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C–H functionalization through benzylic deprotonation with π-coordination or cation–π-interactions

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Benzylic C–H functionalization is a valuable tool to make complex aromatic molecules from simple, readily available alkylbenzenes. While methods that involve benzylic radicals or cations generated by hydrogen atom transfer or oxidation have been well demonstrated, they often require oxidative conditions. In contrast, deprotonation methods offer a complementary approach to transform benzylic C–H bonds through a benzylic carbanion generated by deprotonation. Electrophilic transition metal complexes acidify benzylic protons upon π-coordination to the phenyl ring of substrates, facilitating deprotonation by stabilizing the corresponding benzylic carbanion. Cation-complexes with group(I) metals also acidify benzylic C–H bonds. These approaches enable a significant expansion of the scope and diversity of alkylarenes with various electrophilic reagents. In this review, we discuss the development of benzylic functionalization through deprotonation of η^6-arene complexes of transition-metals and cation–π interactions with group(I) metals, as well as progress made in catalysis through reversible arene–metal interactions.

1. Introduction

Aryl rings are ubiquitous structural motifs in functional materials, pharmaceuticals, and natural products, underscoring the imperative to advance efficient methods for elevating the structural intricacy of readily accessible alkylarenes. Among these endeavors, the selective functionalization of benzylic C–H bonds emerges as a straightforward avenue toward accessing functionalized molecules bearing aromatic rings.[1,2] Leveraging

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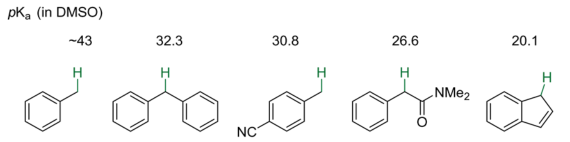
Yu Wu

Yu Wu received her BA in Chemistry from Colorado College in 2020 and started to work with Prof. Patrick J. Walsh at the University of Pennsylvania in 2021. She completed her MS in Chemistry in 2023 and continued her doctoral studies in the same research group. Her work focuses on developing transition-metal-free alkyne synthesis using one-pot processes. Her broader research interests include advancing methodology development in small molecule synthesis and catalysis.



Scheme 1 Benzylic acidity of aromatic compounds with pK_a values in DMSO (compilation by Reich and Bordwell).[11]

the relatively low bond dissociation energy of benzylic C–H bonds, a plethora of reactions have been unveiled involving the generation of benzyl radicals through hydrogen atom transfer under oxidative conditions.[3–9] In contrast, deprotonation of benzylic C–H bonds offers a complementary approach to benzylic functionalization through reactions with electrophilic reagents.

While this approach holds potential, the modest electronegativity difference between carbon and hydrogen atoms, and the mild stabilization of benzylic anions by electronically neutral aryl rings, imparts limited acidity to benzylic C(sp^3)–H bonds (Scheme 1).[10,11] The heterolytic cleavage of these bonds by deprotonation thus remains challanging.[12–26] Therefore, conventional methods for benzylic deprotonation of toluene without directing groups require the use of strong bases, such as ^{n}BuLi and ^{n}BuLi/^{t}BuOK.[13–16,18,22,25] To circumvent this hurdle, the introduction of a functional group capable of stabilizing negative charge *via* strong delocalization and/or inductive effects (*e.g.*, carbonyl, nitro, *etc.*) or the use of polycyclic compounds like indenes and fluorenes that achieve aromaticity upon deprotonation, have been employed to facilitate benzylic functionalization processes. The application of such activating strategies necessitates additional steps for installation of activating groups and post-functionalization conversion, which inevitably limit their applicability. This is particularly true when working with abundant raw materials like alkylbenzenes or complex arylated molecules. Moreover, deprotonation is generally less effective for secondary and tertiary benzylic C–H bonds due to greater steric hindrance (kinetic) and decrease stability of secondary and tertiary carbanions (thermodynamic).

Jianyou Mao

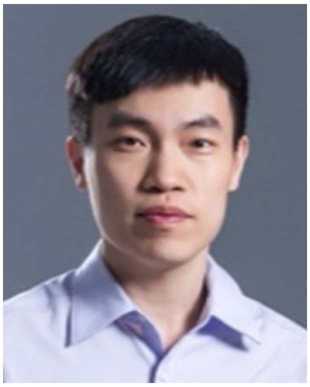
Jianyou Mao is a professor at the Nanjing Tech University. He received his PhD from China Agricultural University with Prof. Min Wang and Prof. Qinghua Bian. During which time, he was a visiting student at the University of Pennsylvania (USA) under the guidance of Prof. Patrick J. Walsh (2013-2015). He finished his postdoctoral study with Prof. Patrick J. Walsh in the same group (2015-2016). His research focuses on alkali-metal-mediated functionalization of weakly acidic C–H bonds.

Jingkai Xu

Jingkai Xu completed his undergraduate studies in Chemistry at Nanjing University, China, in 2022, where he developed a solid foundation in scientific principles and research methodologies. After studying for half a year in Hang Shi's group at Westlake University, he further honed his expertise at King Abdullah University of Science and Technology in Jeddah, Saudi Arabia, earning an MS degree in Material Science and Engineering in 2024. His research interests now lie in spintronics, focusing on developing innovative materials with applications in sustainable technologies.

Patrick J. Walsh

Patrick J. Walsh is the Rhodes-Thompson Professor of Chemistry at the University of Pennsylvania (USA). He received his BA from UC San Diego with Prof. Charles Perrin and PhD from UC Berkeley with Prof. R. G. Bergman. He was an NSF postdoctoral fellow with Prof. K. B. Sharpless at Scripps Research Institute. He began his independent career in 1994 at San Diego State University and moved to Penn in 1999. His research is in the area of transition metal-catalyzed reactions, development of methods for organic synthesis and the study of reaction mechanism.



Hang Shi

Hang Shi earned his bachelor's degree from Hunan University in 2008, under the guidance of Prof. Shuangfeng Yin. He then pursued his PhD at Peking University under the mentorship of Prof. Zhen Yang, focusing on the synthesis of natural products. In 2013, Hang joined Prof. Tobias Ritter's lab at Harvard University as a postdoctoral fellow. In 2015, he moved to Scripps Research Institute to work with Prof. Jin-Quan Yu as a research associate. Hang began his independent research career at Westlake University in 2018. In 2023, he was promoted to Associate Professor.

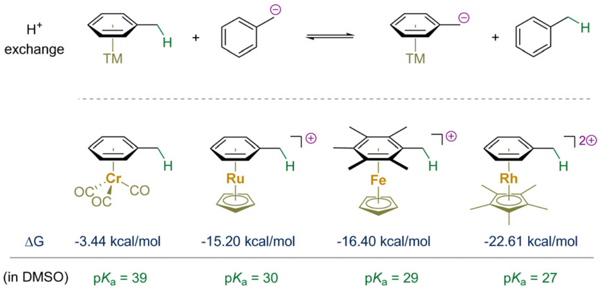
In pursuit of strategies for benzylic deprotonation that avoid reliance on electron-withdrawing substituents, chemists have shifted their focus to activating the aromatic π-system. Unlike covalently bound substituents that facilitate benzylic deprotonation through resonance and/or inductive effects, electrophilic metal complexes activate aromatic methyl groups by removing electron density from the π-system through coordination with transition-metals or the formation of electrostatic cation–π complexes with main group metals. These interactions enhance the acidity of the benzylic C–H bonds by removing electron density from the π-cloud and stabilizing the resultant benzylic anion.

In this review, we survey the latest advances in benzylic C–H functionalization through deprotonation, bolstered by π-coordination with transition-metals or cation–π interactions. Coverage of this review is up to the end of 2023. Our focus is on the deprotonation of unbiased benzylic C–H bonds, highlighting illustrative examples featuring both alkyl and saturated cyclic ring systems.

2. Transition-metal-facilitated deprotonation through π-coordination

With the advancement of organometallic chemistry and its applications to organic synthesis, the interactions between transition-metals and unsaturated organic molecules have gained significant recognition.[27–31] Since the 1950s, researchers have delved into the realm of sandwich and half-sandwich complexes, with a notable focus on η^6-arene complexes.[32–38] The discovery of bis(η^6-benzene)chromium in 1955 marked a significant milestone.[39] Subsequently, the preparation of half-sandwich (η^6-arene)chromium tricarbonyl complexes demonstrated their electronically inverted reactivity of the bound aromatic ring, further advancing the field.[40–43] This unique reactivity was rationalized by (arene) → M donation and electrostatic interactions.[28,44,45] The activation model would not only increase the electrophilicity of bound aromatic rings, but also enhance the acidity of their benzylic C–H bonds if present.[46–51] Upon the deprotonation of these C–H bonds, the resulting benzylic carbanions are stabilized through robust delocalization within the bound arene and onto the electrophilic metal center and its accompanying ligands (if π-acidic).

The energy stabilization was quantitatively assessed through the reversible proton exchange reaction between a transition-metal η^6-arene complex and phenylmethanide (Scheme 2).[52–55] Consequently, the proton affinity of the benzyl anion is decreased by approximately 3.4–22.61 kcal mol^{-1} upon η^6-coordination, depending on the specific metal and its ligands. Compared to toluene (pK_a = 43 in DMSO), the energy barrier for benzylic deprotonation of a bound toluene molecule is significantly diminished.[56–59] This section centers on the evolution of benzylic functionalization through deprotonation of η^6-arene complexes with transition-metals, shedding light on the progress made in catalysis *via* reversible arene π-coordination.



Scheme 2 Computed stabilization energies of transition-metal complexes in the equilibrium above.

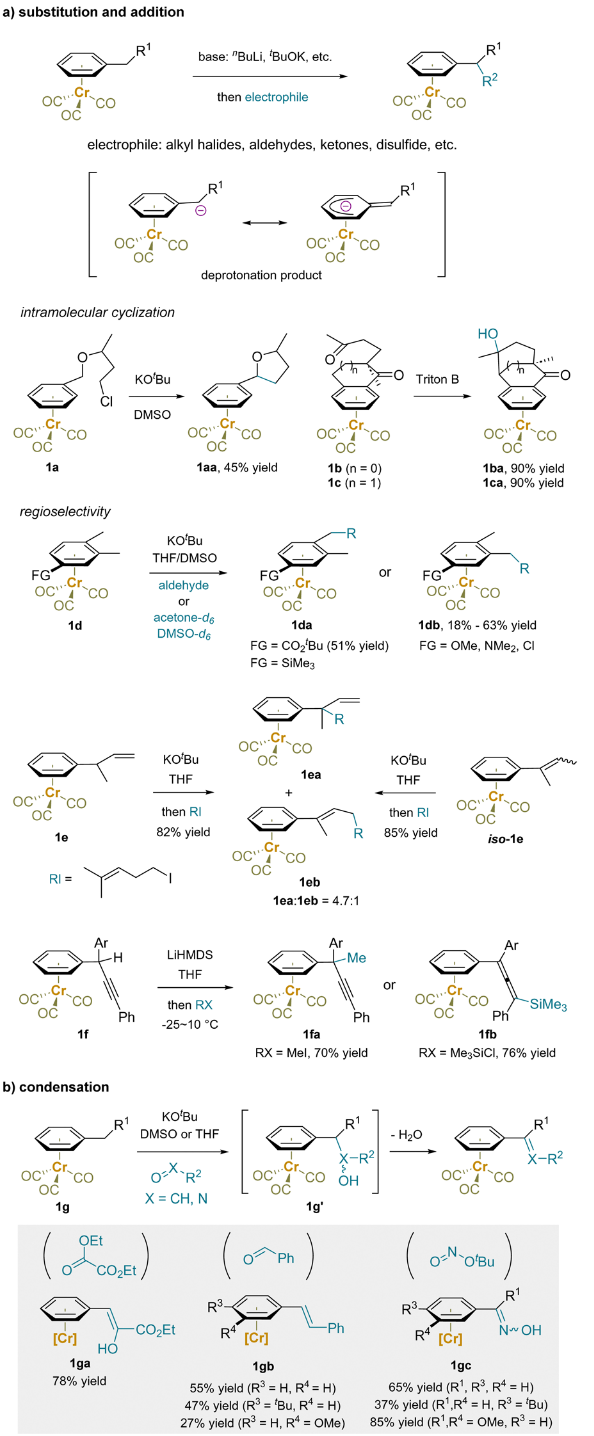
2.1. Substitution and addition

2.1.1 Chromium complexes. Chromium η^6-arene complexes have been extensively explored in organic synthesis, as they can be synthesized *via* ligand exchange between chromium hexacarbonyl and aromatic compounds.[60] The electron-withdrawing effect of the [Cr(CO)$_3$] unit allows selective benzylic deprotonation with a variety of bases, including KO^{t}Bu, NaH, KH/18-crown-6, ^{n}BuLi, lithium diisopropylamide (LDA), potassium bis(trimethylsilyl)amide (KN(SiMe$_3$)$_2$) and NaNH$_2$. It is noted here that in many cases the original researchers chose to use very strong bases, like LDA, organolithiums and even super bases, which the authors of this review suggest were unnecessarily strong given the increased acidity of (η^6-toluene)TM derivatives (TM = transition-metal). Weaker bases, such as MN(SiMe$_3$)$_2$ (M = Li, Na, K) are used in some of the highlighted examples below.

