho*-xylene could be borylated with $B_2(pin)_2$ in the presence of KF, upon transient activation through in situ arene exchange with a chromium η^6–naphthalene complex; notably, the reaction did not proceed at all in the absence of the chromium precursor (**Scheme 8a**). A preliminary experiment demonstrated the possibility of catalytic η^6-coordination to chromium to activate an electron-deficient arene, albeit in low yield (**Scheme 8b**). A nucleophilic aromatic substitution mechanism was proposed based on the experiment and computation (**Scheme 8c**).

An example of nucleophilic aromatic substitution of benzene enabled by η^6-coordination to ruthenium was recently reported.[27]

3 C–H Bond Functionalization Enabled by η^6-Coordination to Other Metals

In 2017, Walton reported that palladium-catalyzed arylation of electron-deficient arenes is accelerated by η^6-cordination to ruthenium.[28] Fluoroarene complex **22** was arylated with iodoarenes under similar reaction conditions to those employed by Larrosa, to produce *ortho*-biaryl complex **23** with moderate to high conversion, but low yield (**Scheme 9a**). The reaction proceeded with good conversion and *ortho* selectivity with fluoroarenes, but other arenes were less successful. The ruthenium complexes **23** could be readily demetallated under photochemical conditions (**Scheme 9b**). The use of ruthenium complexes is of interest because it could potentially be extended to a catalytic process, as nucleophilic aromatic substitutions through transient ruthenium complexes are known.[8]

While the arene activations discussed previously involved the η^6-coordination mode, Sergeev and coauthors reported an intriguing activation of alkylbenzenes through η^4/η^3-coordination to iridium, resulting in *ortho*-selective C–H functionalization through transient benzylic C–H activation.[29,30] A Cp*Ir precursor was reacted with an alkylbenzene such as isopropylbenzene under mild conditions to produce η^4-arene iridium complex **24** in high yield; upon treatment of this complex with trimethylphosphine at 100 °C, the *ortho* C–H bond was selectively cleaved to give iridium complex **25** in quantitative yield (**Scheme 10**). Counterintuitively, the *ortho* selectivity increased with the steric bulk of the alkyl group. A mechanistic study revealed that the alkyl group acts as a “directing group” through the transient formation of a key η^3-benzyl hydride complex **26**, which promotes oxidative addition of the adjacent *ortho* C–H bond to iridium to give metallacycle **27**. Reductive elimination, followed by coordination of PMe_3, gives the observed product **25**. Both kinetic and thermodynamic factors were proposed to favor the activation of the *ortho* C–H bond over the benzylic C–H. While the reaction requires a stoichiometric amount of iridium, this proof-of-principle study is expected to lay the foundation for future developments toward catalytic *ortho*-functionalization.



Scheme 10 *Ortho*-Selective C–H activation of simple arenes in an iridium complex.

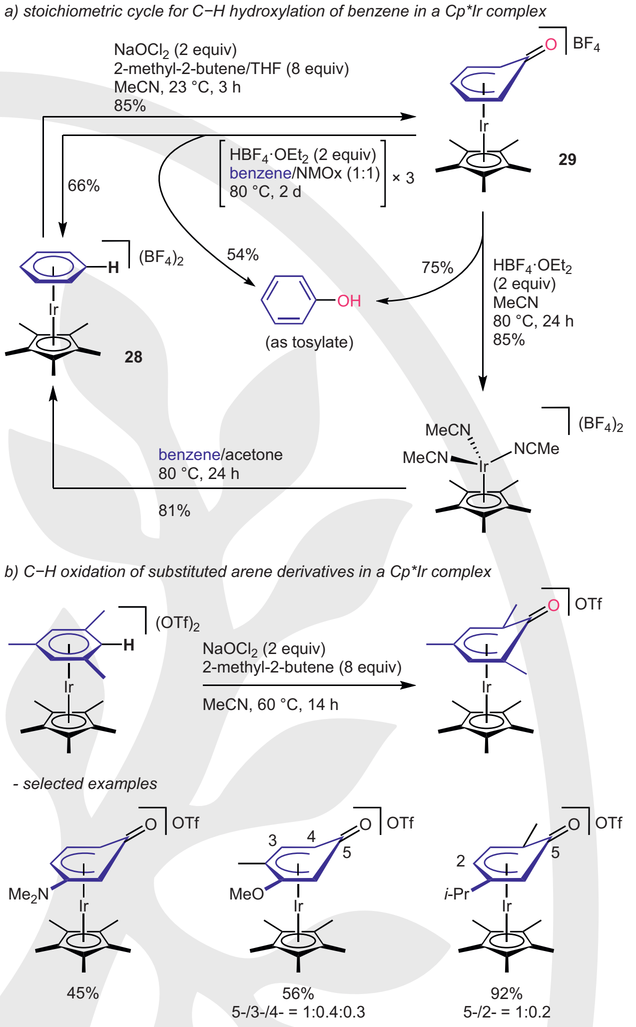
While not involving a C–H activation step, functionalization of alkylbenzene through (3+2) cycloaddition with 1,1-bis(phenylsulfonyl)ethylene, enabled by catalytic π-coordination to rhodium, was reported by Shi and coworkers.[31]

