Metal-catalyzed activation of ethers via C–O bond cleavage: A new strategy for molecular diversity

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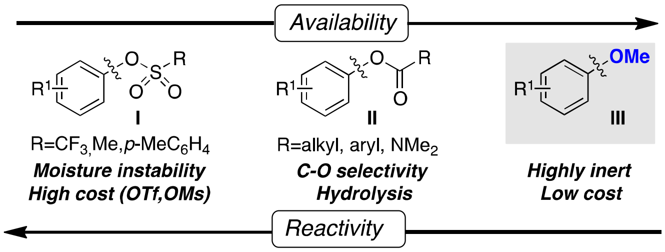
In 1979, the seminal work of Wenkert set the standards for the utilization of aryl and vinyl ethers as coupling partners via C–O bond-cleavage. Although the topic remained dormant for almost three decades, the last years have witnessed a renaissance in this area of expertise, experiencing an exponential growth and becoming a significant discipline within the cross-coupling arena. The means to utilize readily accessible aryl or vinyl ethers as counterparts does not only represent a practical, powerful and straightforward alternative to organic halides, but also constitutes an excellent opportunity to improve our chemical knowledge on a relative unexplored area of expertise. This review summarizes the most significant developments in the area of C-O bond-cleavage when employing aryl or vinyl ethers, providing a detailed overview of the current state of the art and including future aspects, when applicable.

1. Introduction

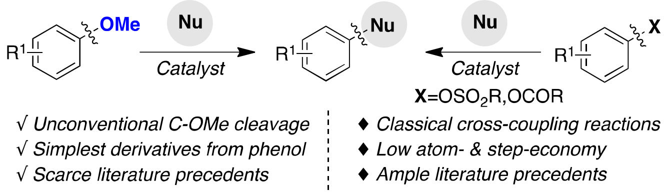
In 1972, Kumada and Corriu independently reported the cross-coupling reaction of organic halides with Grignard reagents in the presence of Ni or Pd catalysts.[1,2] Such discovery triggered unimaginable consequences in organic synthesis, resulting in a new and useful technique that allowed for unconventional bond disconnections. A few years later, Mizoroki-Heck, Sonogashira-Hagihara, Negishi, Stille and Sukuki-Miyaura-type protocols set the standards for modern cross-coupling reactions employing aryl or vinyl halides with much less nucleophilic coupling partners.[3] The impact of some of these methodologies was finally recognized with the Nobel Prize in Chemistry 2010. As judged by the wealth of literature data reported in the last 40 years, the use of organic halides as coupling partners has become routine in the cross-coupling arena.[3] Indeed, chemists have now the perception that catalytic C–C or C–heteroatom bond-forming reactions should include an organic halide as coupling counterpart and that the use of alternatives might be considered a futile effort. Although there is little doubt that the use of aryl halides has profoundly changed the landscape of metal-catalyzed cross-coupling reactions, there are still certain drawbacks associated to their use in organic synthesis: (a) formation of halogenated waste, and (b) low accessibility of densely functionalized aryl halides, particularly aryl iodides and aryl bromides.

In recent years, the use of C–O electrophiles has shown to be a viable and powerful alternative to the use of aryl halides in cross-coupling reactions.[4] Among their advantages are the absence of halogenated waste, the greater availability of phenol derivatives as compared to aryl halides and the possibility for orthogonal approaches in the presence of aryl halides (Scheme 1). Aryl sulfonates (**I**) constitute the most widely employed C–O electrophiles in cross-coupling reactions due to their low activation barrier for C–O bond-cleavage and their natural proclivity towards oxidative addition.[3] However, the use of aryl sulfonates (**I**) invariably produces stoichiometric amounts of sulphur-containing waste and their high price might lower down the application profile of such counterparts.



Scheme 1. C-O electrophiles in metal-catalyzed cross-coupling reactions.

Recently, elegant catalytic C–O bond-cleavage procedures have been reported using much simpler aryl ester or aryl carbamate derivatives (**II**).[5] Intriguingly, while Pd catalysts have been typically employed in cross-coupling reactions with aryl sulfonates, the use of aryl esters or carbamates have been predominantly conducted with Ni catalysts. Although one might consider such observation a mere curiosity, the low reactivity of Pd catalysts clearly manifests the superiority of Ni catalysts for particularly challenging substrate combinations.[6] However, aryl esters or carbamates (**II**) are not commercially available and their use in cross-coupling reactions results in a considerable amount of waste, particularly when using aryl pivalates or aryl carbamates. Beyond any reasonable doubt, the use of much simpler and commercially-available aryl methyl ethers (**III**) would constitute an attractive alternative due to the fact that aryl methyl ethers (**III**) are the simplest derivatives from phenol and little generation of waste is produced in these reactions. However, the activation energy for effecting C–OMe bond-cleavage is significantly higher than for any other phenol derivative.[7] This is probably due to the reluctance of the C–OMe bond towards oxidative addition and the lower propensity of the methoxy residue to act as a leaving group, an observation that is in contrast with the use of aryl sulfonates, pivalates or carbamates.[4] These drawbacks contributed to the perception that aryl methyl ethers could not be employed as counterparts in cross-coupling methodologies. Fortunately, the recent years have witnessed a dramatic progress in this area of expertise, allowing the use of innovative catalytic technologies that employ aryl alkyl ethers as C–O electrophiles in a wide variety of synthetically relevant transformations. While the use of aryl methyl ethers or related compounds as coupling counterparts is still at its infancy compared to the employment of aryl halides or other C–O electrophiles, the widespread use of aryl alkyl ethers could potentially open up new perspectives in the cross-coupling arena while changing logics in organic synthesis (Scheme 2).



Scheme 2. Catalytic functionalization of aryl alkyl ethers *vs.* “classical” C-O electrophiles.

Taking into consideration the enormous potential of aryl alkyl ethers as coupling counterparts, we decided to summarize the recent catalytic methods described in the literature involving the cleavage of C–O(alkyl) bonds. Although significant contributions have been described in a stoichiometric fashion or within the realm of heterogeneous catalysis, the purpose of this review is to focus on the most important developments in *homogeneous metal-catalyzed activation of C–O bonds in ether derivatives*. Undoubtedly, these methods face notorious difficult challenges, primarily due to the high activation barrier required for effecting C–O(alkyl) bond-cleavage[7] and the site-selectivity in the presence of multiple C–O bonds.[4] Since the catalytic reactions largely depend on the nature of the nucleophile employed, we have organized this tutorial review based on the type of transformation, ranging from C–C to C–heteroatom bond-forming reactions. This account also includes the description of the rather puzzling catalytic reductive cleavage events in which the aryl ether is formally used as a temporary protecting group, a matter of great synthetic significance.[8] This review also highlights the challenges and prospective impact of all these transformations, without losing sight their preparative scope and including mechanistic aspects, when appropriate.

Ruben Martin received his PhD in 2003 from the University of Barcelona under the guidance of Prof. Antoni Riera. In 2004, he moved to the Max-Planck Institut für Kohlenforschung as a Humboldt postdoctoral fellow with Prof. Alois Fürstner. In 2005 he then undertook postdoctoral studies at MIT with Prof. Stephen L. Buchwald as a MEC-Fulbright fellow. In September 2008 he initiated his independent career as an assistant professor at ICIQ. In July 2013 he was promoted to associate professor and subsequently to ICREA Research Professor. His research is focused on the development of new metal-catalyzed activation of inert bonds. His work has been rewarded by the RSEQ Sigma-Aldrich prize for Emerging Investigators (2010), Thieme Chemistry Award (2011), Eli Lilly Young Investigator Award (2011), and he currently holds a ERC Starting Grant (2011).

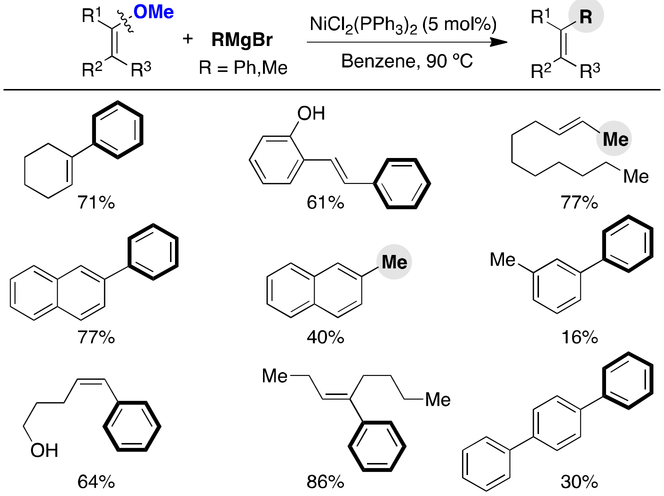
Dr. Josep Cornellà was born in Barcelona and graduated with distinction from the University of Barcelona (Spain) with a M.Sc in Organic Chemistry in 2008. Subsequently, he joined the group of Prof. Igor Larrosa at Queen Mary University of London (United Kingdom). In early 2012, he earned his PhD working on the development of metal-catalyzed decarboxylative reactions. In 2012, he was granted a Marie Curie Fellowship at Prof. Ruben Martin's group at ICIQ and he is currently studying the discovery of novel transformations involving metal-catalyzed C–O bond activation and CO_2 fixation.

Cayetana Zárate received her B.Sc. from the University of Valladolid in 2012 with Extraordinary Award. During her B.Sc., she was an undergraduate fellow for two years carrying out research in gold-catalyzed reactions at Prof. Espinet´s group. In October 2012 she began graduate studies under the supervision of Prof. Ruben Martin at ICIQ, where she earned her M.Sc from the University Rovira i Virgili in July 2013. She is currently pursuing her PhD studies at Prof. Ruben Martin´s group in the area of metal-catalyzed C–O bond-activation.