Once deprotonated, the resulting benzylic anions readily react with electrophiles, providing a range of complexes diversified at the benzylic position (Scheme 3a).[41,59,61–73] Besides various intermolecular alkylations, intramolecular cyclization reactions have been developed to generate the tetrahydrofuran derivative **1aa**[74] or tricyclic compounds **1ba** and **1ca.**[75]

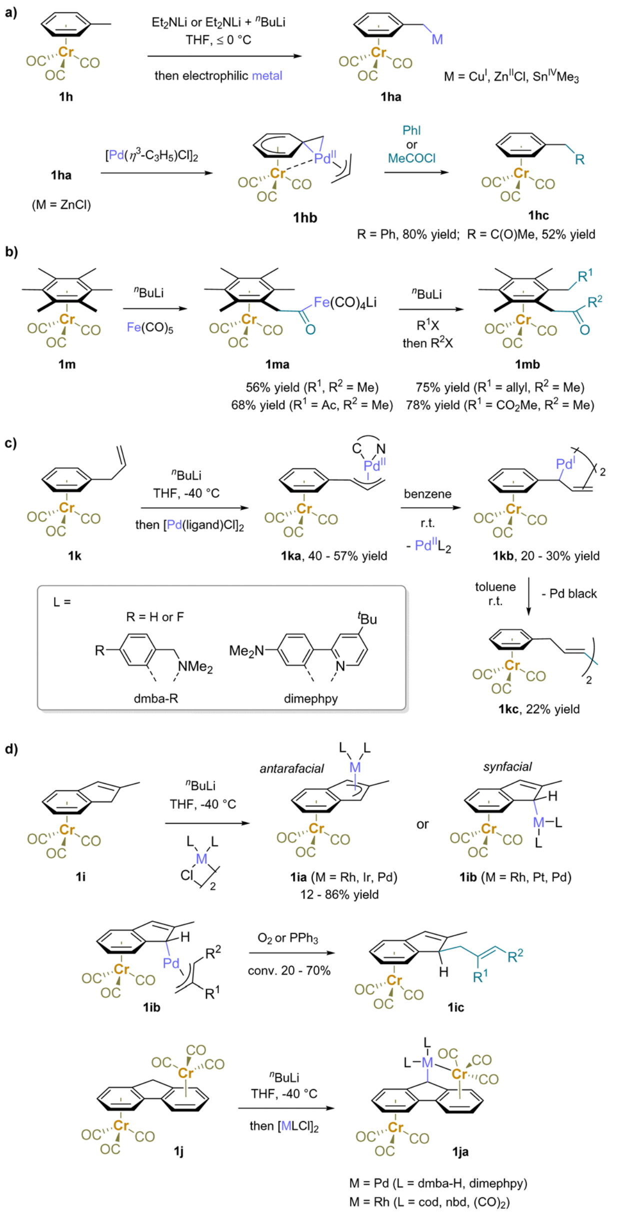
The regioselectivity of benzylic deprotonation is influenced by substituents on the aromatic ring.[76–80] For example, in the presence a carbonyl or silyl substituents, a *para* methyl group is preferentially functionalized over a *meta* methyl group, as shown in the reaction of **1d** to produce **1da**. Conversely, an electron donor group conjugated to the arene, such as methoxy or dimethylamino, steers reactions to occur with opposite selectivity, yielding **1db.**[65,76,79,80]

(η^6-arene)Cr(CO)$_3$ complexes bearing an unsaturated bond at the benzylic site have also been examined. For example, alkylation of the but-3-en-2-ylbenzene (**1e**) preferentially takes place at the benzylic position (**1ea** : **1eb** = 4.7 : 1), likely due to the anticipated stabilization of the benzylic anion.[81] The isomer of **1e**, but-2-en-2-ylbenzene complex (**iso-1e**) gave the same results under these conditions. Interestingly, regiodivergent substitution reactions of a complex bearing a benzylic triple bond (**1f**) were revealed, with the regioselectivity attributed to the size of the attacking electrophile. Specifically, methyl iodide gave the propargyl derivative **1fa**, while trimethylsilyl chloride yielded the allenyl product **1fb.**[82]



Scheme 3 Functionalization of $Cr(CO)_3$-complexed alkylarene: (a) substitution and addition reactions. (b) Condensations.

When compounds bearing an oxo motif were used as electrophiles with $Cr(CO)_3$-complexed toluene and derivatives (**1g**) in the presence of KO^{t}Bu, a sequence of deprotonation, addition, and elimination occurred (Scheme 3b).[63–65,68,83] Condensation products such as styrenes and benzaldehyde oximes were obtained, along with water as the byproduct.

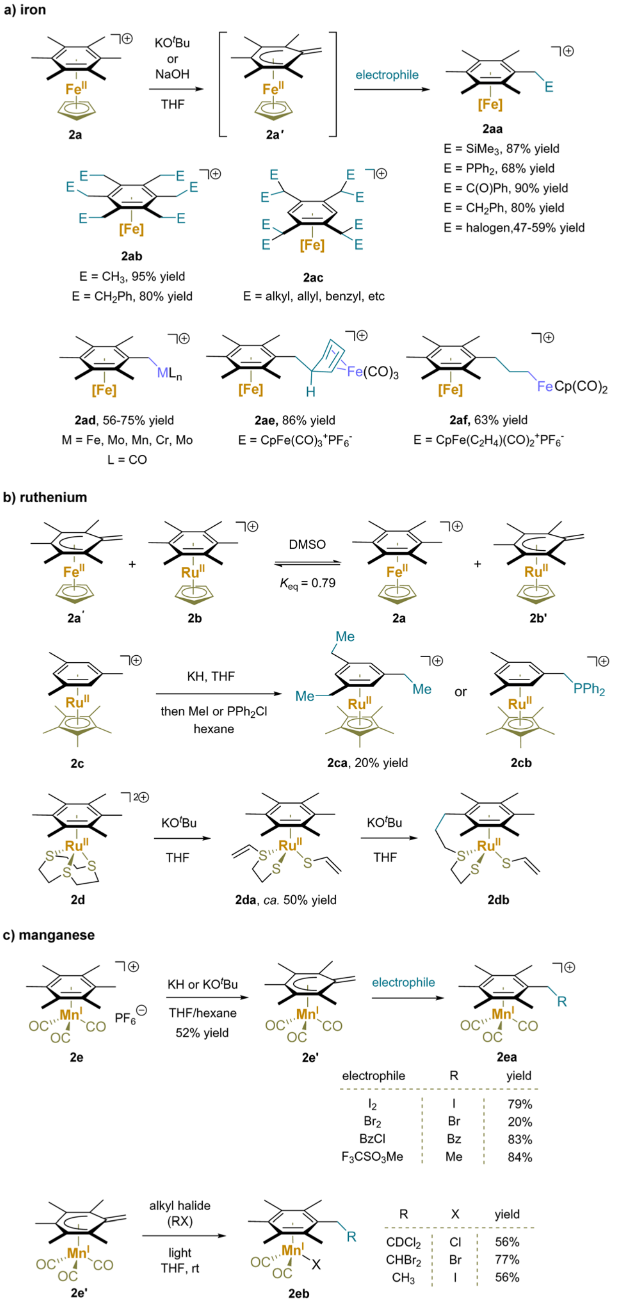


Scheme 4 Synthesis of bimetallic complexes and their use in C–C bond formation: (a) metallation-cross coupling reactions, (b) acylation reactions, (c) synthesis of Pd(I)-Pd(I) dimer, and (d) benzyl metallation and functionalization of η^6-coordinated indene and fluorene complexes.

In addition to reactions with carbon-based electrophiles, π-coordination-enabled deprotonation has also been utilized in the preparation of organometallic complexes (Scheme 4). Deprotonation of toluene complex **1h**, followed by quenching with electrophilic metal reagents, such as CuI, $ZnCl_2$, and Me_3SnCl, provided the corresponding organocopper, organozinc, and organotin compounds, respectively.[61,84–89] Notably, these metal reagents exhibited diverse reactivities. For instance, a benzylic copper complex underwent conjugate addition to methyl vinyl ketone, rather than 1,2-addition.[85] Interestingly, the organozinc reagent (**1ha**) was further used to prepare a palladium complex (**1hb**), in which the distance between palladium and chromium is approximately 2.76 Å, indicating an interaction between the metal centers.[84] The palladium motif further underwent oxidative addition with electrophiles, such as iodobenzene or acetyl chloride, followed by reductive elimination, installing a phenyl or an acetyl group at the benzylic position (**1hc**). Moreover, the benzylic carbanion reacted with a carbonyl ligand of iron pentacarbonyl, providing a bismetal complex **1ma**. Directed *ortho* metalation of a proximal methyl substituent of **1ma** by ^{n}BuLi was followed by nucleophilic attack by the benzylic anion. The second electrophile reacted first with the anionic iron center to form an Fe–C bond before undergoing reductive elimination yielding the difunctionalization products (**1mb**).[90] The deprotonation of $Cr(CO)_3$-complexed allylbenzene (**1k**) followed by transmetalation with a ligated palladium(II) complex resulted in the formation of a π-allyl palladium motif **1ka**. This Pd(II) complex slowly decomposed to μ-allyl-bridged bis-Pd(I) complex **1kb** (20–30% yield, characterized by X-ray crystallography) and a $Pd^{II}L_2$ (with the structure of L shown in the box). The reaction is accompanied by formation of a green precipitate, presumed to be Cr oxidation products generated on formation of the Pd(I) dimer.[88] After prolonged stirring in toluene the tetranuclear bis-Pd(I) complex **1kb** undergoes reductive coupling of the two allylbenzene moieties to furnish **1kc** with precipitation of Pd black.

Furthermore, the deprotonation of (η^6-indene)$Cr(CO)_3$ (**1i**) and transmetalation resulted in the formation of heterobimetallic indenyl complexes **1ia** and **1ib**, which were observed to form with Pd,[91,92] Pt,[91] Rh,[93–99] and Ir[100] complexes. The disposition of the two metal centers was dependent on the specific metal and ligands used. Interestingly, the *syn*-facial heterobimetallic indenyl complex **1ib** was found to decompose upon exposure to air or excess PPh_3, and *exo*-allylation products (**1ic**) as well as a homocoupling product of indenyl were obtained.[100] Additionally, the transmetalation of bis(tricarbonylchromium)fluorene (**1j**) and a palladium or rhodium complex yielded the formation of organopalladium or organorhodium species (**1ja**) with metal–metal interactions.[87,101]

2.1.2 Other transition metal complexes. In addition to chromium, other transition-metals such as iron, manganese, and ruthenium, have been shown to facilitate benzylic deprotonation *via* π-coordination (Scheme 5). The hexamethylbenzene-ligated analogue of ferrocene, $[CpFe(\eta^6\text{-}C_6Me_6)]^+$, has been studied since the late 1970s.[102–112] By varying electrophiles (including halogens, methyl iodide, acetyl chloride, and trimethylsilyl chloride) under basic conditions, a range of mono-substituted products (**2aa, 2ad–2af**)[102–104,106–108,113] and dendritic functional molecules (**2ab, 2ac**)[105,107–112] were obtained (Scheme 5a). Metal carbonyl complexes were also found to be suitable electrophiles, leading to the formation of bimetallic complexes (**2ad**), with the electrophilic metal center located at the benzylic position.[103] In contrast, using coordinatively saturated metal carbonyl complexes without leaving groups as electrophiles led to addition to the ligand (such as cyclopentadienyl and ethylene) instead of the metal center (**2ae–2af**).[103,104]



Scheme 5 Functionalization of metal-complexed alkylarene: (a) iron-complex, (b) ruthenium-complex and (c) manganese-complex.

Ruthenium(II) complexes have exhibited similar reactivity to the iron(II) analogues towards benzylic deprotonation due to the same valence d electronic structure and oxidation state (Scheme 5b).[114–118] Specifically, the acidity of [(hexamethylbenzene)RuCp]$^+$ (**2b**) was found to be very similar to that of the iron analogue **2a.**[59] In addition to intermolecular reactions (**2ca, 2cb**),[116] an intramolecular addition reaction of the dicationic (hexamethylbenzene)Ru([9]aneS_3) (**2d**) was also reported.[119] Abstraction of a proton from [9]aneS_3 caused cleavage of an adjacent C–S bond and formed the chelate vinylthioether-thiolate complex. Repetition of this process at a thioether

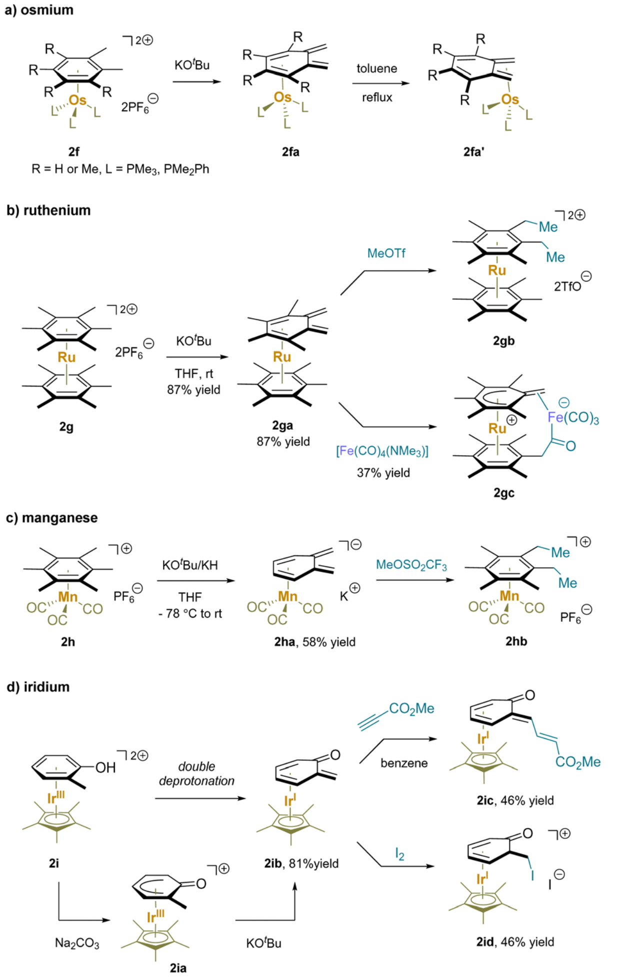
CH_2 group broke a second C–S bond giving complex **2da**. Under basic conditions this intermediate then underwent benzylic deprotonation and intramolecular nucleophilic addition to form **2db**.