While π-coordination is not directly involved in the C–H cleavage step, the nickel-catalyzed hydroarylation of unactivated arenes with alkenes reported by Nakao and Hartwig[32] involves a key nickel η^6-arene complex, which coordinates an alkene, and then the C–H bond is cleaved by ligand-to-ligand transfer of a proton from the arene to the bound alkene. It should be mentioned that ruthenium(II) η^6-arene complexes have also been used as catalyst precursors for C–H activation. This topic was reviewed elsewhere.[33]

While not strictly a C–H bond activation process, the oxidation of benzene enabled by π-coordination to iridium was reported by the groups of Ritter[34] and Chirik.[35] The authors hypothesized that π-coordination to iridium decreases the electron density on the arene and makes it more susceptible to nucleophilic attack.[7]

The Ritter group used NaOCl$_2$ as the oxidant in combination with an alkene as an HOCl scavenger to oxidize η^6–arene iridium complex **28** to η^5–phenoxo complex **29** in high yield at 23 °C; treatment of **29** with HBF$_4$ in acetonitrile released the phenol and gave the dicationic iridium complex [Cp*Ir(NCMe)$_3$](BF$_4$)$_2$, which could be reconverted to starting complex **28** upon treatment with benzene/acetone (**Scheme 11a**). Direct conversion of phenoxo complex **29** into starting arene complex **28** with release of phenol was possible by using *N*-methyl-2-oxazolidinone, showing promise toward a catalytic reaction.

The Chirik group further explored the scope of this protocol to achieve the oxidation of monosubstituted, disubstituted, and trisubstituted arenes, with a focus on site selectivity; they also investigated the functionalization of electron-rich and sterically hindered arenes (**Scheme 11b**).



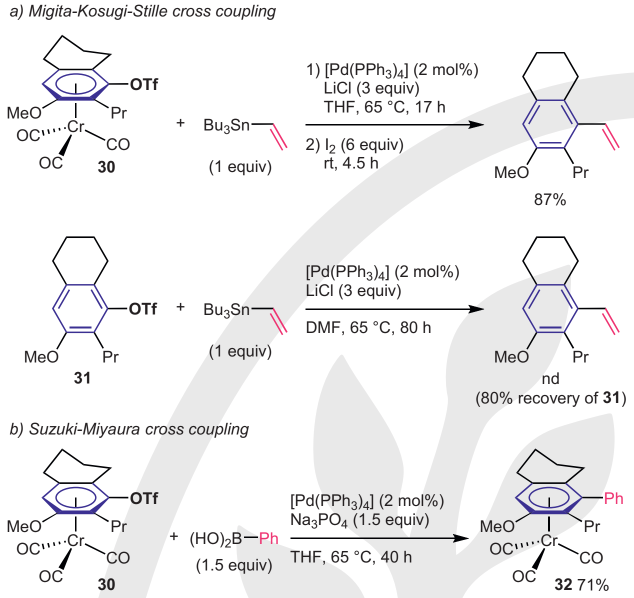
Scheme 11 C–H oxidation of arenes in an iridium complex. NMOx = *N*-methyl-2-oxazolidinone.