2. C-C Bond-Forming Reactions

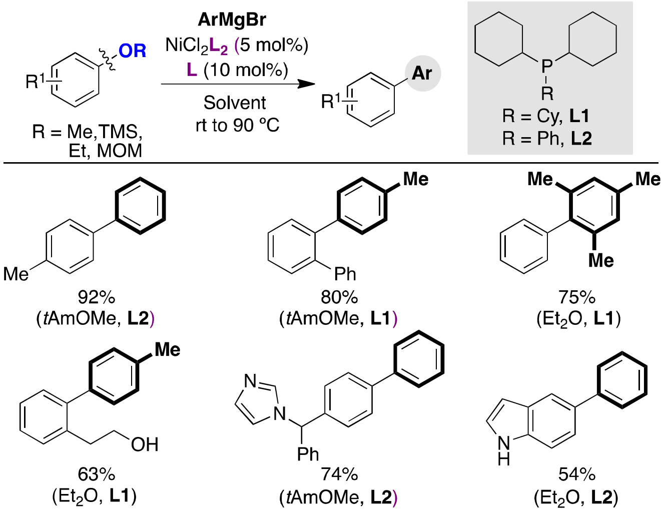
2.1 Kumada-Tamao-Corriu type Reactions

In 1979, a pioneering study by Wenkert demonstrated that simple aryl or vinyl methyl ethers could be employed as coupling partners in Ni-catalyzed Kumada-Tamao-Corriu reactions (Scheme 3).[9] The scope of the reaction included the coupling of PhMgBr or MeMgBr utilizing commercially available $NiCl_2(PPh_3)_2$ as catalyst. Interestingly, enol ethers reacted at a faster rate than the corresponding aryl ethers. It is worth noting, however, that alkyl Grignard reagents possessing β-hydrogens such as EtMgBr resulted in a significant reduction of the C–OMe bond. Likewise, non π-extended aromatic rings afforded low yields of the coupling products, thus showing the intrinsic limitations of this protocol. Despite the obvious interest of such methodology at the Community, Wenkert´s discovery was disclosed the same year in which Suzuki and Miyaura reported their work on the Pd-catalyzed cross-coupling reaction of alkylboron reagents with aryl and vinyl halides.[10] Unfortunately, Wenkert´s seminal work using more accessible aryl methyl ethers was probably overlooked by the myriad of excellent contributions reported in mid 70´s that established the use of Pd catalysts and organic halides as coupling partners.[3]



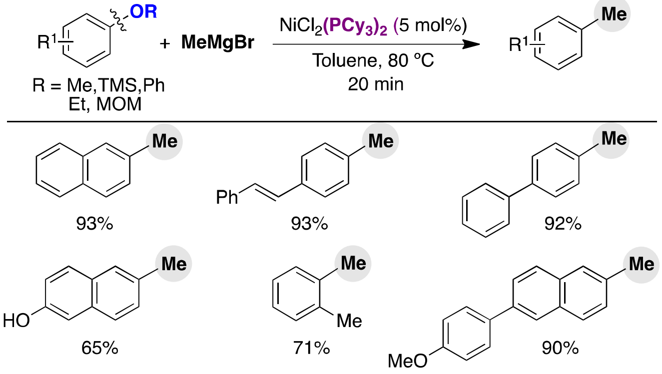
Scheme 3. Ni-catalyzed Kumada-Tamao-Corriu coupling of vinyl and aryl methyl ethers with PhMgBr or MeMgBr under Wenkert´s conditions.

The means to utilize aryl or vinyl ethers as an alternative to aryl or vinyl halides remained dormant for almost three decades, at which time Dankwardt, a pharmaceutical chemist at DSM pharmaceuticals, revisited Wenkert´s work.[11] The method developed by Dankwardt operated with a much broader substrate scope, including the use of the rather elusive nonactivated aryl ethers lacking π–conjugation (Scheme 4). The key contributory factor for success was the combination of an electron-rich phosphine ligand with a high cone angle (PCy_3 or $PhPCy_2$) and an ethereal solvent. Notably, Dankwardt´s procedure allowed for the coupling of other aromatic alkyl ethers with equal efficiency (ArOEt, ArOTMS or ArOMOM, among others), a remarkable finding that illustrated the robustness of such method. Unfortunately, an excess of Grignard reagent was typically utilized, making particularly problematic the corresponding isolation of products and the inclusion of sensitive functional groups. It was found that alkyl or alkenyl Grignard reagents could not be utilized as coupling partners, an observation that was in contrast with the ability of Wenkert´s procedure to couple simple MeMgBr.[9]



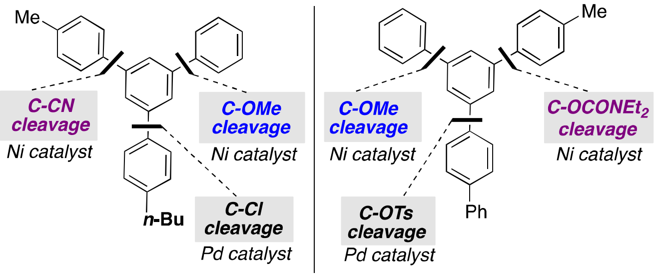
Scheme 4. Ni-catalyzed Kumada-Tamao-Corriu coupling of aryl alkyl ethers with ArMgBr under Dankwardt´s conditions.

In 2008, the Shi group reported an extension of Wenkert´s[9] and Dankwardt´s work[11] on the Ni-catalyzed cross-coupling reaction of aryl methyl ethers with MeMgBr (Scheme 5).[12] Although Wenkert´s original disclosure included the utilization of MeMgBr,[9] the scope of these reactions was essentially limited to the use of activated π-extended systems such as naphthalene derivatives. Shi´s procedure, however, employed a catalytic system based upon $NiCl_2(PCy_3)_2$ that allowed for the use of less activated aryl alkyl ethers or even diaryl ethers at shorter reaction times. As expected from Wenkert´s studies,[9] competitive experiments showed that methyl ethers within a π-extended system reacted at a faster rate than regular aryl motifs, an observation that illustrates the intriguing role exerted by π-extended aromatic systems on the reaction outcome.



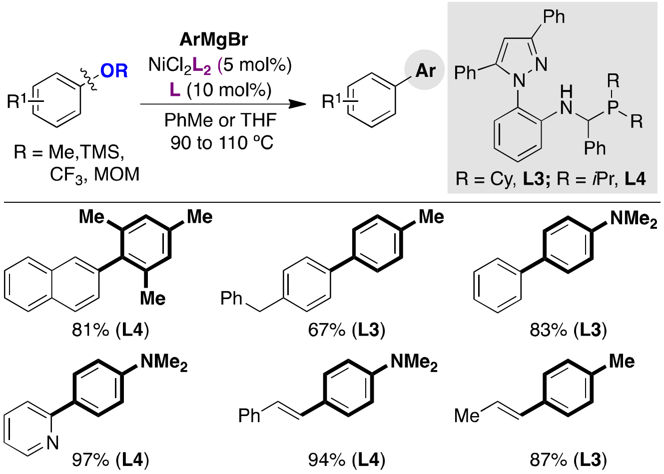
Scheme 5. Ni-catalyzed Kumada-Tamao-Corriu coupling of aryl alkyl ethers with MeMgBr.

Taking into consideration the high energy required for C–OMe bond-cleavage,[7] it was anticipated that a synthesis of polyarenes could be within reach via programmed metal-catalyzed C–C bond-forming reactions in the presence of other coupling partners. In line with this notion, the Shi group reported a synthesis of polyarenes via consecutive C–C bond-formation using the acquired knowledge gathered in the literature for the activation of aryl halides or pseudohalides and their inherent distinctive reactivity with Pd or Ni catalysts (Scheme 6).[13] As expected, Ni-catalyzed Kumada-Tamao-Corriu C–OMe bond-cleavage was conducted at late-stages once C–Cl, C–OTs, C–OCONEt$_2$ or C–CN functionalization was secured via Suzuki-Miyaura reactions.



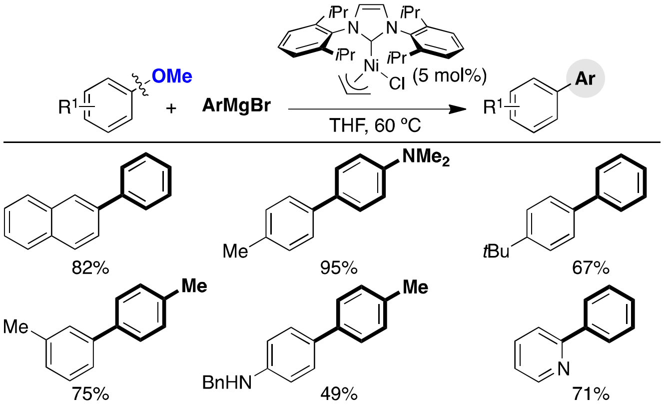
Scheme 6. Iterative Ni and Pd-catalyzed C-C bond-formations.

In recent years, the design of supporting ligands has been a notorious contributory factor for improving the efficiency and selectivity of metal-catalyzed cross-coupling reactions.[14] In 2010, the Wang group developed a series of electron-rich and sterically-encumbered pyrazolyl amino phosphines.[15] While such ligands were originally designed for Kumada-Tamao-Corriu reactions of aryl chlorides,[16] it was found that these ligands could also be employed for the coupling of much more challenging aryl methyl ethers via C–OMe bond-cleavage (Scheme 7). The substrate scope included the utilization of π-extended aromatic backbones, vinyl ethers and regular anisole derivatives. As expected, naphthyl and vinyl ethers were considerably more reactive than regular aryl alkyl ethers.



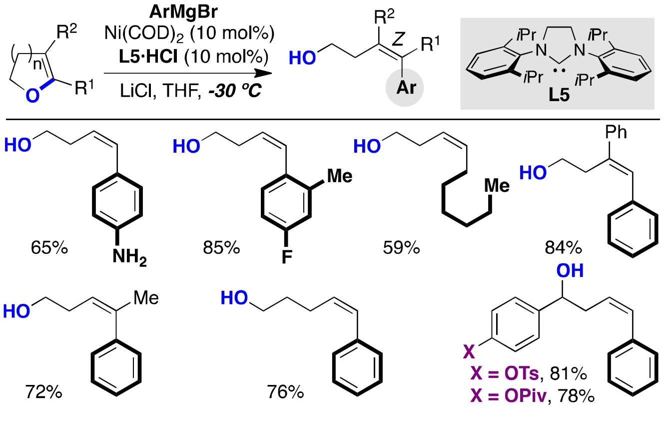
Scheme 7. Kumada-Tamao-Corriu reactions of aryl alkyl ethers using pyrazolyl amino phosphines.

Although trialkylphosphine ligands have largely dominated the cross-coupling arena,[3] the use of N-heterocyclic carbenes (NHCs) has shown to be viable alternatives for modulating the properties of metal catalysts.[17] Specifically, Nicasio and co-workers reported that one-component Ni precatalysts bearing NHC ligands were particularly competent for effecting Kumada-Tamao-Corriu reactions of aryl alkyl ethers via C–OMe bond-cleavage under relatively mild reaction conditions.[18] As shown in Scheme 8, a variety of π-extended aromatics and regular anisole derivatives could be equally employed. As for other Kumada-Tamao-Corriu reactions of alkyl ethers,[9,11,12,13] however, the method could not be applied in the presence of particularly sensitive functional groups.