Mono benzylic C–H functionalization of [(hexamethylbenzene)Mn$(CO)_3]^+$ (**2e**) has also been demonstrated (Scheme 5c).[120–123] Compared to chromium(0) complexes, the benzylic protons of manganese(I) complexes are more acidic due to the stronger electron-withdrawing effect of the cationic Mn motif. Deprotonation with KH or KO^{t}Bu provided a stable neutral complex **2e′**, which readily underwent substitution reactions with various electrophiles.[120] Remarkably, under light irradiation, benzylic substitution and ligand exchange of complex **2e′** took place with alkyl halides. The author proposed a mechanism with light induced ejection of a CO ligand to open a coordination site at Mn. Binding of the electrophile X–R to Mn results in halide abstraction and generation of the radical $R^{\bullet}$, which adds to the methylene, restoring aromaticity to the arene (**2eb**).

Cationic η^6-multimethylbenzene complexes can undergo double deprotonation in the presence of excess strong base. For instance, treatment of η^6-arene osmium(II) complexes (**2f**) with KO^{t}Bu yielded the cyclohexadiene-ligated complex of *o*-xylylene in the *endo*-coordinated form **2fa**. Complexes **2fa** isomerized quantitatively to the corresponding *exo*-isomer **2fa′** upon refluxing in toluene (Scheme 6a).[124,125] Similar properties were observed for ruthenium(II) with phosphine ligands.[115,117,124,126] On the other hand, double deprotonation of the dicationic bis(hexamethylbenzene)Ru complex (**2g**) exclusively resulted in an endocyclic complex **2ga** that underwent double methylation to give **2gb**. Interestingly, the combination of **2ga** with a tetracarbonyl iron complex led to the addition of one methylene to an iron-bound carbonyl ligand followed by proton shuttling from the neighboring bound C_6Me_6 unit to afford cyclic **2gc**.[114,118] The cationic [(hexamethylbenzene)Mn$(CO)_3]^+$ (**2h**) also underwent double deprotonation by KO^{t}Bu or KH and alkylation with MeOTf to afford **2hb** (Scheme 6c).[121] It is noteworthy that π-coordination of arenes to the $[IrCp^*]^{2+}$ moiety results in highly electron deficient π-systems. An η^6-phenol complex (**2i**) readily underwent deprotonation with Na_2CO_3 to generate an η^5-phenoxo **2ia** (Scheme 6d).[127] Surprisingly, further deprotonation of the η^5-phenoxo (**2ia**) occurred in the presence of KO^{t}Bu, yielding an η^4-(o-quinone methide) complex (**2ib**). Michael addition of **2ib** to an electrophilic alkyne generated the conjugate addition product **2ic**; the addition of iodine to **2ib** afforded iodination product **2id** *via* oxidation of the Ir through reaction with the methylene to install the C–I bond.[128,129]

2.2. Stereoselective reactions

Stereoselectivity is a crucial aspect of C–H functionalization at sp^3-hybridized carbon centers. In reactions of an η^6 complex, the ligated transition-metal motif differentiates the two faces of the bound aromatic ring, affecting both the benzylic deprotonation and the subsequent reaction of the resulting carbanions. This leads to *endo*/*exo*-selectivity of planar benzocyclic compounds and stereoselectivity of acyclic arenes.

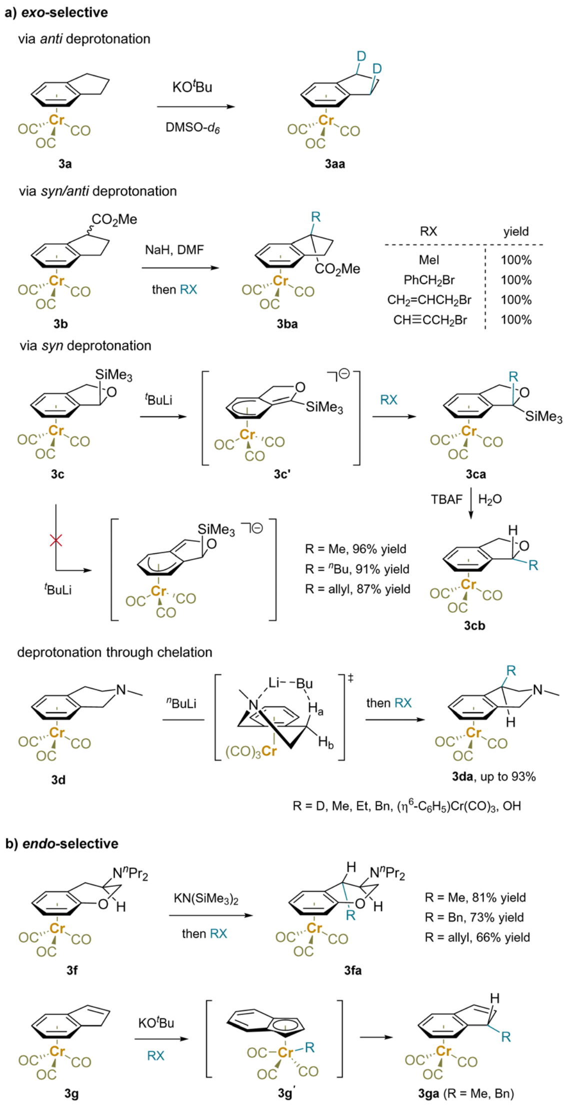


Scheme 6 Functionalization *via* double deprotonation with: (a) osmium, (b) ruthenium, (c) manganese and (d) iridium complexes.

2.2.1. Stereoselective functionalization of cyclic substrates.

The benzylic deprotonation of benzocyclic compounds produces rigid, planar intermediates that undergo stereospecific reactions with external electrophiles under the influence of both the metal unit, often $Cr(CO)_3$, and substituents on the cyclic rings. Generally, reactions of benzylic carbanions with electrophiles occur *anti* to the $Cr(CO)_3$ group, leading to the formation of the corresponding products in high *exo*-selectivity.[73,76,130–133] So far, methods for *exo*-selective benzylic C–H functionalization have been applied in the late-stage functionalization of complex molecules with cyclic skeletons.[60,73,132–134]

For example, the H/D exchange of (indane)$Cr(CO)_3$ (**3a**) under basic conditions with DMSO-d_6 yielded exclusively the *exo*-selective product **3aa** without geminal-dideuterated product, suggesting a dominant *anti*-deprotonation/*anti*-reprotonation (Scheme 7a).[130] In contrast, an electron-withdrawing group, such as an ester, led to benzylic deprotonation regardless of the stereochemistry of the α-C–H bonds. Reaction with electrophiles provided the *exo*-product **3ba**.[135] Moreover, the benzylic deprotonation of a (trimethylsilyl)dihydroisobenzofuran complex **3c** with ^{t}BuLi as the



Scheme 7 Stereoselective functionalization of *exo*-cyclic substrates: (a) *exo*-selective reactions and (b) *endo*-selective transformations.

base showed *syn*-deprotonation. This may be due to steric blocking of the benzylic *anti*-C–H by the bulky SiMe$_3$ group and the α-silyl effect.[136] Reaction of deprotonated **3c′** with an array of alkyl halides afforded *exo*-alkylated products **3ca**. Subsequent desilylation of product **3ca** with tetrabutyl ammonium fluoride (TBAF) most likely generated a benzylic anion that is delocalized into the arene-Cr system and is protonated from the *exo*-face to produced **3cb** as pure *endo*-diastereomers. The regioselectivity of deprotonation of tetrahydroisoquinoline **3d** was proposed to proceed through a chelated 6-membered cyclic transition state.[62,137] Here again, electrophiles reacted on the *exo*-face of the ring system, including (η^6-C$_6$H$_5$–F)Cr(CO)$_3$ in an S$_N$Ar reaction.

Some examples of *endo*-selectivity have also been demonstrated (Scheme 7b). For example, the *endo*-alkylation reactions of (η^6-arene)chromium complexes **3f** with the bulky N^{n}Pr$_2$ group were reported. The selectivity was controlled by the amino substituent rather than the Cr(CO)$_3$ moity.[138] Moreover, an inner sphere mechanism was proposed to rationalize the *endo*-selectivity observed in the reactions of (η^6-indene)Cr(CO)$_3$ (**3g**) with electrophiles.[139,140] Benzylic deprotonation is followed by η^6- to η^5-tautomerization to form the thermodynamically stable (η^5-indenyl)Cr complex. The electrophile is then attacked by the Cr center, forming an intermediate with a Cr–R bond (**3g′**). Migration of the R group to the indenyl carbon and Cr back to the arene explains the *endo*-selective functionalization. Similar reactivity was observed with (η^6-fluorene)Cr(CO)$_3$, which also gives *endo*-alkylation products.[139,140]

2.2.2. Stereoselective functionalization of acyclic substrates.

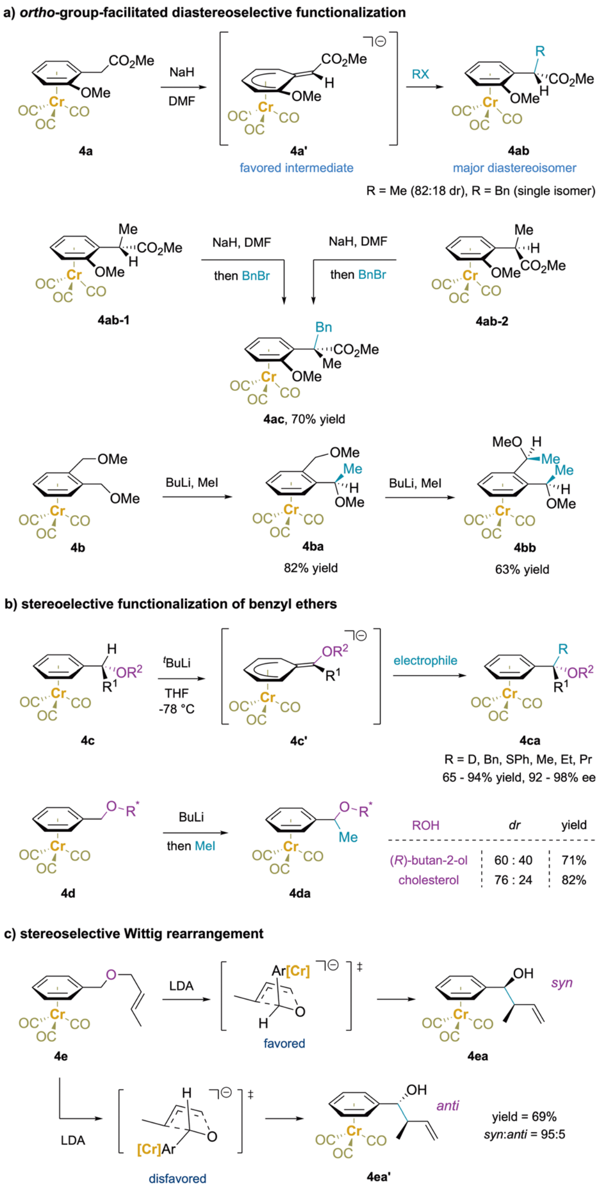
Compared to the cyclic substrates outlined above, less stereoselective benzylic functionalization reactions of acyclic complexes were reported, possibly due to free rotation about the C(aryl)–C bond of the bound arene. One strategy to differentiate between the two prochiral faces of a benzylic anion relies on the presence of an *ortho*-substituent (Scheme 8a). For example, deprotonation of the 2-(2-methoxyphenyl)acetate complex **4a** with NaH was proposed to form a more stable anion **4a′**, with the carbonyl group *anti* to the proximal methoxy group. Electrophiles would then approach intermediate **4a′** from the opposite site of the Cr(CO)$_3$ unit to yield benzylic alkylation products in good to high diastereoselectivities.[135] This method was also applied to the alkylation of complexes **4ab** bearing a tertiary benzylic C–H bond. Interestingly, upon deprotonation of diastereomers **4ab-1** and **4ab-2**, the resulting carbanions were converted to a single diastereoisomer (**4ac**) with the electrophile benzyl bromide. Moreover, a stepwise procedure for double methylation of a bis(methoxymethyl)benzene complex (**4b**) produced the *meso* product **4bb**, as would be anticipated by generation of the least sterically hindered benzylic deprotonation intermediates.[41,59,62–73]

In addition to *ortho* substitution strategies outlined above, benzylic functionalization reactions of enantioenriched Cr(CO)$_3$-complexed benzyl ethers have been shown to undergo stereospecific deprotonation. The resulting deprotonated intermediate (**4c′**) from complex **4c** is planar chiral and reacts with electrophiles at the face opposite to Cr and provides enantioenriched product **4ca** (Scheme 8b).[74,141] A different strategy using enantioenriched ethers **4d** (derived from Ar–CH$_2$OR*) with the chirality located distal to the benzylic protons was employed with the goal of stereoselective benzylic methylations. Unfortunately, the methylations exhibited low levels of diastereoselectivity, likely because the chirality was located too far from the benzylic site.[142–145]

Additionally, reaction of (benzyl (*E*)-crotyl ether)Cr(CO)$_3$ (**4e**) with LDA afforded a diastereomeric mixture of [2,3]-Wittig products in a ratio of 95 : 5.[146] An envelope transition state was proposed for this anionic rearrangement in which the aryl motif lies in the pseudo-axial position to avoid the strong *gauche* interaction of the bulky (arene)Cr moiety. This leads to formation of the *syn*-product **4ea** with high diastereoselectivity. In contrast, the corresponding *Z* isomer of **4e** gave a 1 : 1 mixture of diastereomers.