4 C–O Bond Functionalization

While the main topic of this short review is the activation (and/or functionalization) of C–H bonds, in order to illustrate the potential of the π-coordination strategy for organic synthesis, we briefly discuss in the following sections the activation of other strong bonds.

The oxidative addition of pseudohalides such as aryl triflates to palladium is accelerated by π-coordination to chromium.[36] Thus, the Migita-Kosugi–Stille reaction of aryl triflate chromium complex **30** with tributylvinylstannane proceeds well in the presence of [Pd(PPh$_3$)$_4$] as a catalyst (**Scheme 12a**); by contrast, the uncoordinated triflate **31** does not react at all under the same conditions, presumably because of the reluctance of this electron-rich aryl triflate to undergo oxidative addition by palladium. Suzuki–Miyaura cross-coupling of aryl triflate complex **30** with phenyl boronic acid also proceeded well to give biphenylarene complex **32** in good yield (**Scheme 12b**).

The C–O bond in aryl ethers is a strong bond (in anisole, BDE for Ph–OMe: 100 kcal/mol; in diphenyl ether: 78 kcal/mol);



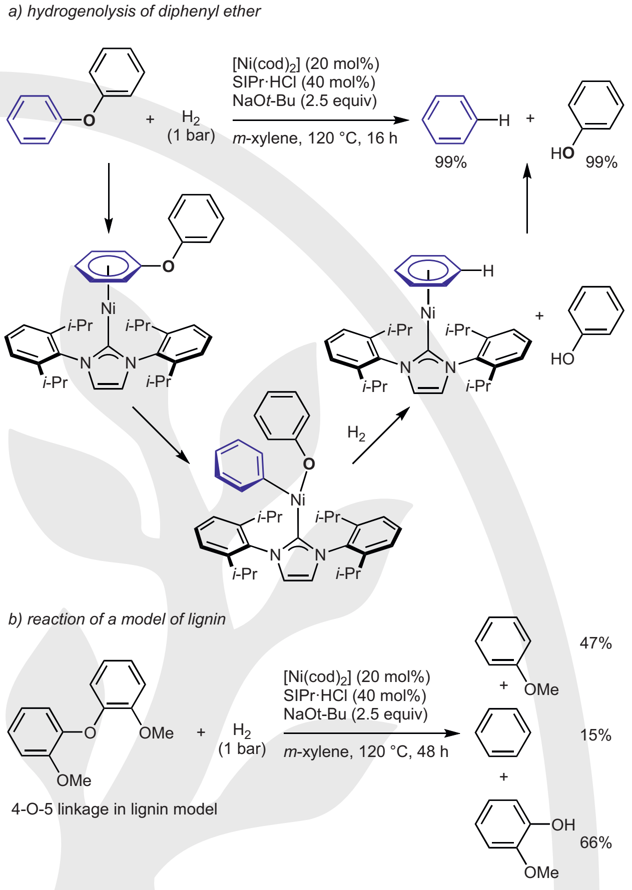
Scheme 12 Cross-coupling of an electron-rich and sterically hindered aryl triflate in a chromium complex. nd = not detected.

nickel has been one of the most investigated catalysts for C–O activation to date.[37] The group of Hartwig reported that an Ni(0)/NHC catalyst can hydrogenolyze diarylethers with 1 atm of hydrogen (**Scheme 13a**).[38] Subsequent mechanistic studies revealed that nickel transiently η^6-coordinates the aryl ether to facilitate the oxidative addition of the C–O bond.[39] As a synthetic application, the authors demonstrated the hydrogenolysis of the diaryl ether models of lignin under 1 atm of hydrogen at 120 °C to obtain anisole, benzene, and phenols in moderate yields (**Scheme 13b**). A computational study by Surawantanawong[40] suggested that isomerization between the η^6- and η^2-complexes precedes oxidative addition. A mechanistic study by Agapie and coworkers on the hydrogenolysis of aryl alkyl ethers by nickel concluded that an η^2–arene nickel(0) complex is involved in the key C–O bond cleavage step.[41]