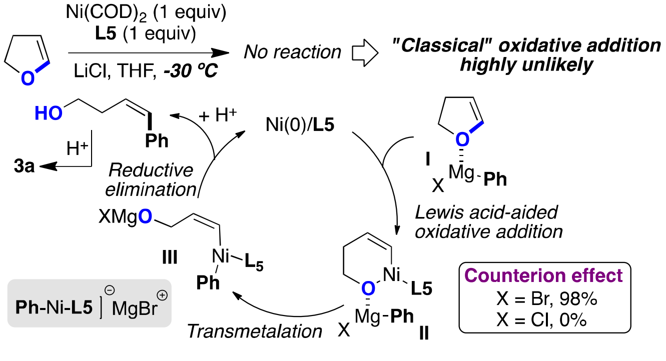
Scheme 8. NHC ligands in Kumada-Tamao-Corriu reactions of aryl alkyl ethers.

The successful development of Kumada-Tamao-Corriu reactions of alkyl ethers via C(sp^2)–O bond-cleavage can easily be rationalized by the employment of highly reactive Grignard reagents. Issues with functional group compatibility, however, make Grignard reagents not particularly useful for densely functionalized backbones. To such end, Knochel pioneered the development of highly functionalized Grignard reagents.[19] However, their thermal instability limits somewhat the application profile of these reagents at the temperatures typically required in cross-coupling reactions. Recently, the Martin group has described a Ni-catalyzed Kumada-Corriu reaction of cyclic vinyl ethers that operates at temperatures as low as -40 °C using NHC as ligands (Scheme 9).[20] The mild reaction conditions achieved allowed for the utilization of Knochel-type Grignards and, more importantly, in the presence of functional groups, a notable finding that is in sharp contrast with classical Kumada-Tamao-Corriu reactions of alkyl ethers.[9,11,12,13,18] Remarkably, it was found that cyclic vinyl ethers reacted with an exquisite stereoselectivity control, thus providing access to the rather elusive Z-homoallylic alcohols. Since other related coupling approaches invariably deliver *E*-configured isomers,[21] the ability to obtain selectively *Z*-configured homoallylic alcohols shows the complementarity of this method. Interestingly, the reaction was also amenable for the utilization of alkyl Grignard reagents possessing β-hydrogens such as *n*-hexylMgBr in good yield.



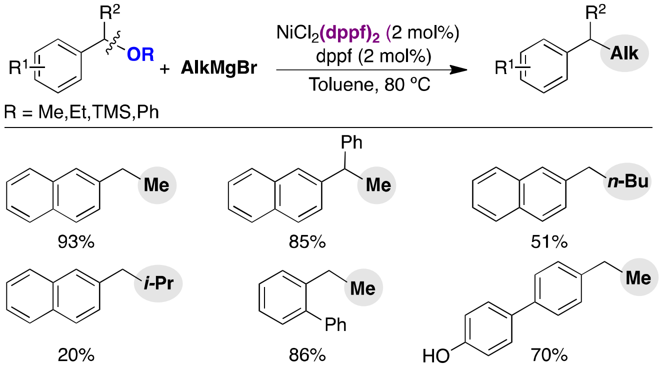
Scheme 9. Low temperature Kumada-Tamao-Corriu reactions.

As for many other cross-coupling reactions,[3] the cleavage of C–O(alkyl) bonds is believed to proceed via "classical" oxidative addition with an *in situ* generated Ni(0)L_n complex.[4] However, no mechanistic studies have been proposed to confirm such assumption. The Martin group described preliminary experiments that pointed towards a rather unusual Lewis-acid aided oxidative addition, an observation that was corroborated by stoichiometric experiments in the presence or absence of Grignard reagents (Scheme 10).[20] Such proposal suggested that the intermediacy of Ni(0)-ate complexes could not be ruled out and that a Lewis-basic oxygen was critical for success. In line with this notion, it was found that the Kumada-Tamao-Corriu reaction could be even conducted in the presence of activated C–O electrophiles such as aryl tosylates or pivalates (Scheme 9, bottom right).[20] This observation can hardly be underestimated, since it shows that a metal-catalyzed methodology could favour the cleavage of the, a priori, less reactive C–O bond.



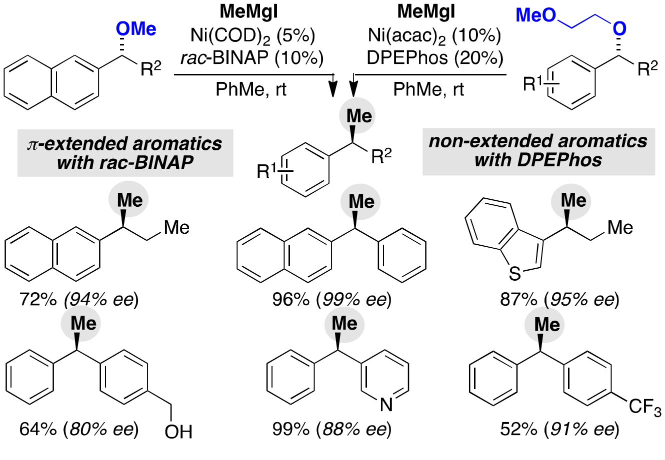
Scheme 10. Mechanistic proposal via "*non-classical*" oxidative addition into C-O(alkyl) bond.

While the methods reported by Wenkert[9] and Dankwardt[11] established the use of aryl methyl ethers as coupling partners in Kumada-Tamao-Corriu reactions, these protocols were essentially limited to the cleavage of C(sp^2)–O(alkyl) bonds. The Shi group described a Ni-catalyzed methodology that allowed for the coupling of activated benzyl alkyl ethers with MeMgBr via C(sp^3)–O bond-cleavage (Scheme 11).[22] Interestingly, while $NiCl_2(PCy_3)_2$ delivered traces of the coupling product, $NiCl_2$(dppf)$_2$ provided the best results in toluene at 80 °C. Under these reaction conditions, a wide variety of primary or even secondary benzyl alkyl ethers could be utilized with similar efficiency. As expected, benzylic C(sp^3)–OMe bonds were significantly more reactive than C(sp^2)–OMe motifs, an observation that could be turned into a strategic advantage in site-selectivity approaches. Although not explored in detail, the authors showed that the use of *n*BuMgBr or *i*PrMgBr provided lower yields, probably due to competitive β-hydride elimination pathways.



Scheme 11. Ni-catalyzed Kumada-Tamao-Corriu coupling of benzyl alkyl ethers with alkyl Grignard reagents (dppf=1,1´-bis(diphenylphosphino)ferrocene).

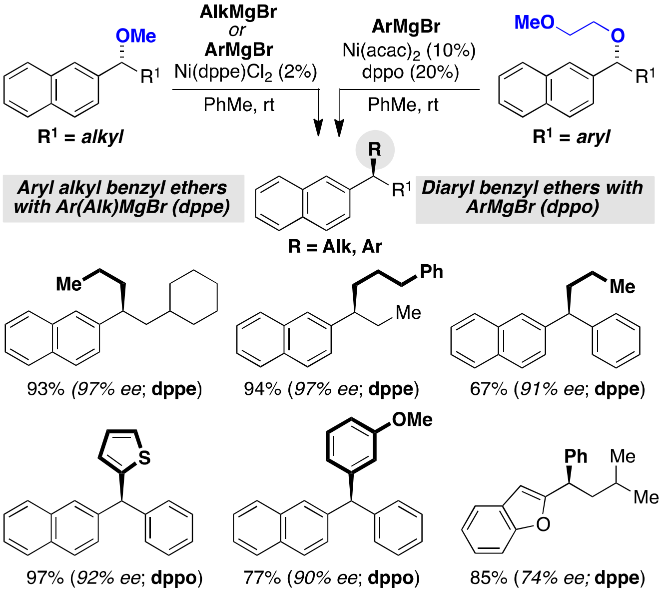
Prompted by the work of Shi, the Jarvo group described the successful development of a stereospecific Ni-catalyzed Kumada-Tamao-Corriu reaction of enantioenriched benzyl alkyl ethers with MeMgBr (Scheme 12).[23] As anticipated, the use of π-extended aromatics was found to be critical for success (Scheme 12, left).[23a] Indeed, regular benzyl methyl ethers derivatives were found to be unreactive under these reaction conditions. Interestingly, such limitation could be overcome by using traceless directing groups on the ether motif that likely facilitates the oxidative addition step within the catalytic cycle (Scheme 12, right).[23b] The cross-coupling reaction proceeded with inversion of configuration, an outcome that is consistent with an oxidative addition that occurs with inversion of configuration followed by a retentive transmetallation event.



Scheme 12. Stereoselective Kumada-Tamao-Corriu reaction of enantioenriched benzyl ethers with MeMgBr (BINAP=2,2'-

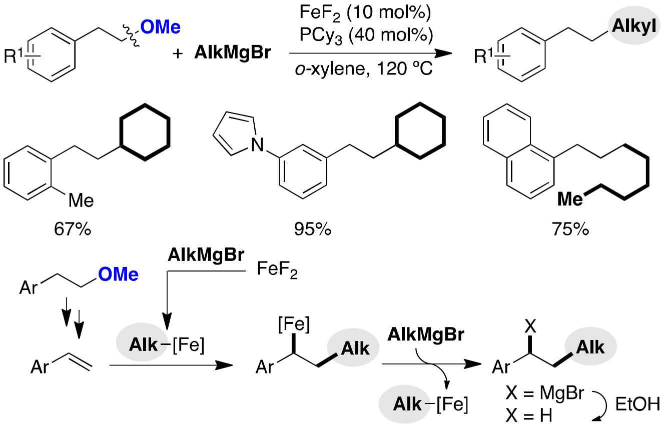
bis(diphenylphosphino)-1,1'-binaphthalene; DPEPhos=Bis[(2-diphenylphosphino)phenyl]ether).

Subsequently, the Jarvo group reported a stereospecific event using diaryl benzyl ethers and ArMgBr en route to triarylmethanes (Scheme 13, top right).[24] The nature of the ligand was found to be critical, and the best results were accomplished when using bidentate ligands with a large bite angle such as dppo.[24a] The outcome of the reaction, however, did not include secondary benzyl ethers containing alkyl residues. Gratifyingly, the use of dppe as the ligand was perfectly suited for such purpose (Scheme 13, top left).[24b] Interestingly, the catalytic system based upon dppe was general enough to accommodate the coupling of alkyl Grignard reagents possessing β-hydrogens.[24b] In contrast with cross-coupling reactions that operate via radical-based manifolds,[3] the erosion in enantioselectivity for some substrate combinations was proposed to proceed by a bimolecular reaction of π-benzyl Ni oxidative addition intermediates with low valent Ni species.