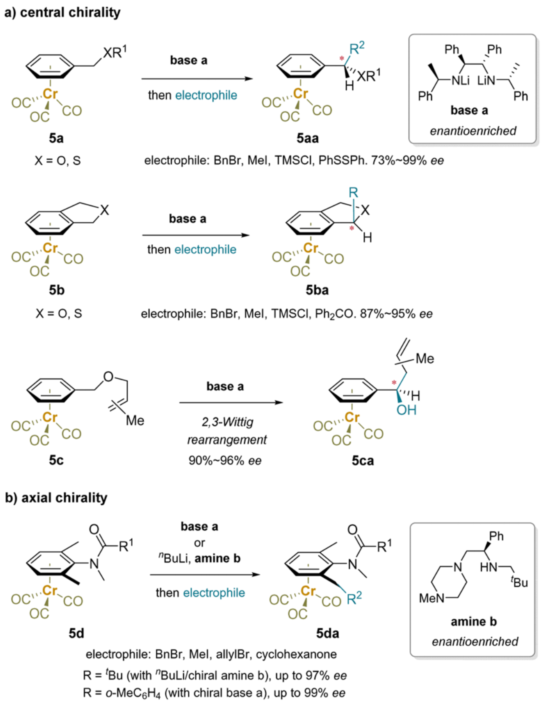
2.2.3. Enantioenriched-base-mediated enantioselective functionalization reactions.

Deprotonation with an enantioenriched



Scheme 8 Stereoselective functionalization of acyclic substrates: (a) *ortho*-substituent-facilitated diastereoselective funtionalization, (b) stereoselective functionalization of benzyl ethers, and (c) stereoselective Wittig rearrangement.

base is an effective strategy for achieving enantioselective C–H functionalization reactions of $Cr(CO)_3$-complexed benzyl ether derivatives with prochiral C–H's. In Scheme 9a, the use of a enantioenriched C_2-symmetric lithium amide base enabled the enantioselective substitution reactions.[147] The enantioselectivity determining step in the case of acyclic systems (**5a**) is likely the deprotonation to give a planar-chiral intermediate that has a substantial barrier to racemization. Both acyclic (**5a**) and cyclic (**5b**) compounds were deprotonated enantioselectively and functionalized with a variety of electrophiles to produce the corresponding products in good to high enantioselectivities.[142–145,148] Additionally, [2,3]-Wittig rearrangement reactions of allyl benzyl ethers were carried out using the same chiral base, resulting in the formation of enantioenriched benzyl alcohols (**5ca**).[149]



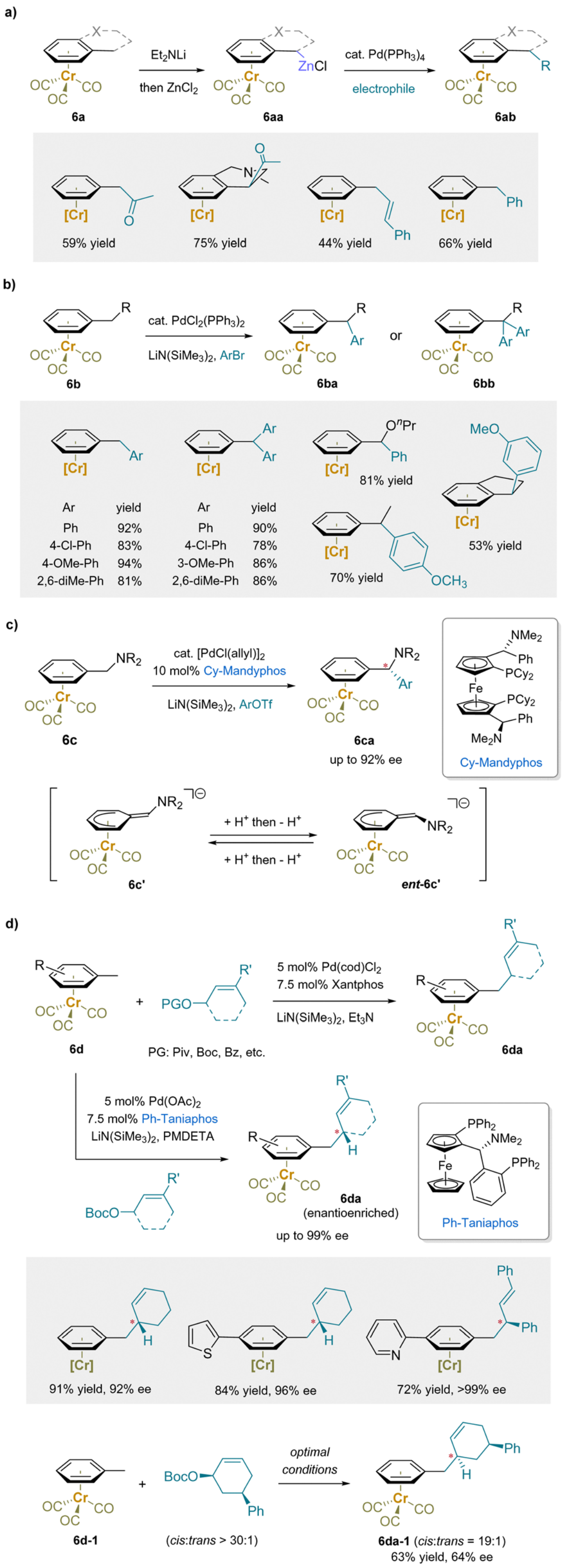
Scheme 9 Enantioselective functionalization enabled by enantioenriched bases: (a) central chirality and (b) axial chirality.

In Scheme 9b, a class of *N*-methylanilides containing axial and planar chirality were synthesized through desymmetrization of prochiral chromium tricarbonyl complexes using an enantioenriched base.[150,151] The steric hindrance of the *N*-methyl amide and flanking methyl groups in **5d** block rotation about the C–N bond and the benzylic methyl groups are prochiral. A chiral lithium amide discriminates the enantiotopic benzylmethyl groups of the $Cr(CO)_3$-complexed anilide for the asymmetric deprotonation.

2.3. Palladium-catalyzed cross-coupling

Palladium-catalyzed cross-coupling is a versatile method for forming C–C bonds using various carbon-based nucleophiles, such as preformed organometallic compounds.[152–159] In early studies, benzylic zinc derivatives (**6aa**) prepared from (alkylbenzene)$Cr(CO)_3$ (**6a**) were found to be suitable coupling partners for acetylation with acetyl chloride (Scheme 10a).[61] Arylation and vinylation were also achieved by varying the electrophiles to the corresponding halides using the same palladium catalyst, $Pd(PPh_3)_4$.

Instead of preparing the main group organometallic nucleophiles beforehand, soft carbanions can be readily generated by deprotonation of pro-nucleophiles, including ketones and β-keto-esters, and used as nucleophiles in palladium-catalyzed cross-coupling reactions.[160–176] In particular, an array of palladium-catalyzed C–C bond formation reactions of $Cr(CO)_3$-complexed toluene derivatives with $LiN(SiMe_3)_2$ as the base has been reported. Arylation reactions with aryl bromides provided either diarylmethane or triarylmethane products in good yields depending on the ratio between (arene)chromium complexes (**6b**) and aryl



Scheme 10 Pd-catalyzed cross-coupling and allylic substitution reactions: (a) Negishi reactions, (b) arylation reactions, (c) asymmetric arylation reactions, and (d) Tsuji–Trost reactions.

bromides (Scheme 10b).[177] Excellent *exo*-selectivity was observed in the reactions of the indane and tetrahydronaphthalene complexes. Notably, an asymmetric version of the above arylation was developed with an enantioenriched Cy-Mandyphos ligand, providing the diarylmethylamines (**6ca**) in high enantioselectivity.[178] This reaction is particularly challenging, because the intermediate anionic [(Ar–CHNR$_2$)Cr]$^-$ based intermediate is planar chiral and must be racemized under the reaction conditions by reversible protonation/deprotonation(Scheme 10c).

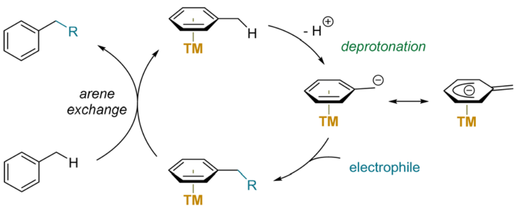
In addition to arylation, palladium-catalyzed Tsuji–Trost allylation reactions of (toluene)Cr(CO)$_3$ complexes (**6d**) with allyl carbonates or pivalates were reported (Scheme 10d).[179] Asymmetric allylation reactions with the enantioenriched ligand Ph-Taniaphos yielded allylic benzylation products (**6da**) in high enantioselectivities. Moreover, the stereoretentive substitution of a *cis*-disubstituted cyclohexene was obtained under the above reaction conditions (Scheme 10d), suggesting that the π-coordination with Li$^+$ stabilized the benzylic anion, which served as a ''soft'' nucleophile and attacked the π-allyl palladium complex through an *anti*-addition mechanism (net double inversion) to give **6da-1**.

2.4. Catalysis *via* π-coordination activation

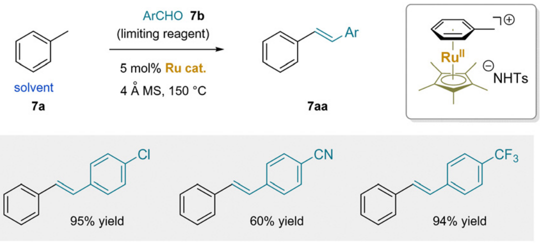
Despite the successful π-coordination activation in benzylic functionalization of preformed η^6-arene complexes, the utility of these reactions is limited by using stoichiometric amounts of transition-metals and ligands. To overcome this significant limitation, researchers are interested in developing methods using catalytic amount of arenophilic transition-metal complexes. This approach promises high atom economy by reducing the amount of transition-metals and ligands from stoichiometric to catalytic levels. Moreover, it would avoid the need for additional steps to prepare arene complexes and remove products from the metal centers. Scheme 11 outlines a general catalytic cycle, including an arene exchange step, following the benzylic functionalization step.

The realization of a catalytic cycle, however, faces a major hurdle due to the strong (η^6-arene)-transition-metal arene interactions that disfavors arene exchange. Additionally, the substrate may contain other weakly acidic protons that might be activated by stoichiometric amounts of strong base. Strong bases can react undesirably with electrophiles and may also decompose arene complexes or coordinatively unsaturated metal species, which are intermediates in arene exchange processes. To date, only a limited number of successful catalytic arene-activation reactions have been documented.

In 2016, a ruthenium-catalyzed dehydrative condensation between toluene and aldehydes was developed (Scheme 12).[180]



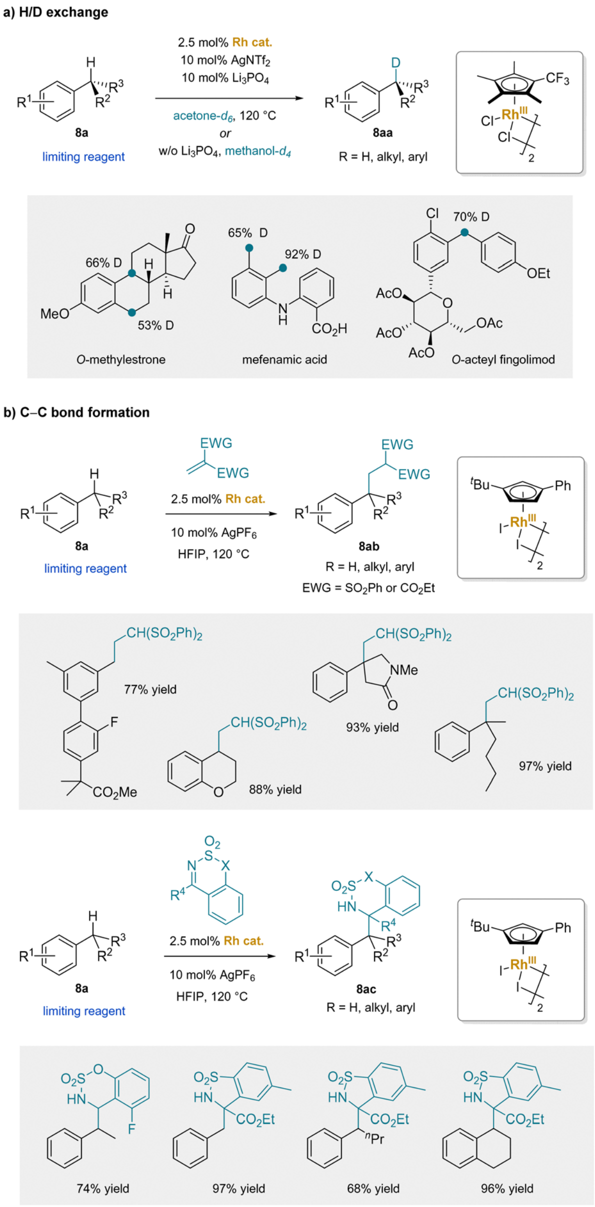
Scheme 11 Idealized catalytic cycle for benzylic C–H functionalization *via* π-coordination activation.



Scheme 12 Ru-catalyzed condensation of toluene with aldehydes.

The reactions employed solvent quantities of toluene or xylene as the pro-nucleophile with $[Cp^*Ru]^+$ as catalyst, yielding either stilbenes or distyrylbenzenes. The narrow scope of this method, limited to primary C–H bonds, may be attributed to the inefficient activation by the Ru(II) catalyst. Nonetheless, this work represents a significant advance, demonstrating proof-of-concept of Scheme 11.