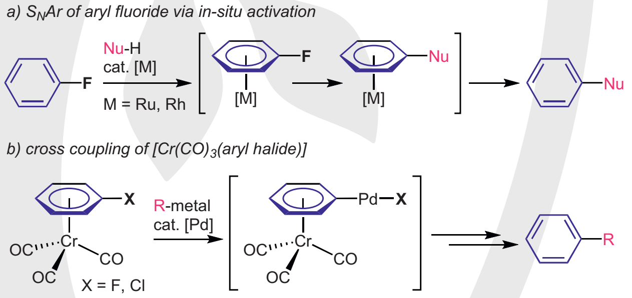
Another interesting application of π-coordination for C–O bond functionalization is the rhodium-catalyzed amination of phenols, where rhodium η^6-coordinates the phenol substrate to enable its tautomerization to a ketone intermediate, which then undergoes condensation with an aniline to give the corresponding imine, which finally rearomatizes to give the aniline product.[42a] A similar reaction using ruthenium as the catalyst was also reported.[42b]

5 C–Halogen Bond Functionalization

Among C–halogen bonds, C–F (in fluorobenzene, BDE = 126 kcal/mol) and C–Cl (in chlorobenzene: BDE = 96 kcal/mol)[3] are considered strong bonds, typically requiring highly active metal catalysts and/or harsh reaction conditions to activate.[43,44] As also mentioned in the introduction, one of the most investigated applications of the π-coordination strategy is the nucleophilic aromatic substitution of fluoroarenes (**Scheme 14a**), which was extensively reviewed to date,[7,8] and therefore will not be detailed here.[45] Because the oxidative addition of a C–halogen bond to a transition metal proceeds faster for electron-deficient aryl halides, the π-coordination strategy was used to accelerate the oxidative addition of aryl fluorides and aryl chlorides to nickel or palladium, including applications to catalytic cross-coupling, amination, etc. (**Scheme 14b**).[9]

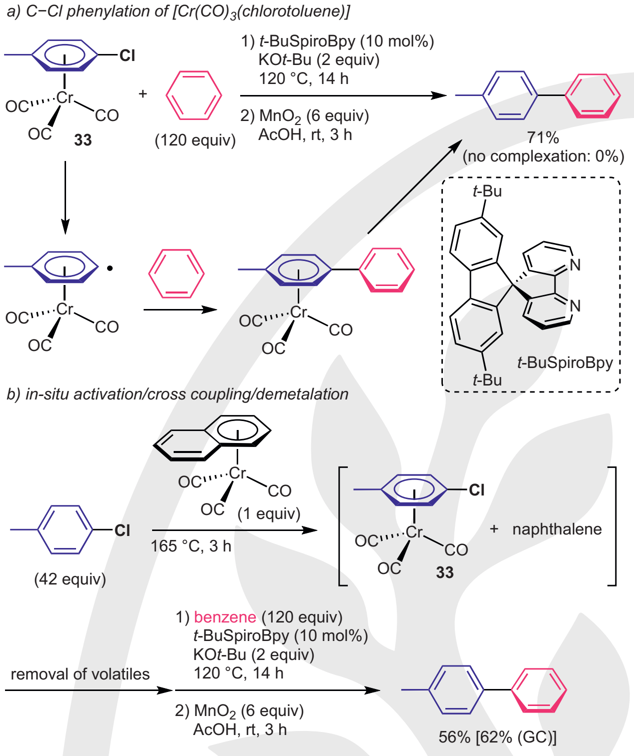


Scheme 13 Nickel-catalyzed hydrogenolysis of diaryl ethers.



Scheme 14 S_NAr and cross-coupling of aryl fluorides and chlorides through π-coordination.

The radical cleavage of a C–Cl bond in a chloroarene can also be accelerated by η^6-coordination to chromium,[46] and this reactivity was recently exploited for the radical coupling of chloroarenes with arenes.[47] Thus, a chromium η^6–chloroarene complex



Scheme 15 Radical cross-coupling of [Cr(CO)$_3$(chlorotoluene)] with benzene.

33 reacted with a solvent amount of an arene in the presence of potassium *tert*-butoxide and a spirobipyridine compound[48] as radical initiators (**Scheme 15a**); the chloroarene could also be reacted upon ligand exchange with a chromium η^6–naphthalene complex precursor in a one-pot, two-step process (**Scheme 15b**). The reaction did not proceed at all without π-coordination.