Scheme 13. Stereoselective Kumada-Tamao-Corriu reaction of enantioenriched benzyl ethers with RMgBr. (dppe and dppo=1,2-bis(diphenylphosphino)ethane or -octane).

While the cleavage of C(sp^3)–O bonds in benzyl alkyl ethers undoubtedly constitutes a significant step forward (Schemes 11-13), the cleavage of unactivated C(sp^3)–OMe bonds still represents a tremendous challenge in C–O bond-cleavage reactions. Unlike benzyl ethers, unactivated alkyl ethers are particularly reluctant towards oxidative addition.[7] The Shi group has recently described the cross-coupling reaction of slightly activated homobenzylic methyl ethers with alkyl Grignard reagents possessing β-hydrogens at high temperatures (Scheme 14).[25] Interestingly, FeF_2 was used as the catalyst, a notorious difference from the commonly employed Ni catalysts for the cleavage of C–O bonds.[4] The scope encompassed π-extended backbones as well as regular aromatic moieties; unfortunately, the reaction was not amenable to secondary homobenzylic ethers or to substrates containing β-substituents. Based on such data, the authors proposed a scenario consisting of a carbometallation of organoiron species with *in situ* generated styrenes derived from the initial homobenzylic alkyl ethers (Scheme 14, bottom). Subsequent transmetallation with an additional Grignard reagent afforded an alkyl metal species that upon hydrolytic workup with EtOH afforded the targeted products. Interestingly, the use of electrophiles other than EtOH such as MeI or R_3SiCl allowed for the formal 1,2-functionalization of styrene derivatives, albeit in lower yields.

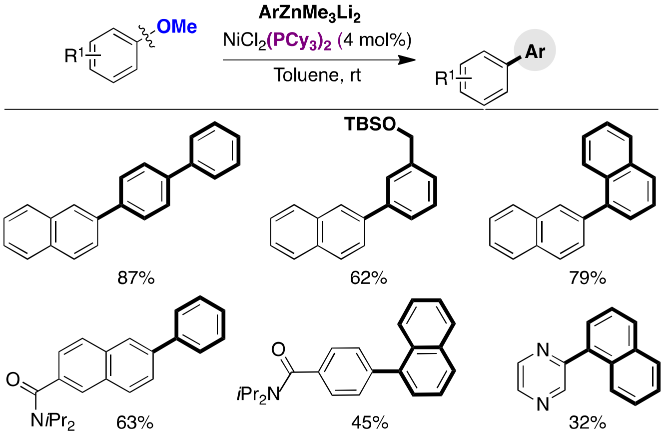


Scheme 14. Fe-catalyzed Kumada-Tamao-Corriu reaction of homobenzyl alkyl ethers.

Overall, the results compiled in Schemes 3-14 summarize the state-of-the-art for the Kumada-Tamao-Corriu reactions of aryl, vinyl, benzyl and homobenzyl alkyl ethers with Grignard reagents via C(sp^2)– or C(sp^3)–O bond-cleavage. While impressive advances have been realized, there are still several challenges that need to be addressed: (1) the development of Kumada-Tamao-Corriu reactions of aryl or benzyl alkyl ethers with Grignard reagents that tolerates the presence of sensitive functional groups; (2) the design of cross-coupling reactions using unactivated alkyl ethers via C(sp^3)-O bond-cleavage; (3) the means to effect an asymmetric Kumada-Tamao-Corriu reaction of racemic alkyl ethers. Regardless of the challenges posed by these transformations, probably the most regrettable omission is the lack of *in depth* mechanistic aspects for the Ni-catalyzed Kumada-Tamao-Corriu reaction of alkyl ethers via the cleavage of C(sp^2)– and C(sp^3)–O bonds as well as a comprehensive description of computational methods for these processes. At present, the mechanisms from which these reactions operate, particularly when dealing with the activation of C(sp^2)–O(alkyl) bonds, are rather speculative. The current dogma for such reactions relies on the ability of low valent Ni species to promote a "classical" oxidative addition into a C(sp^2)–O(alkyl) bond followed by a transmetallation with the Grignard reagent and a final reductive elimination. However, the inherent reluctance of alkyl ethers to undergo oxidative addition together with the high activation energy required for C–O bond-cleavage and the low temperatures achieved in some cases indicate that other scenarios might come into play. In line with this notion, alternatives dealing with the non-innocent role of Lewis acidic Mg(II) centers and the involvement of putative Ni(0)-ate complexes cannot be ruled out.[20]

2.2 Negishi type Reactions

Based on the available literature data, chemists have reached the conclusion that Grignard reagents display a significantly higher catalytic reactivity than other organometallic species in the cross-coupling arena. This is probably due to the high polarization of the C–Mg bond and the high nucleophilicity of organomagnesium reagents, making them particularly useful for challenging substrate combinations.[3] However, the low chemoselectivity of Grignard reagents in the presence of sensitive functional groups inherently restricts the application profile of these methodologies. Prompted by these limitations and the challenge associated to the cleavage of C(sp^2)–O bonds in aryl methyl ethers, Wang and Uchiyama described a Ni-catalyzed cross-coupling reaction employing less basic and widely tolerant organozinc reagents (Scheme 15).[26] The authors observed a notable difference in reactivity depending on the organozinc reagent utilized. While commonly employed ArZnX or Ar_2Zn resulted in low conversions to products, a high reactivity was found with dianion-type organozincates $ArZnMe_3Li_2$ generated from Me_4ZnLi_2 (prepared upon exposure of $ZnCl_2$ to an excess of MeLi in THF/Et_2O) and differently substituted aryl iodides.[27] The acquired knowledge on the use of aryl alkyl ethers via C(sp^2)–O bond-cleavage suggested that π-extended aromatic frameworks would be particularly suited as coupling partners, an assumption that was corroborated when studying the substrate scope. While simpler anisole derivatives could not be employed, particularly activated substrate combinations provided the targeted coupling product, although in comparatively lower yields (Scheme 15, bottom right). Despite the apparent high reactivity of dianion zincate derivatives, the scope did not include the coupling of benzyl alkyl ether derivatives via C(sp^3)–OMe bond-cleavage.

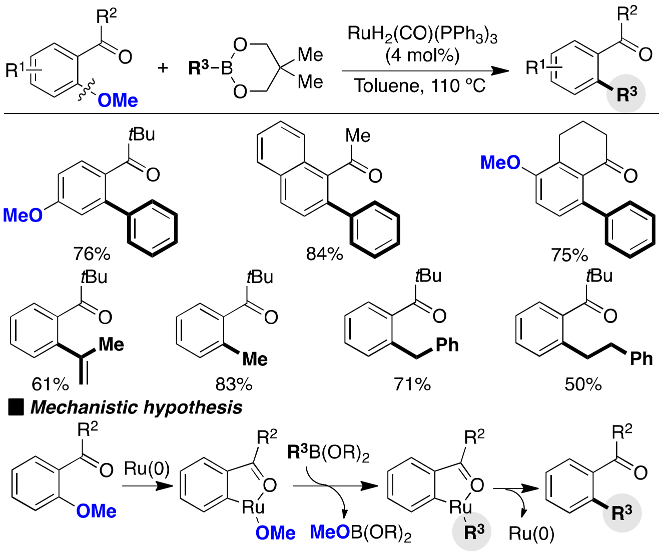


Scheme 15. Negishi cross-coupling reactions of aryl methyl ethers with dianion organozincate derivatives.

The means to conduct the C(sp^2)–OMe bond-cleavage at room temperature and the puzzling reactivity of dianion organozincate derivatives as compared with their arylzinc halide congeners could suggest a mechanistic scenario not consisting of a "classical" oxidative addition into the C–OMe bond. Unfortunately, no mechanistic studies have been reported for unravelling the intriguing dichotomy exerted by the dianion organometallic species; although speculative, the Lewis acidic character of the latter may play a decisive role within the catalytic cycle. Independently on whether the mechanistic scenario differs from the commonly accepted catalytic cycle for cross-coupling reactions, the methodology developed by Wang and Uchiyama[26] might pave the way for new perspectives when using less nucleophilic components for the utilization of aryl methyl ethers as coupling partners.

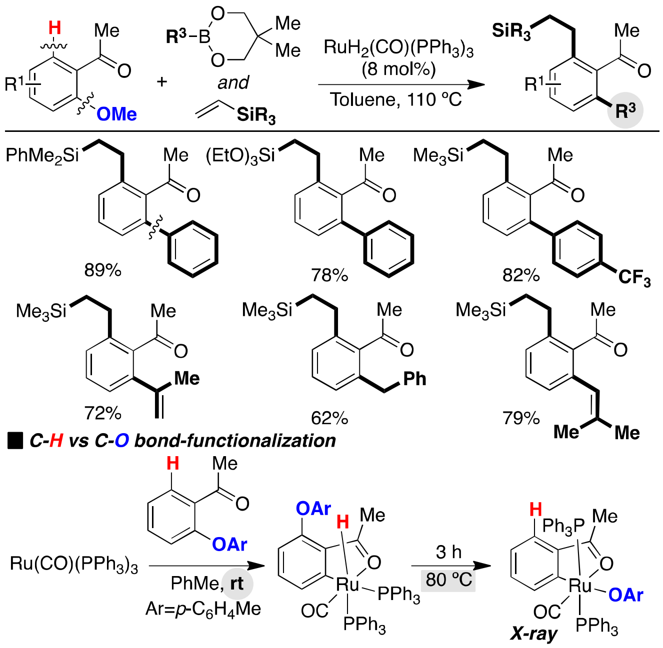
2.3 Suzuki-Miyaura type Reactions

There is little doubt that the Suzuki-Miyaura cross-coupling reaction has become arguably one of the methods of choice for building up the core of biaryl or polyaromatic frameworks.[28] Such perception is supported by the fact that these reactions have been rapidly embraced by chemical industry.[29] The attractiveness of the Suzuki-Miyaura reaction is primarily associated to the utilization of organoboranes as coupling partners. Among their advantages over organozincs or Grignard reagents are their commercial availability, thermal, moisture and air-stability of boronic acids and the ease of handling boron-containing residues.[30] Not surprisingly, Wenkert´s seminal discovery on the Kumada-Tamao-Corriu reaction of aryl methyl ethers[9] set the basis for implementing a Suzuki-Miyaura protocol. Kakiuchi, Chatani and Murai elegantly demonstrated the feasibility of such concept in a Ru-catalyzed Suzuki-Miyaura reaction of aryl methyl ethers with boronic esters by chelation assistance (Scheme 16).[31] Specifically, it was found that aromatic ketones located in *ortho* position uniquely assisted the cleavage of the corresponding C–OMe bond. Among the boronic esters utilized, it was found that neopentyl boronates reacted at a faster rate than commonly employed pinacol or ethylenglycol derivatives, suggesting an intimate interplay between structure and reactivity.