In comparison to Ru(II) species, Rh(III) analogues exhibit stronger electron-withdrawing effects, increasing the acidity of the benzylic C–H's of the corresponding η^6-arene complexes. This advantage of Rh(III) catalysts has been successfully applied to develop catalytic nucleophilic aromatic substitution of non-electrophilic aryl halides and phenols.[51] In 2022, rhodium-catalyzed (5 mol% Rh) benzylic H/D exchange reactions with a wide range of alkylarenes (**8a**) were reported. Of note, these reactions featured primary, secondary, or tertiary C–H bonds (Scheme 13a).[181] In the presence of the dicationic $[CpRh]^{2+}$ catalyst with a catalytic amount of the weak base Li_3PO_4 in acetone-d_6, or without any base in methanol-d_4, deuterium exchange occurred exclusively at the benzylic positions. The mild reaction conditions allowed for tolerance of a diverse range of functional groups and enabled late-stage labeling of pharmaceuticals and their analogues. Shortly afterwards, this approach was extended to the addition of benzylic C–H bonds across electrophilic Michael acceptors (Scheme 13b).[182] Notably, the rhodium-catalyzed addition reactions could overcome the steric hindrance of alkylarenes bearing a tertiary C–H bond, allowing for the construction of all-carbon quaternary centers. Beside Michael additions, 1,2-addition reactions of alkylbenzenes were also established under the conditions with electrophilic imines.[183] The keys to these arene-activating transition-metal catalysts are facile exchange of arene pro-nucleophiles and acidification of the benzylic protons. The use of catalytic arene activation is an area of research that leaves much room for future development. In the next sections, main group metals are examined, which are known to rapidly swap arenes, potentially providing an alternative avenue for benzylic C–H functionalization.



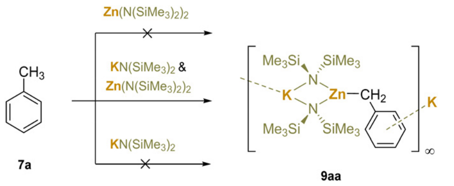
Scheme 13 Rh-catalyzed benzylic C–H bond functionalization: (a) H/D exchange, and (b) C–C bond formation.

3. Alkali-metal-facilitated deprotonation through cation–π-interactions

3.1. Cation–π interaction

Cation–π interactions are a type of noncovalent interaction between a cation and a π system, most commonly an aromatic ring. The electron-rich π system forms relatively strong electrostatic[184] and induction[185] (polarization) interactions (up to 20 kcal mol^{-1}) with the positively charged cation. Cation–π interactions are different from the covalent interaction between a transition-metal and an arene π system, where the π system exhibits orbital overlap with the transition-metal orbitals and the interaction can be considerably stronger. Cation–π interactions can form between organic cations, like ammonium salts, with arene π-systems. Such interactions are an important component of organocatalysis and were recently reviewed.[186] Here, the focus is on main group cations that can increase the acidity of benzylic C–H bonds by formation of cation–π interactions.

In 2003, it was discovered that neither $Zn(N(SiMe_3)_2)_2$ nor $KN(SiMe_3)_2$ could unilaterally metalate toluene. However, when



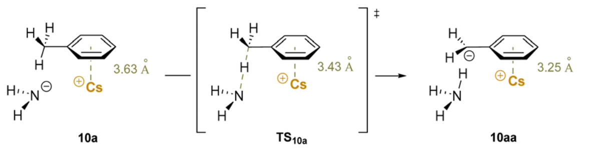
Scheme 14 Synergic deprotonation using $KN(SiMe_3)_2$ and $Zn(N(SiMe_3)_2)_2$.

$KN(SiMe_3)_2$ and $Zn(N(SiMe_3)_2)_2$ (1 : 1) were added to toluene and stirred for 15 min, toluene was smoothly deprotonated at the benzylic site, generating benzylic metalation products $\{KZn(N(SiMe_3)_2)_2(CH_2Ph)\}_\infty$ (**9aa**) (Scheme 14).[187] The structure of the product was determined by X-ray crystallography and contains cation–π interactions. The authors did not mention the possibility of cation–π interactions to acidify the benzylic hydrogens in this pioneering study with silylamide bases. The study confirms that the deprotonative metalation requires both bases and presumably cooperativity between them. Interestingly, the deprotonation failed when $Zn(N(SiMe_3)_2)_2$ was replaced by $Mg(N(SiMe_3)_2)_2$, which is presumably more basic due to the greater polarization of the Mg–N bonds over the Zn–N bonds in $M(N(SiMe_3)_2)_2$. Subsequently, the authors demonstrated that toluene derivatives, such as *m*-xylene and mesitylene could be deprotonated.

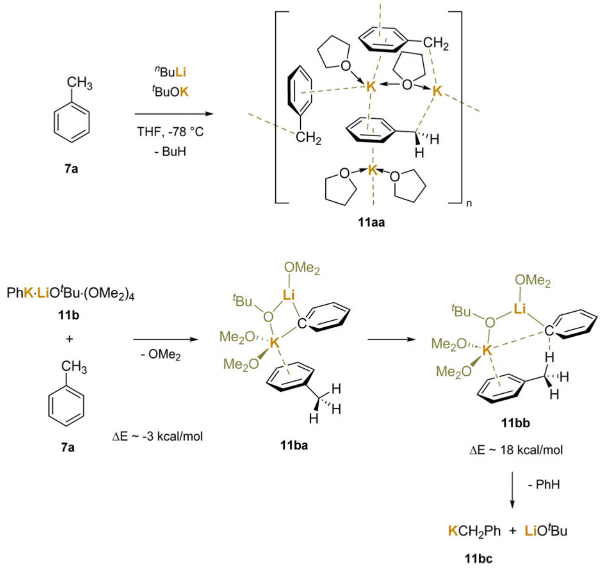
An early computational study[188] elucidated details of the role of cation–π interactions in the deprotonation of benzylic C–H bonds by alkali metal amides (M–NHR, R = H, Cy). The calculations indicate that the metal-ring centroid distance decreases from a cation–π interaction moving toward the transition state for deprotonation and finally the deprotonated product (Scheme 15). This observation shows the polarization of electron density in the π system as the cation–π interaction assists in the C–H bond cleavage process. Hammett studies show that the bond cleavage is also facilitated by EWGs in both *para*- or *meta*-positions on the arene, and that resonance and inductive effects have similar influence on the barriers. It was found that Cs^+ results in the largest decrease in the barrier to benzylic deprotonation relative to the smaller alkali metals. This is due to the greater basicity of nitrogen in the $Cs–NH_2$ bond arising from the higher electropositivity of Cs^+ and lower electron–electron repulsion. Overall, this important computational study documents the role that alkali metal cation–π interactions can play in benzylic deprotonations. It is also noteworthy that larger group(I) metal centers have a greater ability to interact with the π-system of the benzyl anion, as shown in both crystallographic and early computational studies.[22,189] The implications of these studies for development of synthetic methods are highlighted below.

Another study[22] arrived at similar conclusions in a more focused experimental system that employed Schlosser's base[190] and related species in the deprotonation of toluene. The researchers reacted Schlosser's base (^{n}BuLi/^{t}BuOK) with toluene at −78 °C in THF, which is known to give the orange benzylic metalation product. Concentration and crystallization led to isolation of $[(PhCH_2K)_3(THF)_4]$ (**11aa**), which contains potassium coordinated to the benzylic anion in a variety of ways, including η^6-coordination (Scheme 16). The authors also demonstrated that Schlosser's base would deprotonate benzene and isolated a Li/K bimetallic complex $[(PhK)_4(PhLi)(^tBuO\text{-}Li)(THF)_6(C_6H_6)_2]$ containing several phenyl anions and a *tert*-butoxide bonded to either Li or K. Using a truncated model for computational purposes $[(PhK)(LiO^tBu)(OMe_2)_4]$ (**11b**), they explored the deprotonation of toluene with a phenyl bridged bimetallic. The authors calculated that the exchange of a dimethyl ether on K^+ for a free toluene was downhill by about 3 kcal mol^{-1}. An interaction between K^+ and toluene was shown to reduce the barrier to the deprotonation to about 18 kcal mol^{-1}. Computational and experimental evidence suggest that the softer potassium cation is preferred over the hard lithium cation in the interaction with the delocalized π system. A four-membered ring Li–C–K–O is formed in the bimetallic cluster as the π system is added to the base system of ^{n}BuLi and ^{t}BuOK.

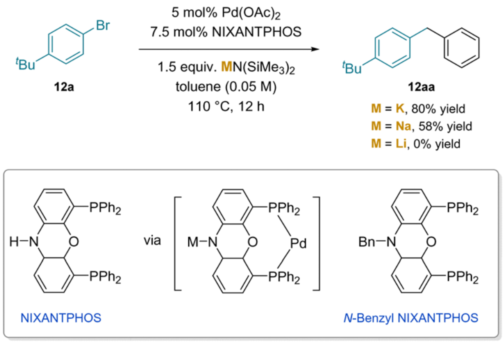
The importance of cation–π interactions in the cleavage of benzylic C–H bonds in the palladium catalyzed arylation of toluenes was shown both computationally and experimentally (Scheme 17).[191] This study is significant for several reasons. The first is that the reaction was performed with $KN(SiMe_3)_2$, which is a considerably weaker base than Cs–NHR or Schlosser's base.[190] Second, the reaction stops at the mono-arylation product (**12aa**), despite the enormous increase in acidity of



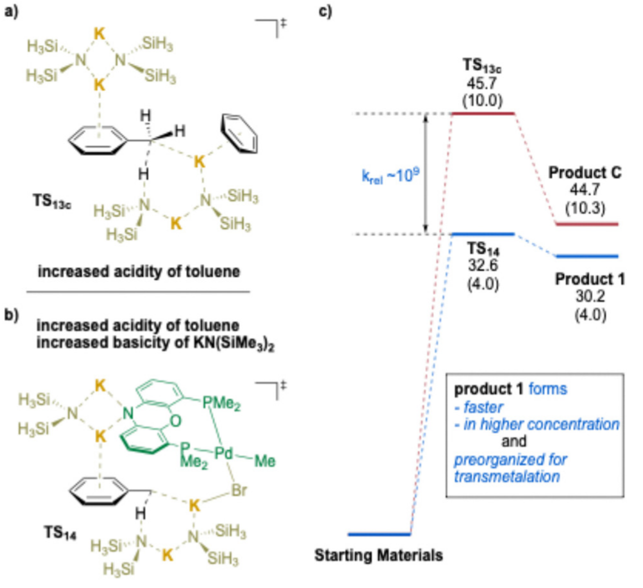
Scheme 15 Calculated deprotonation of toluene. Cation π-interaction between $Cs–NH_2$ and toluene (**10a**), transition state (**TS10a**) for deprotonation and deprotonated product (**10aa**).



Scheme 16 Calculated transition state for deprotonation of toluene with a model Schlosser base system *via* K^+–π–toluene interactions.



Scheme 17 Arylation of toluene catalyzed by a (NIXANTPHOS)Pd catalyst.

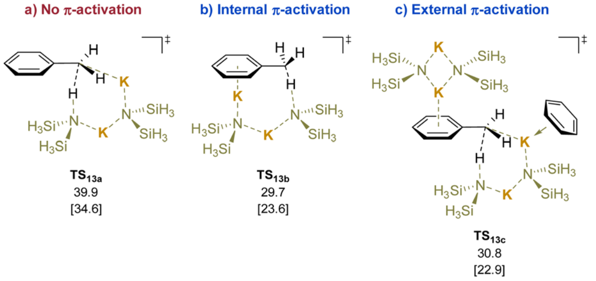


Scheme 19 Calculated relative Gibbs free energies [and enthalpies] for the deprotonation of toluene (kcal mol^{-1}) for (a). **TS$_{13c}$**, (b). (NIXANTPHOS)Pd complex (**TS$_{14}$**), and (c). relative rates.

diphenylmethane compared to toluene (32 *vs.* ∼43 in DMSO).[11] The reaction employed van Leeuwen's NIXANTPHOS ligand[192] which has a relatively acidic N–H ($pK_a \approx 22$)[11] that is deprotonated under the reaction conditions.[21] The reaction was found to have a significant dependency on the main group cation of the base (M = K, 80%; Na, 58% and Li, 0%). Experimental evidence for the involvement of the deprotonated ligand was gained using Xantphos and *N*-benzyl NIXANTPHOS. Both ligands lack sites that are easily deprotonated, and both gave no products.

Calculations were performed using di-potassium systems, because $KN(SiMe_3)_2$ is predominantly oligomeric in low polarity solvents.[193] The calculated transition states for deprotonation reveal that the coordination of the potassium cation to the π systems lowers the activation energy of the deprotonation (Scheme 18, **TS$_{13a}$** *vs.* **TS$_{13b}$**). External activation had little impact on the energies (**TS$_{13c}$**). Experimental support for the calculated TS in Scheme 18 was found in the reaction of toluene with $KN(SiMe_3)_2$ in the presence of trapping agent $ArCH_2Br$ at 110 °C. The reaction gave an unoptimized yield of 20% of the corresponding bibenzyl ($PhCH_2CH_2Ar$).