6 Conclusions

In conclusion, the η^6-coordination of an arene to a metal fragment is a promising strategy for activating simple arenes toward transition metal–catalyzed C–H functionalization that proceeds through oxidative addition or CMD, for example, which favors electron-deficient substrates. Most of the reports to date have focused on palladium-catalyzed arylation of arene chromium complexes, and while developments remain slow, other reactions have also been reported. A main limitation is the need to synthesize and isolate the arene metal complex as a starting material and then to remove the metal in order to release the product. The conditions required for these steps (high temperature, metal oxidants, photoirradiation, etc.) are sometimes incompatible with sensitive functional groups. From an atom economy point of view, the use of a stoichiometric amount of a transition metal such as chromium, often in combination with catalytic or stoichiometric amounts of palladium and silver, is not synthetically attractive. We expect that further efforts will target catalytic activation through transient η^6-coordination to achieve a general and synthetically appealing strategy for the functionalization of arenes. In this context, an effort toward this goal was recently reported by our group.[26] While just briefly discussed in this short review, the activation of other strong bonds using the π-coordination strategy is also expected to expand the repertoire of molecular activation in organic synthesis.

Author affiliations

RIKEN Center for Sustainable Resource Science, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan.

Statements and additional information

Conflict of Interest The authors declare that they have no conflict of interest.

Funding Information This work was supported by JSPS KAKENHI Grant-in-Aid for Transformative Research Areas No. JP24H01101 (Digi-TOS) (L.I.), JSPS KAKENHI Grant Number JP22K05104 (Y.M.), and RIKEN Incentive Research Project grant (Y.M.).

References

1 (a) Dyker G. Handbook of C–H Transformations. Weinheim: Wiley-VCH; 2005: 2–661 (b) Dixneuf PH, Doucet H. Topics in Organometallic Chemistry: C–H Bond Activation and Catalytic Functionalization. Berlin, Heidelberg: Springer; 2016 (c) Catalytic transformations via C–H activation. In: Science of Synthesis. Yu J-Q, ed. Vol. 1–2. Thieme: Stuttgart; 2016 (d) Maiti D. Handbook of CH Functionalization. Weinheim: Wiley-VCH; 2022

2 Selected reviews: (a) Yamaguchi J, Yamaguchi AD, Itami K. Angew Chem Int Ed 2012; 51: 8960 (b) Wencel-Delord J, Glorius F. Nat Chem 2013; 5: 369 (c) Hartwig JF. J Am Chem Soc 2016; 138: 2 (d) Lam NYS, Wu K, Yu JQ. Angew Chem Int Ed 2021; 60: 15767 (e) Guillemard L, Kaplaneris N, Ackermann L, Johansson MJ. Nat Rev Chem 2021; 5: 522 (f) Zhang L, Ritter T. J Am Chem Soc 2022; 144: 2399 (g) Docherty JH, Lister TM, McArthur G et al. Chem Rev 2023; 123: 7692

3 Luo Y-R. Comprehensive Handbook of Chemical Bond Energies. Boca Raton: CRC Press; 2007

4 Rej S, Das A, Chatani N. Coord Chem Rev 2021; 431: 213683

5 Sambiagio C, Schonbauer D, Blieck R et al. Chem Soc Rev 2018; 47: 6603

6 (a) Hartwig JF, Larsen MA. ACS Cent Sci 2016; 2: 281 (b) Khake SM, Chatani N. Chem 2020; 6: 1056 (c) Kaltenberger S, van Gemmeren M. Acc Chem Res 2023; 56: 2459

7 Selected reviews: (a) Berger A, Djukic JP, Michon C. Coord Chem Rev 2002; 225: 215 (b) Kündig EP. Topics in Organometallic Chemistry: Transition Metal Arene π-Complexes in Organic Synthesis and Catalysis. Heidelberg: Springer-Verlag Berlin; 2004 (c) Rosillo M, Domínguez G, Pérez-Castells J. Chem Soc Rev 2007; 36: 1589 (d) Takemoto S, Matsuzaka H. Tetrahedron Lett 2018; 59: 697 (e) Walton JW, Wilkinson LA. Organomet Chem 2019; 42: 125 (f) Williams LJ, Bhonoah Y, Wilkinson LA, Walton JW. Chem Eur J 2020; 27: 3650