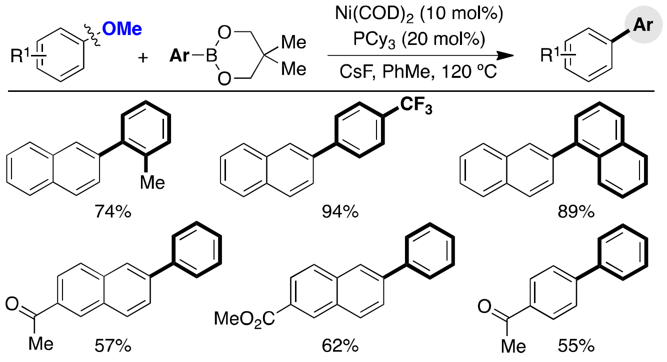
Scheme 16. Ru-catalyzed Suzuki-Miyaura reaction of aryl alkyl ethers with neopentyl boronates

As shown in Scheme 16, it was found that aryl, alkenyl and even alkyl boronates could be employed with equal efficiency, a notorious finding that illustrates the robustness of this Suzuki-Miyaura protocol. More interestingly, the authors found that the presence of alkyl ethers in *meta* or *para* position resulted in little conversion to products. These results indicated that the coordination of the carbonyl group to the Ru center is essential for the C–OMe bond-cleavage to occur. As a result, the authors suggested a mechanistic scenario that is in analogy with the related C-H functionalization protocol originally developed by Murai and co-workers (Scheme 16, bottom).[32] Subsequently, Kakiuchi and Chatani shed light into the mechanism highlighted in Scheme 16 by the successful isolation of the oxidative addition complex of an aryl C–O bond using low-valent ruthenium complexes and ketones as directing groups at the *ortho* position (Scheme 17, bottom right).[33] Interestingly, no Ru(II) metallacycle derived from the functionalization of *ortho* C-H bonds could be detected in the crude reaction mixtures. Careful monitoring of a stoichiometric reaction revealed a rather surprising finding regarding the relative reactivity of proximal C–H and C–O bonds. While C–H functionalization occurred rapidly at room temperature, C–O bond-cleavage took place at high temperatures (Scheme 17, bottom). These results indicated that the cleavage of C–O bonds operates under thermodynamic control. Such striking difference in reactivity was turned into a strategic advantage by performing a consecutive functionalization of both C–H and C–O bonds in the presence of suitable coupling partners (Scheme 17). Thus, the authors found that the reaction of aromatic ketones with vinylsilanes and boronic esters afforded polysubstituted benzene derivatives. As expected, alkylation took place exclusively at the C–H bond whereas the residue of the boronic ester was transferred preferentially to the C–O bond terminus.



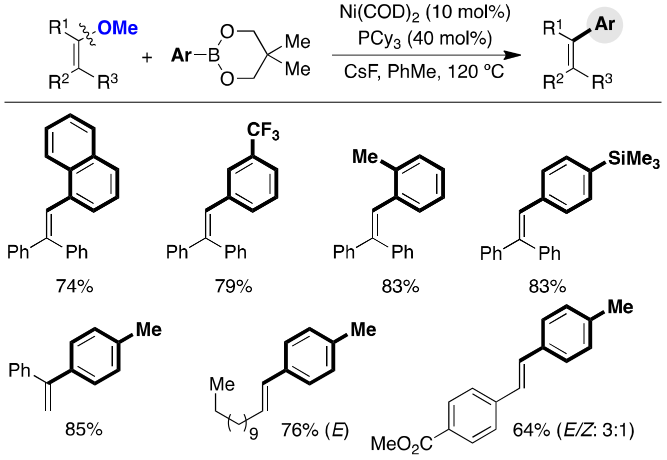
Scheme 17. Ru-catalyzed tandem alkylation/Suzuki-Miyaura reaction of aryl alkyl ethers and mechanistic studies.

Although by no doubt an impressive advance into the field of C–O bond-cleavage, the Ru-catalyzed Suzuki-Miyaura reaction of aryl methyl ethers was inherently restricted to the presence of suitable directing groups at the *ortho* position to the reactive site (Scheme 17).[31,33] In 2008, Chatani and Tobisu overcame such limitation by designing an elegant Ni-catalyzed Suzuki-Miyaura coupling reaction of aryl methyl ethers with organoboron reagents (Scheme 18).[34] Practicality and novelty aside, such a method offered new vistas for the utilization of aryl methyl ethers in cross-coupling reactions, a field that has largely been dominated by the employment of highly reactive and air-sensitive Grignard reagents. As for the previous Ru-based protocol,[31,33] the best results were accomplished with neopentyl boronates as coupling partners. In this case, however, the reaction required the presence of a base (CsF). Among the many interesting findings, it is worth noting that the ligand played a critical role for success, with electron-rich and bulky PCy_3 uniquely assisting the C–C bond-forming event. Unlike the Kumada-Tamao-Corriu reactions (see above), the nature of the aryl ether exerted a profound influence on reactivity, with primary alkyl ethers being ideal for their purposes. In analogy with other C–OMe bond-cleavage reactions, π-extended aromatics were found to be several orders of magnitude more reactive than regular anisole derivatives. The authors found, however, that the presence of electron-withdrawing groups in anisole derivatives could partially alleviate this complication. Although a mechanistic study was not performed, the authors favoured a pathway consisting of an oxidative addition of a C–OMe bond to Ni(0), transmetallation with the four-coordinate organoboron species and reductive elimination. The significantly higher reactivity of π-extended systems as compared to regular arenes was explained by an oxidative addition involving Meisenheimer-type or η^2-arene complexes.



Scheme 18. Ni-catalyzed Suzuki-Miyaura reaction of aryl methyl ethers with organoboranes.

On the basis of Wenkert´s seminal studies,[9] which established that vinyl ethers reacted at a faster rate than regular anisole derivatives, Chatani and co-workers envisioned an extension of their Suzuki-Miyaura reaction to vinyl ethers en route to styrene derivatives (Scheme 19).[35]



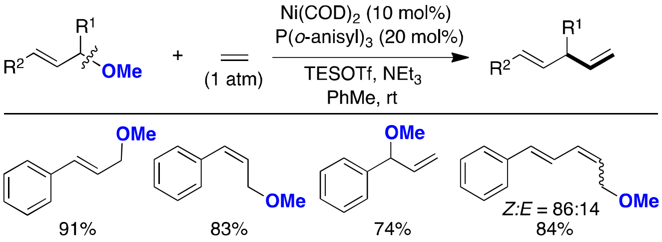
Scheme 19. Ni-catalyzed Suzuki-Miyaura reaction of vinyl methyl ethers with organoboranes.

In line with Wenkert´s results,[9] it was found that *Z*-configured vinyl ethers provided mixtures of E/Z-configured styrenes.[35] These results reinforced the notion that the diastereoselectivity of the double-bond geometry could be a thermal-dependent process; indeed, this turned out to be the case and *E*-selectivity was invariably obtained upon raising the temperature to 120 ºC. Interestingly, *Z*-configured styrenes could be obtained in *Z:E* ratios as high as 88:12 at 50 ºC, albeit in much lower yields. The scope of the reaction included several vinyl ethers and neopentyl boronates with different electronic and steric environments. As expected, it was found that π-extended systems containing a vinyl ether motif reacted preferentially on the vinyl terminus to give rise to styrene derivatives, thus illustrating the relative reactivity of methoxy groups located at vinylic and aromatic positions.

While the Ni-catalyzed Suzuki-Miyaura protocols from Chatani and co-workers represented an enormous step-forward towards the implementation of aryl methyl ethers as coupling partners using air/moisture-insensitive and nontoxic organoboranes,[34,35] there are still several issues to be addressed in these endeavours: (1) the substrate scope seems to be restricted to particularly activated aryl or vinyl methyl ethers via C(sp^2)–OMe bond-cleavage. Indeed, there is no indication on whether the cleavage of C(sp^3)–OMe might occur under these reaction conditions, a matter of great interest that would set the standards for the development of stereoselective transformations; (2) at present, only a rather specific class of organoboranes could be utilized (neopentyl aryl boronates). From an ideal point of view, alkyl boronates, particularly those bearing β-hydrogens as well as boronic acids or trifluoroborate salts would be employed in Suzuki-Miyaura protocols; (3) the mechanism from which the cleavage of the C(sp^2)–OMe still remains elusive. Although some hypotheses have been formulated, it would be necessary to perform *in depth* mechanistic experiments to fully demonstrate whether these reactions are truly initiated by oxidative addition or not. The high activation energy required for C–OMe bond-cleavage (approximately 101 Kcal/mol)[7] and the much lower reactivity of organoboranes as compared to Grignard reagents or organozinc derivatives[3] might suggest that other pathways, not yet conceived, might operate. We anticipate that an investigation combining computational tools with thorough structural studies by isolating putative reaction intermediates would shed light into the mechanism of these reactions. In view of the foregoing discussion, there is a general consensus that the prospective impact of such methodologies have not yet been reached and that spectacular results will be reported in the years to come.