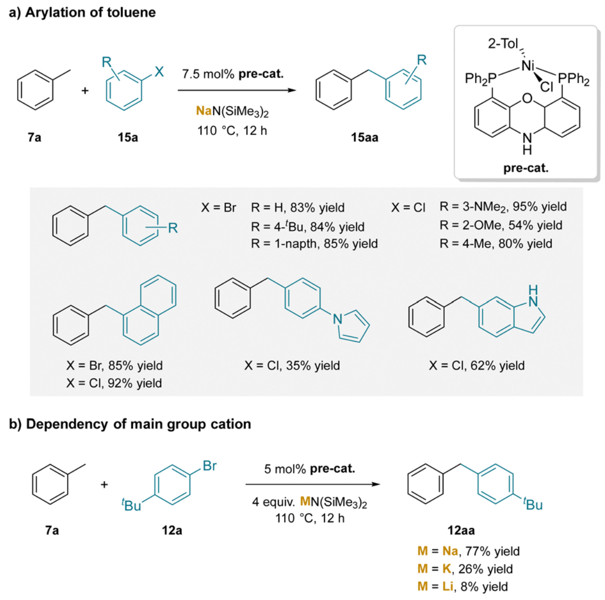
Next, the deprotonation of toluene was calculated using the (NIXANTPHOS)Pd(II) system for comparison with the **TS$_{13c}$** from Scheme 18c. A surprising K···Br–Pd interaction was found to assist the deprotonation transition state structure (Scheme 19b). Interestingly, and in support of the proposed K···Br interaction, the use of aryl chlorides in the (NIXANTPHOS)Pd-catalyzed arylation of toluenes was unsuccessful, despite the known ability of this catalyst system to activate aryl chlorides at room temperature.[194] The results of the comparison between **TS$_{14}$** and **TS$_{13c}$** are illustrated in Scheme 19a *vs.* b and suggest that, although both deprotonations are endothermic, K_{eq} for **TS$_{14}$** is $\sim 10^9$ times greater than for **TS$_{13c}$**. Taken together, deprotonation *via* **TS$_{14}$** is faster, providing a higher concentration of the benzyl organometallic, and the anion is held in the proximity of the Pd(II) and primed for transmetalation. Overall, this study provides experimental and computational support for the importance of cation–π interactions as a key activation mode to increase the acidity of benzylic C–H bonds. As outlined subsequently, this observation has been incorporated into a variety of synthetic methods with transition-metals and under transition-metal-free conditions.



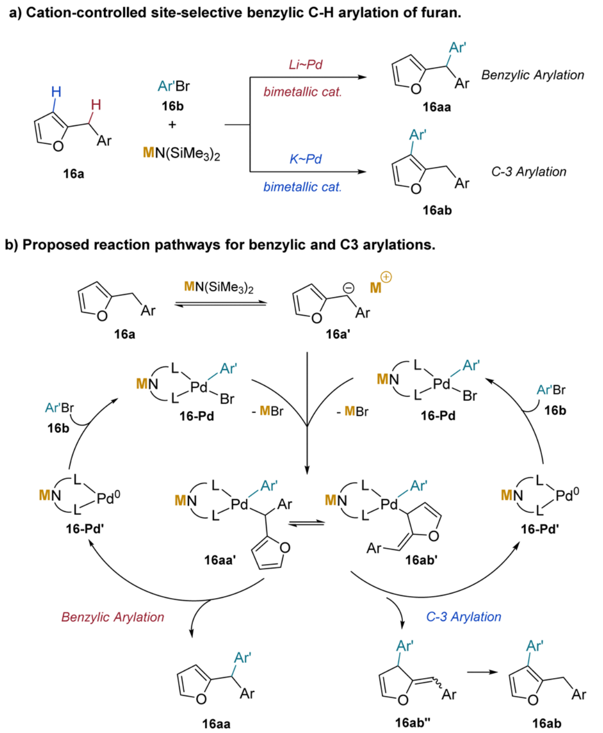
Scheme 18 Calculated relative Gibbs free energies [and enthalpies] for the deprotonation of toluene (kcal mol^{-1}): (a) no π-activation, (b) internal π-activation, and (c) external π-activation.

In a related investigation, a nickel catalyzed toluene arylation with aryl chlorides and bromides was studied.[195] Like the palladium system above, this work used the NIXANTPHOS ligand and silyl amide bases (Scheme 20a). The more electropositive nickel center facilitates the oxidative addition step[196] compared to palladium, so that both aryl bromides and chlorides were applicable in this system. Like the Pd catalyzed reaction above, this reaction also had a dependency on the main group cation of the silyl amide base (Scheme 20b). However, unlike the palladium system, which worked best with $KN(SiMe_3)_2$ (Scheme 17), the nickel catalyst gave the best results with $NaN(SiMe_3)_2$ (77% compared to $KN(SiMe_3)_2$ with 26% and $LiN(SiMe_3)_2$ with 8%).

The yields of coupling products with aryl chlorides and bromides with toluenes were similar (Scheme 20a). A comparison using Xantphos and *N*-benzyl NIXANTPHOS as in Scheme 17, resulted in only 15% yield with *N*-benzyl NIXANTPHOS and 0% with Xantphos, consistent with the need for the deprotonated ligand backbone (bearing the main group metal) to activate the



Scheme 20 Arylation of toluene catalyzed by a (NIXANTPHOS)Ni-based catalyst: (a) arylation of toluene, and (b) dependency on the main group cation.



Scheme 21 Cation-controlled site-selective C3 and benzylic C-H arylation: (a) cation-controlled site-selective benzylic C–H arylation of furan, and (b) proposed reaction manifolds and intermediates for the benzylic and C3 arylations.

toluene derivative *via* cation–π interactions. Further circumstantial evidence for this hypothesis was gained by conducting the reaction under the optimized conditions, but in the presence of 4 equiv. of 15-crown-5. The crown ether inhibited conversion to 7%, likely through coordination to Na^+, blocking the cation–π interaction. While no computational work was done on the nickel system, a similar transition state for the deprotonation to the palladium system in Scheme 19 was assumed.

The selective C–H bond functionalization is challenging, because molecules often have a variety of C–H bonds with similar reactivity. To favor C–H functionalization of specific bonds, chemists often use directing groups to steer reactivity. Directing groups need to be added and removed after the functionalization step. It was found that site-selective arylation at the sp^2 *vs.* sp^3 C–H bonds of 2-benzylfurans could be controlled by cation–π interactions.[197] This research also used the NIXANTPHOS ligand and silyl amide bases to deprotonate the weakly acidic benzylic C–H bonds of 2-benzyl furan (pK_a = 30.2 in DMSO[11]). The selectivity between formation of the benzylic (**16aa**) or C-3 arylation product (**16ab**) is controlled by the main group counterion of the base (Scheme 21a), as detailed below.

The authors found that the main group cation of the silyl amide base $MN(SiMe_3)_2$ is crucial for the selectivity of the reaction between benzylic and C-3 arylation. With (NIXANTPHOS)Pd catalyst and $KN(SiMe_3)_2$, the C-3 arylation product (**16ab**) was generated exclusively. Under nearly identical conditions, but using $LiN(SiMe_3)_2$ with the addition of 12-crown-4, the benzylic arylation product (**15a**) was obtained.

Calculations were performed on the energy states of complex **16aa′** and **16ab′** from Scheme 21b, but without inclusion of the cation on the deprotonated NIXANTPHOS. The energy of $Pd–C_{Bn}$ in complex **16aa′** is 5 kcal mol^{-1} lower than Pd–C-3 (**16ab′**), indicating the preference of forming the benzyl adduct and eventually the benzylic arylation product. Performing the calculations in the presence of the K^+(dioxane), however, resulted in a K^+–π interaction (Fig. 1) that shifts the equilibrium to the C-3 bound intermediate. It was proposed that this shift in the equilibrium toward C-3 guides the reductive elimination to provide the C-3 arylation product (**16ab**). More polarizable K^+ is known to favor cation–π interactions compared to the smaller, harder Na^+ and Li^+ cations in solution.[198,199] However, by adding 18-crown-6, the potassium center's coordination sites were blocked from forming cation–π interactions and the selectivity switched to favor the benzylic arylation (**16aa**).

It was noted that steric and electronic properties of aryl bromide substrates did not influence the site-selectivity, but electronic properties of the furan substrates could impact the cation–π interactions. Indeed, use of (2-fural)–CH_2(3,5-C_6H_3-$(CF_3)_2$) resulted in a shift back towards benzylic arylation, presumably partly due to the diminished strength of the cation–π interaction with the electron-poor aryl ring. This study provides experimental and computational support for the significance of cation–π interactions in controlling regioselectivity of 2-benzylfurans in bimetallic catalytic systems.

3.2. Cation–π complexes in the absence of transition-metals

The examples of benzylic functionalization through deprotonation above were conducted in the presence of transition-metals,

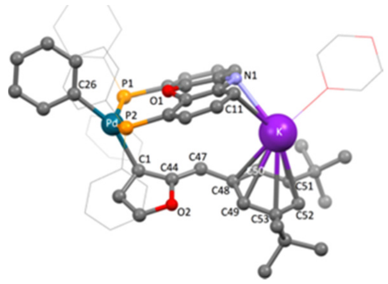
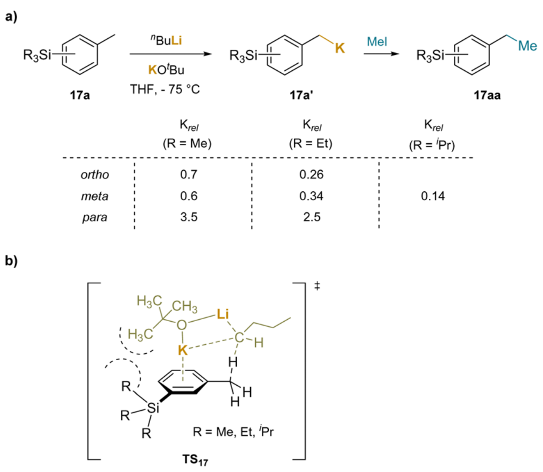


Fig. 1 DFT geometry optimized structure with the bulky 3,5-di-*tert*-Bu phenyl ring.

which are well known to activate arenes. Although the transition-metals are not believed to be involved, it was viewed as prudent to explore benzylic functionalization without added transition metals, which will be discussed below. Of course, the use of strong bases to deprotonate benzylic C–H's and form benzyl organometallic species has been known for many decades.

In an example, the superbasic mixed-metal "LIC-KOR" reagent (KO^{t}Bu + ^{n}BuLi) was used to metalate trialkylsilyl substituted toluenes (**17**). The authors compared the relative rates of metalation to the reaction of the parent toluene (Scheme 22a).[200] It was found that the *para*-substituted trialkylsilyl groups enhanced the rate, while the *ortho* and *meta* groups exhibited rate retardation. To explain this observation, the authors proposed a cation–π interaction between the aromatic ring and the potassium in the transition state (**TS$_{16}$**), as depicted in Scheme 22b. Given the distance between the benzylic methyl group undergoing deprotonation and the *meta*-SiR$_3$ substituent, it was hypothesized that the decrease in rate was due to partial obstruction of the K$^+$–cation–π interaction resulting from buttressing with the SiR$_3$ substituent. In contrast, using ^{n}BuLi with the ligand *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA), which is coordinatively saturated and unable to form cation–π interactions, deprotonation reactions with the *meta*-trialkylsilyl toluenes were faster than with toluene itself. This system used superbasic mixed-metal "LIC-KOR". Subsequent discussion will center on weaker bases where cation–π interactions can play a larger role.

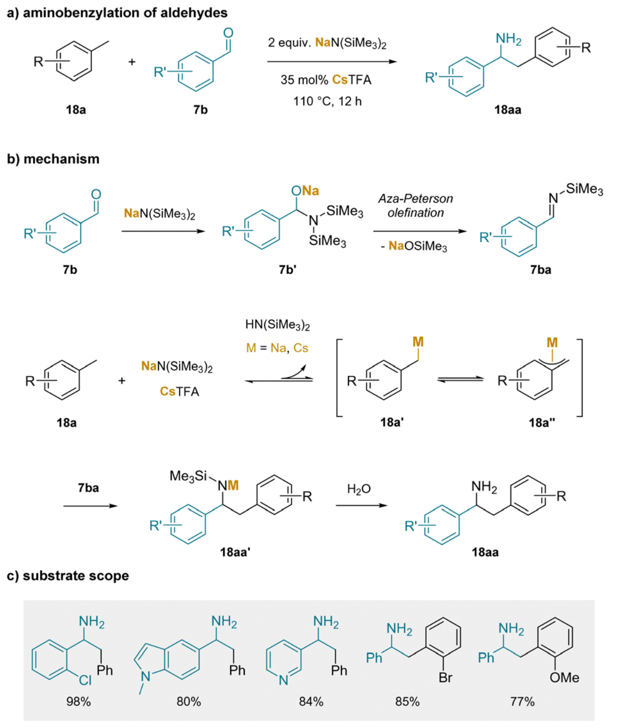


	K_{rel} (R = Me)	K_{rel} (R = Et)	K_{rel} (R = ^{i}Pr)
ortho	0.7	0.26	
meta	0.6	0.34	0.14
para	3.5	2.5	

Scheme 22 Metalation of trialkylsilyl substituted toluenes with "LIC-KOR" reagent: (a) relative metalation rates of trialkylsilyl substituted toluenes, and (b) proposed transtition state.

The idea that weaker bases that benefit from cation–π interactions could be employed to reversibly deprotonate toluene derivatives was not put into practice until more recently (although computational support for the role of cation–π interactions on the deprotonation of heteroaromatic C(sp^2)–H bonds had been reported[201]). In this regard, an early study that proposed the importance of cation–π interactions in the functionalization of toluenes involved the aminobenzylation of aldehydes (Scheme 23). In the first step, the non-enolizable aldehyde reacts with the silyl amide base *via* carbonyl addition to give **7b′**. The resulting adduct undergoes an aza-Peterson olefination-type process to form the *N*-TMS imines (**7ba**).[202] In the presence of toluene solvent, reversible deprotonation of the benzylic C–H bond by the silyl amide base gives the benzylic organometallic **18a′** which could be envisioned to have different hapticities (**18a″**).[189] The benzylic organometallic **18a′** could then undergo reaction with the *N*-TMS imine (**7ba**) to generate **18aa′**, which upon workup affords the aminobenzylation product (**18aa**).