8 Chen K, Shi H. Acc Chem Res 2024; 57: 2194

9 Prim D, Andrioletti B, Rose-Munch F, Rose E, Couty F. Tetrahedron 2004; 60: 3325

10 (a) Shvydkiy NV, Perekalin DS. Coord Chem Rev 2020; 411: 213238 (b) Akana-Schneider B, Guo Y, Parnitzke B, Derosa J. Dalton Trans 2024; 53: 18819

11 Hu F, Szostak M. ChemCatChem 2015; 7: 1061

12 Fuchter MJ, Judge DK, Weimar M, White AJP. Dalton Trans 2013; 42: 5615

13 Ricci P, Krämer K, Cambeiro XC, Larrosa I. J Am Chem Soc 2013; 135: 13258

14 Maurer C, Fleischer R, Mandal A et al. Chem Asian J 2025; 20: e202500139

15 Mandal A, Maurer C, Plett C et al. J Am Chem Soc 2025; 147: 15281

16 (a) Lafrance M, Rowley NC, Woo TK, Fagnou K. J Am Chem Soc 2006; 128: 8754 (b) Lapointe D, Fagnou K. Chem Lett 2010; 39: 1118 (c) Ackermann L. Chem Rev 2011; 111: 1315 (d) Gorelsky SI. Coord Chem Rev 2013; 257: 153

17 Lafrance M, Fagnou K. J Am Chem Soc 2006; 128: 16496

18 Ricci P, Krämer K, Larrosa I. J Am Chem Soc 2014; 136: 18082

19 Whitaker D, Batuecas M, Ricci P, Larrosa I. Chem Eur J 2017; 23: 12763

20 Majumdar KC. RSC Adv 2011; 1: 1152

21 Batuecas M, Luo J, Gergelitsová I et al. ACS Catal 2019; 9: 5268

22 Wöste TH, Oestreich M. Chem Eur J 2011; 17: 11914

23 Whitaker D, Burés J, Larrosa I. J Am Chem Soc 2016; 138: 8384

24 Panigrahi A, Whitaker D, Vitorica-Yrezabal IJ, Larrosa I. ACS Catal 2020; 10: 2100

25 (a) Kündig EP, Perret C, Spichiger S, Bernardinelli G. J Organomet Chem 1985; 286: 183 (b) Howell JAS, Ashford NF, Dixon DT, Kola JC, Albright TA, Kang SK. Organometallics 1852; 1991: 10

26 Mutoh Y, Khalaf R, Asako S, Ilies L. ChemRxiv

27 Melnikov S, Hwang D, Park B, Lutz M, Baik M-H, Broere DL. J Chem Sci 2025

28 Wilkinson LA, Pike JA, Walton JW. Organometallics 2017; 36: 4376

29 Chan APY, Jakoobi M, Wang C et al. J Am Chem Soc 2022; 144: 11564

30 For benzylic C–H functionalization using an η^6-arene chromium complex as a benzyl anion equivalent, see refs 7d and 11, and Zhu(s) H, Wu Y, Mao Y, Xu J, Walsh P, Shi H. Chem Soc Rev 2025; 54: 2520–2542

31 Wu W-Q, Lin Y, Li Y, Shi H. J Am Chem Soc 2023; 145: 9464

32 Saper NI, Ohgi A, Small DW, Semba K, Nakao Y, Hartwig JF. Nat Chem 2020; 12: 276

33 Binnani C, Singh SK. Arene–ruthenium(II) complexes in C–H functionalization: role of ligands. In: Handobook of CH Functionalization. Maiti D, ed. WILEY-VCH: GmbH; 2023: 1–35