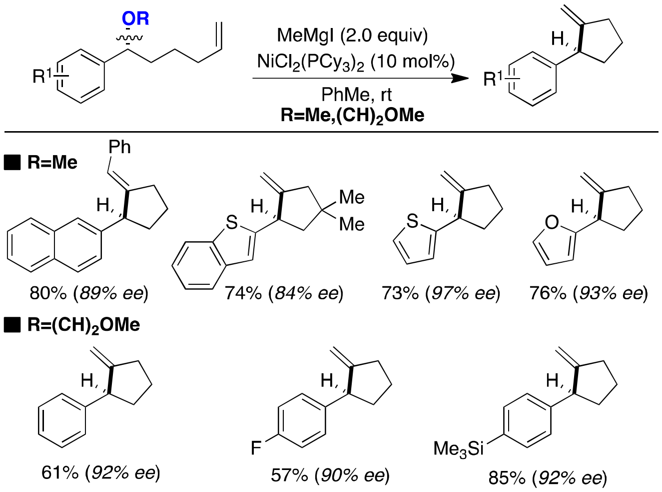
2.4 Mizoroki-Heck type Reactions

In the early 70´s, Mizoroki and Heck independently reported the Pd-catalyzed cross-coupling reaction of aryl iodides with styrenes in the presence of a suitable base to form substituted alkene derivatives.[36,37] In the last 40 years, this reaction has reached a remarkable level of sophistication, allowing for a multiple number of substrate combinations and even asymmetric transformations.[38] Unlike the Kumada-Tamao-Corriu, Negishi or Suzuki-Miyaura reaction, the Mizoroki-Heck reaction has the major advantage of not requiring a stoichiometric amount of organometallic complexes for effecting the desired C–C bond-forming event. Not surprisingly, this reaction found immediate application in industry as well as in the synthesis of molecules of utmost complexity.[38] Despite the advances realized, however, the Mizoroki-Heck reaction has primarily been driven by Pd catalysts and aryl halides or activated aryl sulfonates as substrates.[3] From an ideal point of view, the Mizoroki-Heck reaction should operate with cheaper metal catalysts and with more attractive counterparts such as alkyl ether derivatives. Unlike the corresponding cleavage of C(sp^2)–OMe bonds, the oxidative addition into activated C(sp^3)–OMe bonds in allyl or benzyl moieties is expected to be significantly faster than in aryl backbones due to the rapid formation of η^3-complexes via π-σ-π-equilibria.[3] Prompted by these precedents, the Jamison group reported an elegant Ni-catalyzed Mizoroki-Heck type reaction employing alkenes and allyl ethers, thus enabling the construction of skipped dienes that are highly ubiquitous in nature (Scheme 20).[39] The authors found that the inclusion of TESOTf was a contributory factor for success, probably by facilitating the formation of π-allyl Ni cationic species. The latter was further corroborated by the observation that both *Z*- and *E*-configured linear allyl methyl ethers provided the same coupling product (Scheme 20). A similar behaviour was observed when utilizing α-branched allyl methyl ethers. Among the many interesting results, the ability to use ethylene as coupling partner, an inexpensive chemical feedstock of great value in industry, is particularly noteworthy since classical Mizoroki-Heck reactions typically do not include the use of such alkene counterpart.[38] The use of alkenes other than ethylene allowed for obtaining predominantly 1,1-disubstituted olefins with a high selectivity profile;[39] in this case, however, allyl carbonates were used as substrates.



Scheme 20. Ni-catalyzed allylic substitution of allyl methyl ethers with ethylene.

Very recently, the Jarvo group has expanded the scope of Jamison´s work by designing a Ni-catalyzed stereospecific intramolecular Mizoroki-Heck reaction of secondary benzylic ethers en route to enantioenriched methylenecyclopentanes (Scheme 21).[40] As for other related C–OMe bond-cleavage reactions,[11,12,25,26,34,35] the authors found the best reactivity and selectivity when utilizing PCy_3 as the ligand. Quite intriguingly, stoichiometric amounts of MeMgI were utilized to recover back the active propagating Ni(0) species. Notably, while the addition of MeMgI to the benzyl ether residue was observed in traces amounts when using PCy_3 as the ligand, the corresponding Kumada-Tamao-Corriu reaction was formed preferentially with dppf, thus showing the subtleties of the catalytic system employed. The scope of the intramolecular Mizoroki-Heck reaction included the presence of heteroaromatics and different substitution patterns on the side chain. Interestingly, only products with inversion of configuration were found in all cases. Such observation is consistent with a mechanism initiated by an oxidative addition into the benzylic $C(sp^3)$–OMe bond with inversion of configuration. Although regular aryl groups gave lower yields, the inclusion of traceless directing groups on the benzyl alkyl ether allowed for obtaining the desired methylenecyclopentanes in good yields (Scheme 21, bottom). Unfortunately, the reaction seemed to be restricted to the construction of five-membered rings.

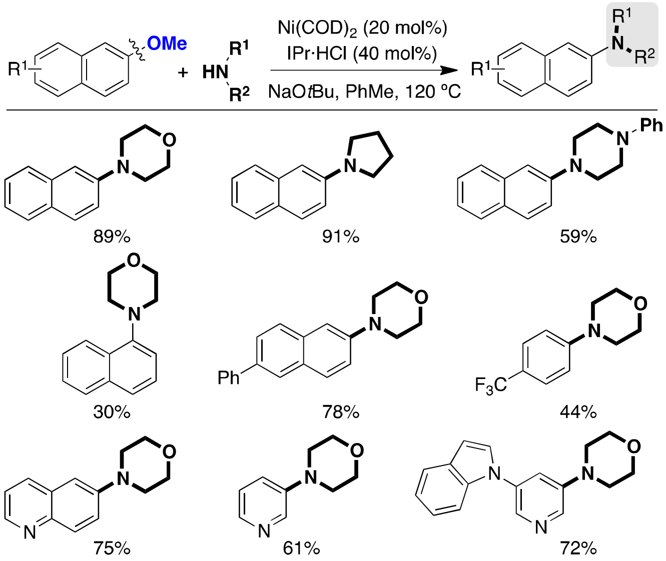


Scheme 21. Ni-catalyzed stereospecific intramolecular Mirozoki-Heck type reactions of secondary benzyl ethers.

Although the design of Mizoroki-Heck type reactions with benzyl alkyl ethers via C–O bond-cleavage is still at early stages of development, it is inevitable to predict a bright future in this particular area of expertise. Specifically, the means to conduct asymmetric catalytic transformations from racemic alkyl ethers, both in an intermolecular or intramolecular fashion, would be a particularly useful technique for our synthetic repertoire. Furthermore, the current developments in this area are restricted to the use of benzyl alkyl ethers, that are particularly activated towards oxidative addition into the $C(sp^3)$–OMe bond. In sharp contrast, the higher activation energy required for $C(sp^2)$–OMe in aryl methyl ethers[7] and the lack of driving force for obtaining the corresponding oxidative addition species constitute serious challenges to be overcome in Mizoroki-Heck type processes.

3. C-N Bond-Forming Reactions

The development of metal-catalyzed C–N bond-forming reactions has had a considerable impact on organic synthesis rapidly evolving as a routine and mature tool in both academic and pharmaceutical laboratories.[41] Indeed, these methods have been adapted in natural product synthesis, material science, biology and pharmaceuticals manufacturing.[42] The field of C–N bond-forming reactions has largely been dominated by the employment of Pd or Cu as catalysts, largely driven by the discovery of new classes of ligands capable of promoting particularly challenging substrate combinations.[43] Comparatively, the use of Ni catalysts in the C–N bond-forming arena has received much less attention, particularly when dealing with coupling partners other than aryl halides. As part of a program aimed at promoting the functionalization of C–O bonds, Chatani and Tobisu envisioned that a C–N bond-forming event could be conducted using aryl methyl ethers as coupling counterparts.[44] The challenges associated to such reaction are diverse: (1) C–N bond-forming reactions do not employ stoichiometric amounts of highly reactive organometallic species such as organozincs, organoboranes or Grignard reagents that typically overcome the high activation barrier for C(sp^2)–OMe bond-cleavage; (2) C–N bond-reductive elimination is considerably more challenging than the covalent C-C reductive elimination found in Kumada-Tamao-Corriu, Negishi or Suzuki-Miyaura protocols.[45] Despite these important drawbacks, Chatani and Tobisu found a Ni-catalyzed protocol based upon the use of NHC carbenes as ligands that was capable of promoting the amination of aryl methyl ethers (Scheme 22).[44] Although the means to effect a C–N bond-forming reaction via C(sp^2)–OMe bond-cleavage is certainly noteworthy, the substrate scope was limited to secondary amines and the utilization of strong NaO*t*Bu as base. As for the previously reported Suzuki-Miyaura protocols, the nature of the aryl methyl ether was critical for success, with π-extended aromatic systems consistently providing the best results. A remarkable exception was found when employing heteroaromatics as substrates, giving access to valuable heteroaryl amines in good yields.[46] Unfortunately, high catalysts loadings were required to effect the targeted transformation.



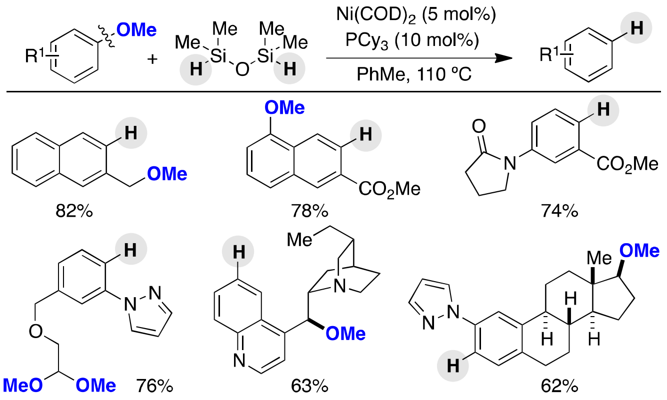
Scheme 22. Ni-catalyzed amination of aryl methyl ethers.

It is evident that the discovery of new knowledge in catalytic design will set the basis for the development of more practical, yet applicable, C–N bond-forming reactions using aryl methyl ethers as coupling counterparts. It is worth noting that Chatani´s amination protocol constitutes the only method currently available for promoting a C-heteroatom bond-forming reaction via C(sp^2)–OMe bond-cleavage. Although it will likely require a titanic effort to bring some light into such unexplored terrain, we have no doubt that it will begin to pay off in the near future.