It is noteworthy that of the MN(SiMe$_3$)$_2$ (M = Li, Na, K) bases, M = Li gave only the imine (no aminobenzylation) and M = Na gave the best results, albeit less than 50% yield of the amine (despite extensive optimization). The K$^+$ salt, which would form the stronger cation–π interactions in solution, gave inferior results, possibly due to difficulty forming the imine. Of significance, it was found that addition of 35 mol% Cs(O$_2$CCF$_3$)



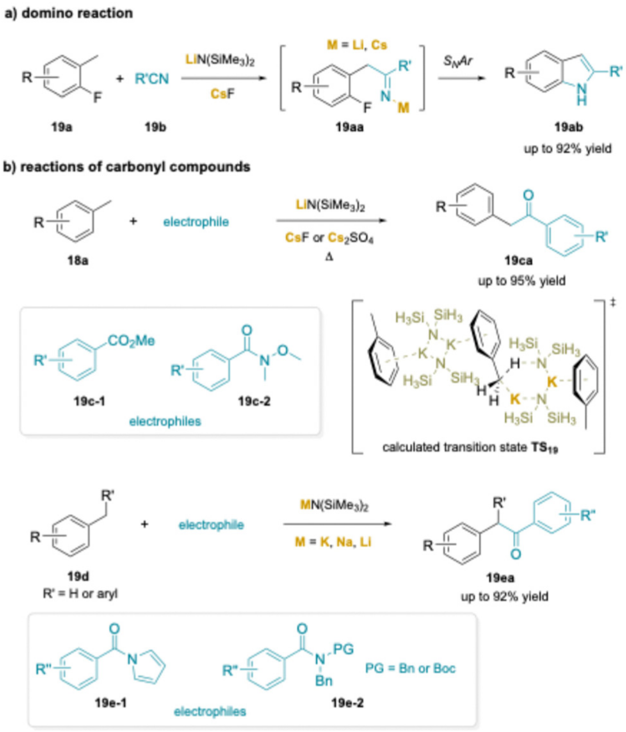
Scheme 23 Aminobenzylation of aldehydes: (a) aminobenzylation of aldehydes, (b) proposed mechanism, and (c) selected substrate scope.

resulted in the formation of the aminobenzylation products (**18aa**) in yields over 90%. In a related work, it was known that combining CsX (X = halide) with $NaN(SiMe_3)_2$ generated $CsN(SiMe_3)_2$,[203] which could be crystallized from toluene to isolate the silyl amide with a cation–π complex between Cs^+ and the toluene in the structure.

Overall, the scope of the aminobenzylation reaction was broad with respect to the starting aldehyde and the toluene derivatives, as shown in a few representative examples in Scheme 23c. It is noteworthy that the reaction could be conducted with 1.1 equiv. $NaN(SiMe_2)_2$ in the presence of 5 mol% Cs_2CO_3. Here, 1 equiv. $NaN(SiMe_2)_2$ was required to form the *N*-TMS imine (**7ba**) and the remaining 10 mol% catalyzed the aminobenzylation reaction.[204]

Two related strategies were developed based on cation–π interactions. In the first example, the synthesis of indoles (**19ab**) from 2-fluorotoluenes (**19a**) and benzonitrile derivatives (**19b**) was introduced (Scheme 24a). As with the aminobenzylation reaction, the indole synthesis provided much higher yields when a Cs^+ source was present.[205] Here, reversible deprotonation was followed by addition to the nitrile to give a metalated imine (**19aa**) that underwent S_NAr.

In the second line of work, toluene was reversibly deprotonated in the presence of methyl benzoate (**19-c1**) (Scheme 24b) or Weinreb amides (**19-c2**)[206] in the presence of $LiN(SiMe_3)_2$ and CsF or 2,5-dimethyl *N*-acyl pyrroles[207] (**19-e1**) in the presence of $KN(SiMe_3)_2$.[26] In a related study, alkyl sodium $NaCH_2SiMe_3$ with chelating PMDTA, or mixing $Zn(TMP)_2$ (TMP = 2,2,6,6-tetramethylpiperidinyl anion) with KO^tBu, significantly enhanced metalating power compared to their organolithium, which can promote the benzylic aroylation of toluene derivatives and addition to Weinreb amides under mild conditions. In all cases, addition of the benzylic organometallic to the carbonyl group forms the tetrahedral intermediate that breaks down to generate an aryl benzyl ketone (**19ca**, **19ea**). Rather than undergo a second addition of the benzyl organometallic, the ketone is rapidly deprotonated to afford the enolate. Upon workup, the enolate product is protonated to furnish the ketone.[208,209]

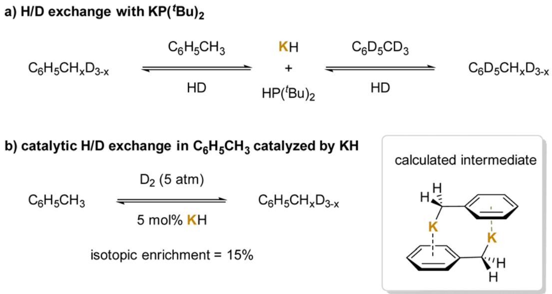


Scheme 24 Applications of cation–π interactions: (a) an indole synthesis from 2-fluorotoluene, and (b) aroylation of toluenes.

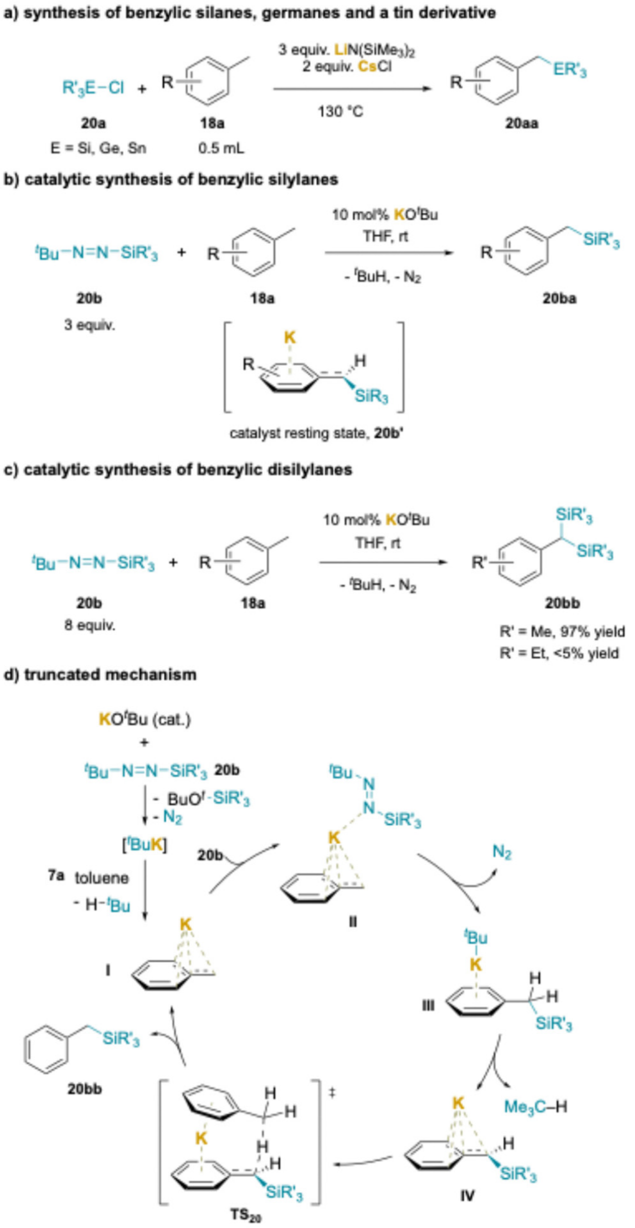
In a subsequent study, researchers found that toluene could be deprotonated in the presence of benzoate esters with $KN(SiMe_3)_2$.[210] Most importantly, they performed a detailed study of the deprotonation using DFT calculations. Due to the oligomeric nature of $MN(SiMe_3)_2$ complexes in non-polar solvents, the authors modeled the deprotonation with a dimer of $KN(SiMe_3)_2$ and modeled the $SiMe_3$ groups with SiH_3 substituents. The barrier to deprotonation was calculated to be 32.5 kcal mol^{-1}, which was found to be the rate determining step of the aroylation reaction. The transition state $\mathbf{TS_{19}}$ calculated by this team is shown in Scheme 24b.

Another application of cation–π interactions is the deuteration reaction. Since K^+ could participate in cation–π interactions that enhance the acidity of the methyl protons to deprotonate toluene,[211,212] phosphide anion $[P(^tBu)_2]^-$ generated from KH and phosphines was used to deprotonate toluene and afford $HP(^tBu)_2$ and KCH_2Ph.[213] The latter species can activate dihydrogen reversibly, promoting the hydrogen isotope exchange in the toluene methyl group *via* FLP (Frustrated Lewis pair) activation of H_2 (Scheme 25a). A similar reaction mechanism can be applied to KH-catalyzed H/D exchange reaction benefiting from cation–π interactions between K^+ and toluene (Scheme 25b). As with the phosphide, KCH_2Ph was computed to exist mainly as the dimeric structure $(KCH_2Ph)_2$, with the monomeric form being 1.8 kcal mol^{-1} higher in free energy.

Cation–π interactions have also been used in the silylation of alkyl arenes under stoichiometric[214] and catalytic conditions.[211,212] Using 3 equiv. $LiN(SiMe_3)_2$ with 2 equiv. CsCl additive for most substrates, a series of methyl arenes (0.5 mL) were converted to benzylic silanes in 53–90% yields (Scheme 26a). As noted earlier, the Cs^+ salt likely generates a $CsN(SiMe_3)_2$ species that forms cation–π interactions with the methyl arene during the deprotonation process. In the scope, a variety of silyl chlorides worked well,



Scheme 25 Deuteration of benzylic C–H bonds: (a) H/D exchange with $KP(^tBu)_2$, and (b) catalytic H/D exchange in $C_6H_5CH_3$ catalyzed by KH.



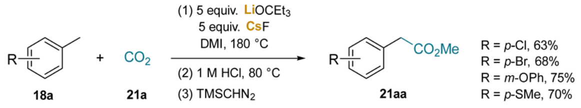
Scheme 26 Synthesis of benzylic silanes, germanes and tin derivatives: (a) reaction of R_3E-Cl with generated benzylic anions, (b) catalytic synthesis of benzylic silylanes, (c) catalytic synthesis of benzylic disilylanes and (d) truncated mechanism.

with the exception of Cl–$SiMe_3$, which may react directly with the silyl amide base. Importantly, the chemistry was further extended to chlorogermanes to produced benzylgermanes in 60–90% yields. Even chlorotributyl tin reacted under the standard conditions to afford $PhCH_2$–Sn(^{n}Bu)$_3$ in 80%.

Shortly after publication of the method in Scheme 26a, a related transformation was introduced.[215] The benefits of this second method are the use of catalytic base, reactions conducted at RT and the employment of stoichiometric methyl arene, while the downside is the necessity for a specialized silylating reagent, ^{t}Bu–N═N–SiR_3 (**20b**) (Scheme 26b). The scope was demonstrated to be surprisingly good with respect to the alkyl arene and various functional groups were compatible with the reaction (F, Cl, $CO_2{}^t$Bu, NHMe, alkene, alkyne, ether) despite the reactive nature of some of the proposed intermediates (see above). The authors also described the novel gem-disilylation of 4-phenyl toluene (Scheme 27b). Small silyl groups, like $SiMe_3$ gave excellent results (97% yield), while use of larger diazine derived silanes resulted in lower yields ($SiEt_3$, <5%). Unsymmetrical disilylanes could also be prepared.

NMR studies demonstrated that the catalyst resting state is the deprotonated benzylic silane (Schemes 26b and **20b′**), the only potassium-containing intermediate that was observed when monitoring the reaction progress. DFT computations were used to map this interesting mechanism, and a simplified version is drawn in Scheme 26d. Entry into the catalytic cycle is shown in the upper left portion. Attack of ^{t}BuOK on the silyl diazene forms a 5-coordinate silicon ate complex that expels N_2 and generates ^{t}BuK. The ^{t}BuK readily deprotonates the toluene derivative to give KCH_2Ph (**I**) and 2-methylpropane. *N*-Coordination of an equivalent of diazene to potassium and attack of the benzylic carbanion on silicon in **II** results in loss of N_2, formation of the Si–C bond and generation of ^{t}BuK stabilized by a cation–π complex of the benzyl silane (**III**). The ^{t}BuK deprotonates the η^6-benzyl silylane to afford **IV**. The authors then proposed activation of toluene through a cation–π complex, as shown in **TS$_{20}$**, followed by intramolecular proton shuffling to regenerate KCH_2Ph (**I**) and close the catalytic cycle. Comparison between the stoichiometric base in Scheme 26a and catalytic base in Scheme 26b is the diazene reagent reacts to generate base and sustain the catalytic reaction.

Carbon dioxide is a useful C1 source, but can be challenging to incorporate into organic scaffolds under mild conditions.[216] Several methods for the carboxylation of organic compounds under basic conditions were developed (Scheme 27).[217–220] The innovation of this work is that it circumvents the traditional two step approach that relies on use of very strong bases, such as ^{n}BuLi/KO^{t}Bu/TMP at −78 °C,[221] followed by treatment of the resulting benzylic organometallics with CO_2. A key feature of this work is that highly reactive bases will react directly with CO_2. The authors found that use of LiO^{t}Bu and CsF in 1,3-dimethyl-2-imidazolidinone (DMI) under CO_2 (1 atm) reacted reversibly, with generation of the adduct $^-OCO_2{}^t$Bu and leaving some unreacted *tert*-butoxide to deprotonate the methyl arene substrate. In some cases, $LiOCEt_3$ proved more effective. A few of the most challenging examples are given in Scheme 27. In the second step, the 80 °C acidification of the reaction mixture is to decarbonylate the dicarboxylated products, $ArCH(CO_2{}^-)_2$.