34 D'Amato EM, Neumann CN, Ritter T. Organometallics 2015; 34: 4626

35 Odena C, Perez-Jimenez M, Lin R, Chirik PJ. Organometallics 2024; 43: 3067

36 Gilbert AM, Wulff WD. J Am Chem Soc 1994; 116: 7449

37 Diao H, Shi Z, Liu F. Synlett 2021; 32: 1494

38 Sergeev AG, Hartwig JF. Science 2011; 332: 439

39 Saper NI, Hartwig JF. J Am Chem Soc 2017; 139: 17667

40 Sawatlon B, Wititsuwannakul T, Tantirungrotechai Y, Surawatanawong P. Dalton Trans 2014; 43: 18123

41 Kelley P, Lin S, Edouard G, Day MW, Agapie T. J Am Chem Soc 2012; 134: 5480

42 (a) Chen K, Kang Q-K, Li Y, Wu W-Q, Zhu H, Shi H. J Am Chem Soc 2022; 144: 1144 (b) Chen K, Ma Y, Lin Y, Li JY, Shi H. J Am Chem Soc 2024; 146: 15833

43 (a) Ahrens T, Kohlmann J, Ahrens M, Braun T. Chem Rev 2015; 115: 931 (b) Eisenstein O, Milani J, Perutz RN. Chem Rev 2017; 117: 8710

44 (a) Grushin VV, Alper H. Chem Rev 1994; 94: 1047 (b) Littke AF, Fu GC. Angew Chem Int Ed 2002; 41: 4176

45 Selected examples of S_NAr through catalyticπ-coordination: (a) Houghton RP, Voyle M, Price R. J Chem Soc Perkin Trans 1984; 1: 925 (b) Otsuka M, Endo K, Shibata T. Chem Commun 2010; 46: 336 (c) Otsuka M, Yokoyama H, Endo K, Shibata T. Synlett 2010; 2010: 2601 (d) Walton JW, Williams JMJ. Chem Commun 2015; 51: 2786 (e) Konovalov AI, Gorbacheva EO, Miloserdov FM, Grushin VV. Chem Commun 2015; 51: 13527 (f) Mueller BRJ, Schley ND. Dalton Trans 2020; 49: 10114 (g) Schulte T, Wang Z, Li CC et al. J Am Chem Soc 2024; 146: 15825

46 Lin H, Chen Q, Cao L, Yang L, Wu YD, Li C. J Org Chem 2006; 71: 3328

47 Nagata M, Itonaga K, Mutoh Y, Endo K, Ilies L. Chem Lett 2024; 53: upae233

48 (a) Ramadoss B, Jin Y, Asako S, Ilies L. Science 2022; 375: 658 (b) Jin Y, Ramadoss B, Asako S, Ilies L. Nat Commun 2024; 15: 2886 (c) De PB, Okamoto K, Sekar J, Asako S, Ilies L. Angew Chem Int Ed 2025; 64: e202419144

About the authors

Yuichiro Mutoh

Yuichiro Mutoh was born in Gifu, Japan. He earned his PhD in 2005 from Gifu University (advisor: Prof. Toshiaki Murai). After a postdoctoral fellowship with Prof. Fumiyuki Ozawa at Kyoto University, he became an Assistant Professor with Prof. Youichi Ishii at Chuo University in 2007. He joined Tokyo University of Science in 2012 and worked in the research group of Prof. Shinichi Saito, where he was promoted to a Junior Associate Professor in 2017. Since 2020, he has been a Senior Scientist (name changed to Senior Research Scientist in 2025) at the RIKEN Center for Sustainable Resource Science, collaborating with Dr. Laurean Ilies. His research focuses on molecular catalysts based on organometallic chemistry and also explores heavier main-group chemistry.

Laurean Ilies

Laurean Ilies was born in Romania and relocated to Japan in 1999. He earned his PhD in 2009 from the University of Tokyo (advisor: Prof. Eiichi Nakamura). He became an assistant professor at the University of Tokyo in 2009 and was promoted to associate professor in 2014. He was appointed team leader (name changed to team director in 2025) at the RIKEN Center for Sustainable Resource Science in 2018, and professor adjunct at Saitama University in 2021. His research focuses on the design of catalysts for efficient and selective reactions, and the exploration of Earth-abundant metals for sustainable organic synthesis.

Mutoh Yuichiro et al. doi: 10.1055/a-2655-4268