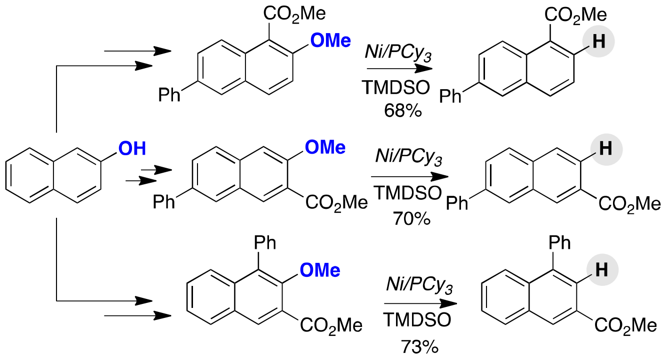
4. Reductive Cleavage Coupling Reactions

In recent years, the development of metal-catalyzed reductive coupling reactions has received a great deal of attention, representing a conceptual alternative to the well-established catalytic oxidative coupling processes.[47] Despite the knowledge acquired in reductive cleavage events, the means to utilize aryl methyl ethers via unconventional C(sp^2)–OMe bond-cleavage would constitute an excellent opportunity to design new reactivity within this field of expertise. The unique role of aryl methyl ethers as synthetic intermediates and for promoting the selective functionalization of aromatic backbones suggest that such motifs could be used as temporary protecting groups in organic synthesis if a reductive cleavage event would come into play.[48] If successful, such scenario would represent an alternative for the functionalization of simple arenes that typically suffer from regioselectivity and chemoselectivity issues in the absence of appropriate directing groups.[49]

In 2010, the Martin group reported a Ni-catalyzed reductive cleavage of aryl methyl ethers via C(sp^2)– and even C(sp^3)–OMe bond-cleavage using commercially available tetramethyldisiloxane (TMDSO) as reducing agent (Scheme 23).[50,8] By definition, such a method constitutes a synthetic alternative to the use of stoichiometric alkali metals or electrocatalytic hydrogenolysis, processes that are relatively expensive and difficult to scale up.[51,52] While the reductive cleavage of π-extended aromatic frameworks under Martin´s conditions invariably resulted in good yields of the corresponding arenes,[50] the use of much simpler anisoles was particularly cumbersome. Interestingly, it was found that the presence of a suitable *ortho*-directing group such as esters, pyrazoles, pyridines or oxazolines facilitated the C(sp^2)–OMe bond-cleavage. Based on competitive studies in which no reaction was observed when the directing group was located at *meta* or *para* position, the authors concluded that chelation assistance might be the responsible for the observed reactivity with anisole derivatives. Such observation could be turned into a strategic advantage when dealing with molecules bearing multiple C(sp^2)–OMe, thus leading to a complete site-selective strategy. Regardless of the substrates utilized, the reaction was found to be particularly chemoselective and a wide variety of functional groups and substitution patterns were perfectly accommodated. Interestingly, C(sp^2)–OMe bonds were selectively functionalized in the presence of a priori more reactive benzylic C(sp^3)–OMe bonds, giving credence to the notion that the reaction might involve a non-classical mechanistic pathway. The successful development of a catalytic reductive cleavage protocol of C(sp^2)–OMe bonds suggested that aryl methyl ethers could be employed in traceless directing group relay strategies.[48] In the same report,[50] the Martin group demonstrated the feasibility of such a process by designing a rapid synthesis of disubstituted regioisomeric arene derivatives from a common precursor by using the ability of aryl methyl ethers to act as directing groups (Scheme 24).

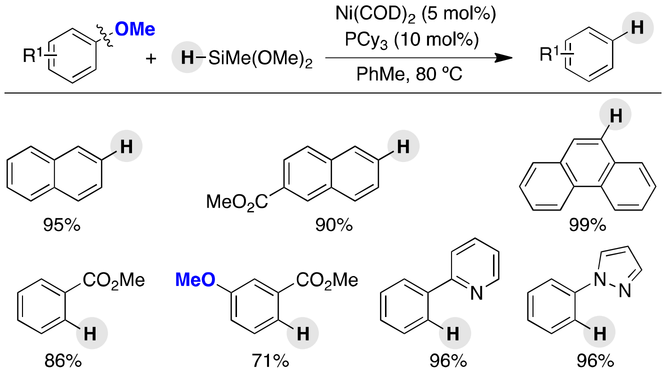


Scheme 23. Martin´s Ni-catalyzed reductive cleavage protocol of aryl methyl ethers.



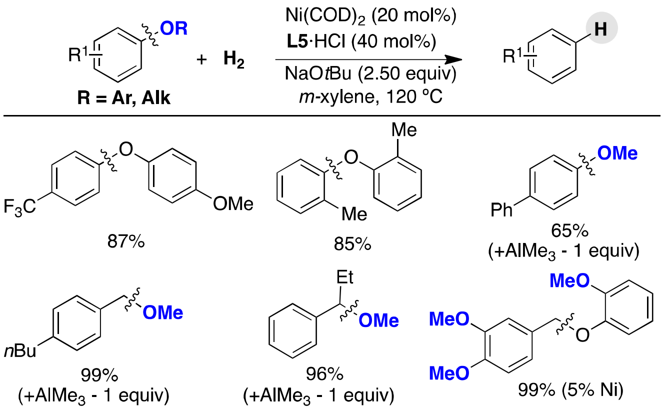
Scheme 24. Aryl methyl ether in traceless directing group relay strategies.

In 2011, Chatani independently reported a similar Ni-catalyzed reductive cleavage of $C(sp^2)$–OMe bonds utilizing a catalytic system based upon $Ni(COD)_2/PCy_3$ and $HSiMe(OMe)_2$ as reductant (Scheme 25).[53] Following the same reactivity pattern than Martin's method,[50] higher yields where obtained for fused aromatic motifs. Nonetheless, the inclusion of an *ortho*-directing group such as ester, pyridine or pyrazole was critical to effect the more challenging cleavage of $C(sp^2)$–OMe bonds in less-activated anisole derivatives. Interestingly, such a method could also be extended to the use of aryl pivaloates as coupling partners under otherwise identical reaction conditions.



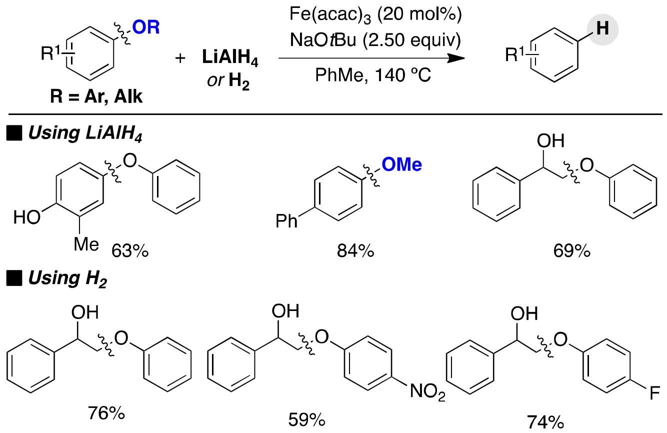
Scheme 25. Chatani´s Ni-catalyzed reductive cleavage protocol of aryl methyl ethers.

Shortly after Martin[50] and Chatani[53] reported their protocols on the reductive cleavage of $C(sp^2)$– and $C(sp^3)$–OMe bonds, a number of groups contributed to this area of expertise using different approaches, substrate combinations and/or reducing agents.[54,55] In mid 2011, Hartwig described a Ni-catalyzed hydrogenolysis of aryl ethers via $C(sp^2)$–O bond-cleavage using hydrogen as reductant.[56] Interestingly, the use of PCy_3, a ligand employed by both Martin[50] and Chatani,[53] resulted in non-negligible amounts of cyclohexane and cyclohexene deriving from PCy_3. These results suggested a different behaviour by simply changing silanes to hydrogen as reductants when attempting the cleavage of $C(sp^2)$–O bonds. After some experimentation, the authors found that Ni complexes derived from *N*-heterocyclic carbenes (NHC) and in the presence of an excess of NaO*t*Bu provided the desired reactivity for diaryl, aryl alkyl and benzyl aryl ethers. In some cases, it was found that the inclusion of Lewis acids such as $AlMe_3$ was critical to effect the cleavage of certain substrate combinations, particularly when dealing with the cleavage of C–O(alkyl) bonds. Importantly, the authors applied such hydrogenolysis event to lignin, probably one of the most stable biopolymers in nature, thus representing a new catalytic technique to conduct the depolymerisation of lignin en route to obtain aromatic scaffolds. Although mechanistic studies were not performed, it was speculated that hydrogen was the origin of the hydride source; recent elegant studies by the Agapie group, however, pointed towards a different pathway consisting of β-hydride elimination from the *in situ* generated oxidative addition species and suggesting that hydrogen was probably involved in the generation of the active Ni species.[57] In a further report, Hartwig presented a similar approach for the C–O cleavage of biaryl units using $Ni(COD)_2$ as catalyst.[58] In this case however, no phosphine was present in the system, thus concluding that the catalytic activity was due to *in situ* formed hetereogenous Ni(0) particles in the absence of the stabilizing phosphine.



Scheme 26. Hartwig´s Ni-catalyzed reductive cleavage of aryl or benzyl ethers.

In 2013, Wang reported a reductive cleavage of aryl ethers using catalytic amounts of $Fe(acac)_3$ (Scheme 27).[59] While the employment of Fe catalysts is certainly a considerable advance, the high temperatures and the need for stoichiometric amounts of $LiAlH_4$ and strong bases such as NaO*t*Bu represent an important drawback, particularly when dealing with sensitive functional backbones. It is worth noting, however, that this Fe-catalyzed method could be applied to molecules related to Lignin-type polymers by changing $LiAlH_4$ to H_2 under otherwise identical reaction conditions. Preliminary mechanistic studies suggested that the reactivity of this Fe-catalyzed process is due to the involvement of heterogeneous Fe catalysts. Such assumption was somewhat expected taking into consideration the catalyst utilized lacking any stabilizing ligand and the high temperatures required to effect the targeted transformation.



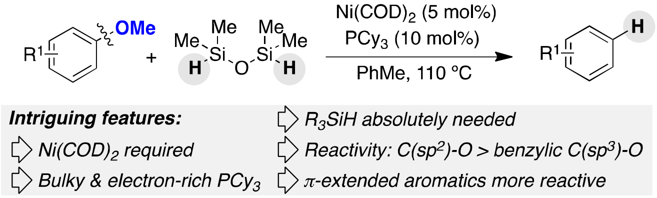
Scheme 27. Wang´s Ni-catalyzed reductive cleavage of aryl or benzyl ethers.

Undoubtedly, the recent developments in catalytic reductive cleavage have opened up new vistas in the field of C–O bond-functionalization.[8,47] The reasonably high temperatures required for effecting the targeted C–O bond-cleavage, however, invites the design of more powerful, yet practical, protocols that deal with such challenge. Although merely speculative, the fine-tuning of the ligand utilized might lead to the foundation of site-selectivity approaches in the presence of multiple C–O bonds that are either sterically or electronically-related. At present, the catalytic reductive cleavage of unactivated $C(sp^3)$–O bonds or the means to promote an asymmetric reductive event still constitute tremendous challenges that will certainly be addressed in the near future.