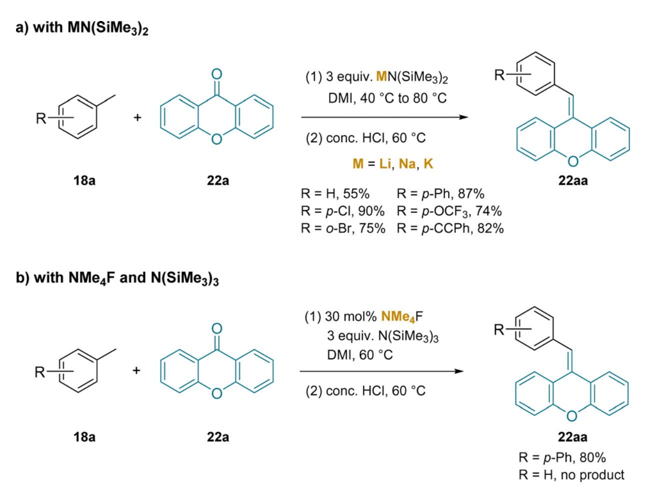
Scheme 27 Carboxylation of methyl arenes under basic conditions.

The dicarboxylated product can also be methylated and isolated as the diester, $ArCH(CO_2Me)_2$.

Several observations were made on the carboxylation reactions that shed light on the reaction details. It was hypothesized that reaction of LiO^tBu and CsF resulted in the formation of CsO^tBu. Use of independently prepared CsO^tBu in the absence of lithium salts, such as LiF, gave similar yields to the standard reactions. Furthermore, ^{133}Cs NMR analysis of a solution of LiO^tBu and CsF that had been heated for 1 h at 180 °C showed the formation of CsO^tBu. The authors proposed that the Cs^+ forms a cation–π interaction with the methylarene in the deprotonation of the benzylic methyl group. Addition of 18-crown-6 was found to decrease the yield of the carboxylation product (**21**) by sequestering K^+ and inhibiting the formation of the cation–π complex.[219]

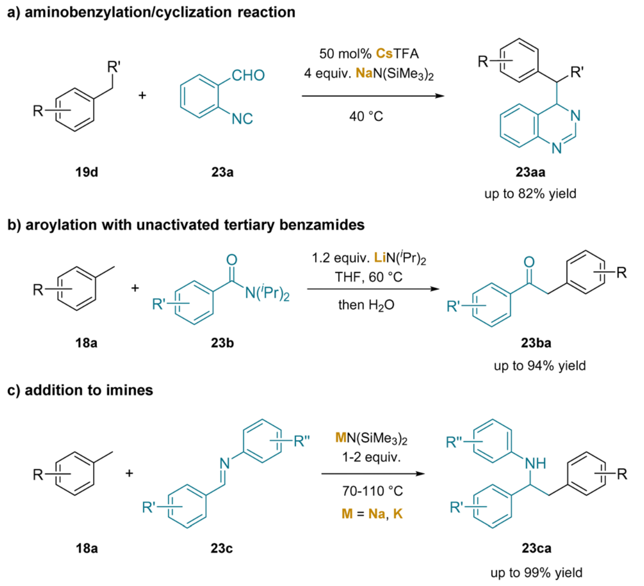
In another application of silylamide bases to toluene deprotonation and functionalization, the addition of *in situ* generated benzylic anions to non-enolazible ketones was examined.[222] In this study, using DMI solvent, $MN(SiMe_3)_2$ (M = Li, Na, K) bases were examined with 4-bromotoluene (limiting reagent) as the pro-nucleophile and benzophenone (**22a**) as the trapping ketone. Acidic workup to eliminate the tertiary alkoxide provided the product olefin. Interestingly, the $LiN(SiMe_3)_2$ afforded the product in 94% assay yield compared to 39% for the Na^+ and 6% for the K^+ analogues. Using xanthone as the trapping ketone, a series of pro-nucleophiles were examined with different toluene derivatives in stoichiometric amounts, as outlined in Scheme 28a.

In related work, the same group[223] introduced an interesting method to generate the silyl amide base under conditions devoid of the main group counterion in the reactions in Scheme 28b. This approach enables a reactivity comparison between silyl amide bases with group(I) metal cations and the naked silyl amide. In the event, treatment of 3 equiv. $N(SiMe_3)_3$ with NMe_4F resulted in fluoride induced removal of a $SiMe_3$ group and generation of the ion pair $^+NMe_4\ ^-N(SiMe_3)_2$. Using 4-phenyl toluene, which has a pK_a of 38.6 in THF[224] (compared to $HN(SiMe_3)_2$ with a pK_a 25.8 in THF[225]), the authors observed 80% yield of the olefin (**22aa**), compared to 87% in Scheme 28a. Of note, it was found that less acidic toluene was not a viable substrate with the ion pair base, $^+NMe_4\ ^-N(SiMe_3)_2$. In contrast, in the presence of $LiN(SiMe_3)_2$ (Scheme 28a)[222] toluene was indeed a successful substrate. One interpretation of this data is that the cation–π interaction between the Li^+ of $LiN(SiMe_3)_2$ and arene can account for the extra reactivity needed for this high pK_a substrate. The impact of the $^+NMe_4$ cation on the reactivity of the toluene derivatives is not known, but it has been proposed that ammonium salts do form electrostatic interactions with arenes.[199]



Scheme 28 Alkene synthesis from toluene derivatives: (a) with $MN(SiMe_3)_2$, and (b) with NMe_4F and $N(SiMe_3)_3$.

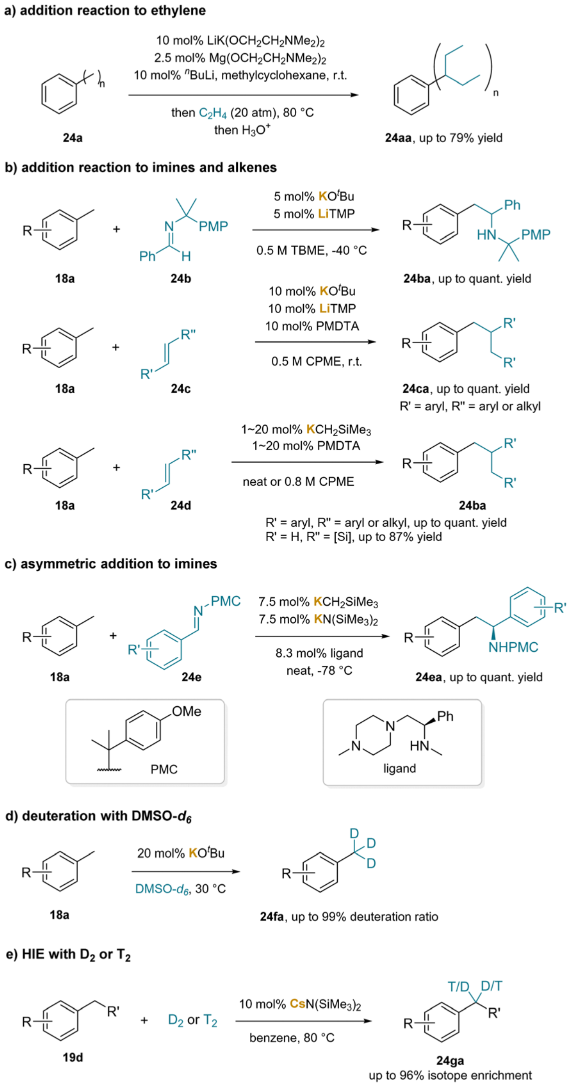
There are likely several related deprotonations involving cation–π interactions that were not hypothesized to be important in the deprotonation process. Such interactions are difficult to characterize, often relying on computational results and with circumstantial experimental support. For instance, the study on $NaN(SiMe_3)_2$/CsTFA co-promoted aminobenzylation/cyclization of 2-isocyanobenzaldehydes (**23a**) with toluene derivatives (**19d**) offers one-pot access to dihydroquinazolines (**23aa**) and quinazolines[226] (Scheme 29a). In this study, the authors proposed $NaN(SiMe_3)_2$ and CsTFA co-promoted deprotonation of the benzylic C–H bonds in toluene to form an η^3-coordinated complex. In the report of benzylic aroylation of toluene derivatives with unactivated tertiary benzamides (**23b**),[24] the researchers proposed an *ortho*-lithiation intermediate to be responsible for benzylic deprotonation through a σ-bond metathesis mechanism (Scheme 29b). In a more recent work, either $NaN(SiMe_3)_2$ or $KN(SiMe_3)_2$ was used in the addition reactions of toluenes to imines (**23c**), producing anilines (**23ca**) bearing branched alkyl motifs (Scheme 29c).[227]



Scheme 29 Other examples involving cation–π interactions: (a) aminobenzylation/cyclization reaction, (b) aroylation with unactivated tertiary benzamides and (c) addition to *N*-aryl imines.

3.3. Base-catalyzed benzylic C–H bond functionalization

Several studies have implemented a catalytic amount of base to facilitate benzylic C–H bond functionalization through deprotonation. In the early stages, a catalytic amount of alkali metal was reported to generate benzylic carbanions, subsequently achieving side-chain functionalization of aromatics through the addition to styrene derivatives.[228–230] In 2000, it was revealed that a mixture of ^{n}BuLi, $LiK(OCH_2CH_2NMe_2)_2$ and $Mg(OCH_2CH_2OEt)_2$ could catalyze addition reactions of aromatic hydrocarbons bearing methyl groups (**24aa**) to ethylene, albeit with low functional group tolerance (Scheme 30a).[231] In 2018, addition reactions of alkylarenes with imines (**24b**) and alkenes (**24c**, **24d**), including four instances utilizing catalytic KO^{t}Bu and LiTMP were reported (Scheme 30b).[232] The authors subsequently expanded the method's scope significantly by employing a combination of KCH_2TMS and PMDTA as catalysts.[233] Furthermore, they achieved asymmetric benzylic C–H bond addition with a chiral amine as the ligand, resulting in enantioenriched (62% to >99% ee) benzylic amine products (**24ea**) (Scheme 30c).[234] In 2021, catalytic KO^{t}Bu was used to realize the hydrogen isotope exchange (HIE) of methylarenes (**18a**) with DMSO-d_6 as a deuterium source (Scheme 30d).[235] In 2023, a group of researchers developed cesium amide-catalyzed benzylic HIE reaction with D_2 or T_2 (Scheme 30e).[236] They proposed that cesium amide could undergo a kinetic deprotonative process to generate the benzyl anion as a thermodynamically uphill intermediate at very low concentrations. Despite this, the benzylic metal species $PhCH_2Cs$ reacted with D_2 to yield the HIE product (**24ga**) and the metal deuteride intermediate Cs–D. This intermediate could then undergo subsequent protonation with either $HN(SiMe_3)_2$ or toluene, resulting in $CsN(SiMe_3)_2$ or a benzylic anion intermediate, initiating another deuteration process.



Scheme 30 Base-catalyzed benzylic functionalization: (a) addition reaction to ethylene, (b) addition reaction to imines and alkenes, (c) asymmetric addition to imines, (d) deuteration with DMSO-d_6, and (e) HIE with D_2 or T_2.

Additionally, beyond alkylbenzenes, particularly toluene derivatives, base-catalyzed addition reactions of ethylbenzene derivatives, such as allylbenzene[237,238] and diarylmethanes,[227,239] have been established. These substrates feature benzylic C–H bonds with increased acidity owing to the benzylic substituent.

4. Conclusions

The π-coordination strategy utilizing transition-metals has emerged as an attractive approach for benzylic C–H bond functionalization *via* a combination of deprotonation and electrophilic attack. Since the 1970s, significant progress has been made in reactions of alkylarene complexes, particularly under conditions with stereocontrol. However, the use of strong bases in the deprotonation step of $Cr(CO)_3$-complexed arenes has limited compatibility with functional groups, posing a challenge in the late-stage functionalization of complex molecules. While cationic metal units such as tricarbonyl manganese(I), cyclopentadienyl iron(II), and pentamethylcyclopentadienyl ruthenium(II) increase the acidity of the benzylic hydrogens of η^6-alkyl arenes, their limited accessibility has hindered their use in studies. Future advancements in this field include the development of ligands that provide a general solution, establish asymmetric catalysis, and create new reactivities. Dual catalysis involving a Lewis acid, which is compatible with the acidic metal catalyst, would also expand the scope of benzylic C–H bond functionalizations. Ultimately, the progression from stoichiometric metal complexes to catalytic processes involving arene exchange steps is crucial for the advancement of this field. This review aims to promote a better understanding of the π-coordination-driven benzylic C–H bond activation and inspire future innovations in the field.

Cation–π interactions can acidify the benzylic hydrogens, facilitating their deprotonation. Unlike transition-metals, which can form strong bonds to η^6-arenes and result in dramatic decreases in the pK_a of the benzylic C–H's, the impact on the cation–π interactions is more subtle. While cation–π interactions are often observed in crystal structures containing group(I) metals, the low strength of the interaction makes arene exchange rapid and difficult to characterize in solution. Further studies are necessary to both better understand these interactions and to develop guidelines for the design of systems that can maximize their beneficial impact to develop more synthetically useful complexes and catalysts.

Author contributions

The manuscript was written by all the authors, who approved the final version.

Data availability

All data for the manuscript is contained in the original manuscripts cited in the text.

Conflicts of interest

There are no conflicts to declare.

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