5. Mechanistic insights

In the past years, a plethora of studies showcasing the ability of transition metals to insert into the C–OMe have been reported.[60] In this regard, Milstein,[61] Goldman[62] Goldberg[63] and Agapie,[57] among others, demonstrated the possibility of undergoing oxidative addition into a C–OMe bond with Rh, Ir, Ni or Pd salts. Nevertheless, all these studies are focused on the use of well-defined pincer-type complexes which in many cases are catalytically not competent due to its extraordinary stability.[60] Despite such formidable advances in the area of C–O bond-cleavage little knowledge has been gathered regarding the mechanism from which homogeneous metal complexes are capable of promoting the catalytic functionalization of aryl ethers in an intermolecular fashion. Unlike benzyl electrophiles that are particularly activated towards oxidative addition by forming the rather stable η^3-benzyl metal species, the lack of a driving force for effecting the related $C(sp^2)$–O bond-cleavage in aryl ethers makes the oxidative addition particularly challenging. Based on literature precedents using pincer-type complexes, oxidative addition has invariably been invoked for virtually all aryl $C(sp^2)$–O bond-cleavage reported to date, even though no supporting evidence for such step has been verified by in depth mechanistic studies. Indeed, the high energy required for C–O bond cleavage in aryl ethers and the reluctance of alkyl ethers to act as leaving groups leaves reasonable doubts about the ability of metal complexes to undergo “classical” oxidative addition. Not surprisingly, the understanding behind the cleavage of aryl $C(sp^2)$–O bonds without chelating assistance still remains unravelled.

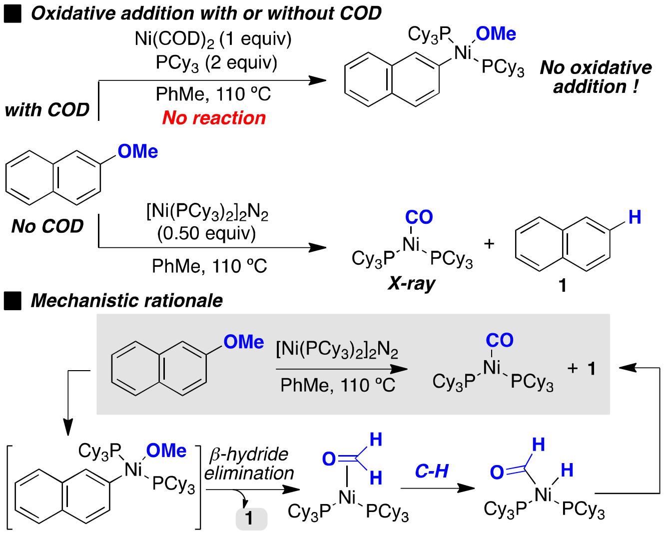
In 2013, the Martin group reported an *in depth* mechanistic study that shed light into the mechanism from which the catalytic reductive cleavage of $C(sp^2)$–OMe bonds operates when using Ni catalysts and without the need for chelating assistance.[64] The motivation was primarily associated by the intriguing features found in this reaction (Scheme 28): (1) no catalysts other that $Ni(COD)_2$ could be employed; (2) bulky and electron-rich PCy_3 was required;[65] (3) $C(sp^2)$–OMe bonds were selectively cleaved in the presence of *a priori* more reactive benzylic $C(sp^3)$–OMe bonds and (3) π-extended aromatic frameworks were considerably more reactive than regular anisole derivatives, an issue already observed in virtually all catalytic reactions dealing with the activation of C–OMe bonds. Not surprisingly, the authors expected that a complete understanding would be far from being trivial due to the fact that monodentate trialkylphosphines are prone to ligand dissociation and the lack of driving force for preparing metal complexes as compared to pincer or bidentate backbones.[60]



Scheme 28. Key features of Ni-catalyzed reductive cleavage of C-OMe bonds with TMDSO.

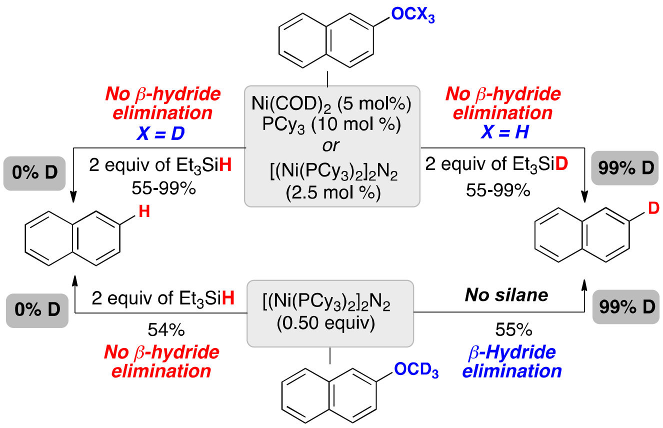
In their mechanistic study,[64] Martin and co-workers demonstrated, both experimentally and by theoretical calculations, that “classical” oxidative addition into the C–OMe bond by $Ni(COD)_2/PCy_3$ does not take place, at least at temperatures up to 110 ºC (Scheme 29, top). Such finding, although controversial, suggested that a different mechanism must operate for catalytic $C(sp^2)$–OMe bond-cleavage, a matter of great significance as it challenges the perception that all these reactions are initiated by oxidative addition. Strikingly, the authors found a different reaction outcome in the absence of COD. Thus, the stoichiometric reaction of 2-methoxy naphthalene with Ni(0) complexes containing PCy_3 such as

$[Ni(PCy_3)_2]_2N_2$ resulted in $Ni(PCy_3)_2CO$ and naphthalene (Scheme 29, top), suggesting that the hydride transfer might not require the use of silanes. In analogy with recent studies using pincer-type complexes,[57] the authors explained such result by a sequence consisting of oxidative addition into the $C(sp^2)$–OMe bond followed by β-hydride elimination, C–H functionalization and H_2 extrusion (Scheme 29, bottom).



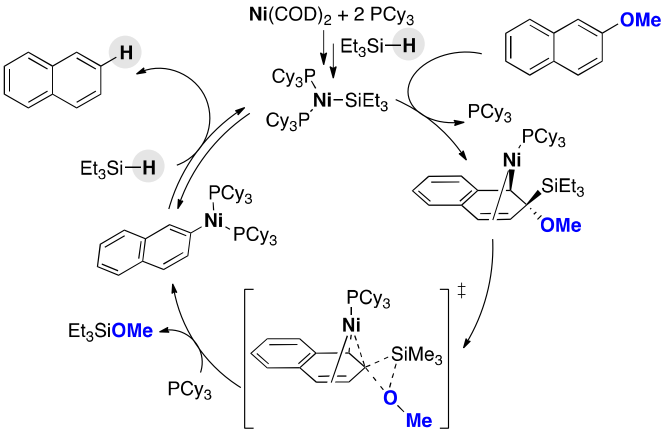
Scheme 29. Study of the oxidative addition of $C(sp^2)$-OMe bonds to low valent Ni(0) complexes.

Interestingly, a related sequence was observed for aryl ethyl ethers en route to $Ni(PCy_3)_2(MeCHO)$, in which an ethanal molecule is coordinated to the Ni(0) center in a η^2-fashion.[64,66] These results indicated that a β-hydride elimination pathway could not be ruled out and questioned whether silanes would be needed or not. Isotope-labelling studies revealed the intriguing dichotomy exerted by the presence or absence of silanes in a both stoichiometric and catalytic fashion. As shown in Scheme 30, the authors unambiguously demonstrated that, if silanes are present in the reaction media, these species provide the hydride sources responsible for the reductive cleavage event; in the absence of silane, however, the reaction could only be conducted stoichiometrically via β-hydride elimination since the in situ generated $Ni(PCy_3)_2CO$ was not catalytically active (Scheme 30, bottom right).



Scheme 30. Isotope-labelling studies.

Based on kinetic and computational studies, the authors concluded that paramagnetic Ni(I) species might play a crucial role in this particular catalytic system.[64] Such observation was further confirmed by *in situ* monitoring using common NMR and EPR spectroscopical techniques. Specifically, the authors favoured an innovative mechanistic scenario based upon the intermediacy of Ni(I)–SiR_3 species (Scheme 31).[67] The proposed redox-neutral mechanism consisted of an initial migratory insertion followed by a [1,2]-shift with concomitant release of R_3SiOMe and a final σ-bond-metathesis that recovers back the active Ni(I)–SiR_3 species.



Scheme 31. Mechanistic proposal for the Ni-catalyzed reductive cleavage of $C(sp^2)$-OMe bonds with silanes.

In light of Martin´s mechanistic studies,[64] it is evident that the cleavage of aryl ethers might occur along different pathways depending on the catalyst of choice. Although such mechanistic study was focused on a rather specific reaction of aryl ethers, it is worth noting that the authors demonstrated that “classical” oxidative addition cannot occur if $Ni(COD)_2$ and tricyclohexylphosphine are utilized. These results reasonably leave some doubt about the proposed mechanisms for C–O cleavage in aryl ethers under a Kumada-Corriu, Negishi or Suzuki-Miyaura regime. Certainly, more mechanistic studies are expected in the near future to shed light into the nature of the C–O bond-cleavage. We have little doubt that such studies will lead to new chemical knowledge and will set the basis for future developments in this area, establishing aryl ethers as viable and powerful alternatives to organic halides in the cross-coupling arena.[68]

5. Summary and Outlook

Metal-catalyzed cross-coupling reactions have evolved from mere curiosities to mature tools in organic synthesis. Although tremendous progress has been achieved in the last years, this field of expertise has largely been dominated by the use of organic halides as counterparts. Sometimes chemists have the perception that we have all the methods that we need to build up molecular complexity and that the search for alternatives is unjustified. However, such a vision cannot be further from the truth and chemists have been challenged to face imperishable myths in organic synthesis, to discover new chemical knowledge and to devise unconventional synthetic strategies, thus improving our ever-growing synthetic repertoire.

In recent years, excellent contributions in the area of cross-coupling reactions have held great promise to utilize C–O electrophiles as alternatives to aryl halides. At present, however, most of the literature data is primarily focused on the coupling of particularly *activated* aryl sulfonates or aryl ester derivatives via C–O cleavage. While no doubt a step-forward, the generation of large amount of waste and the need for derivatization of the starting phenol in these reactions constitute important drawbacks to be overcome both from an atom- and step-economical point of view. As for many other cases, the future has a way of arriving unannounced. Driven by a seminal discovery of Wenkert in the late 70`s, chemists have popularized in recent years the means to utilize simple and available aryl ethers as organic halide surrogates in the cross-coupling arena. Such progress has allowed the Kumada-Corriu, Negishi, Mizoroki-Heck or even the Suzuki-Miyaura reaction to be applied in this field of expertise, reaching high levels of sophistication that were unconceivable some years ago. Recent advances via C–N bond-forming reactions or reductive cleavage events has shown that the use of aryl ethers is beyond the formation of C–C bonds, thus illustrating the prospective impact of these methodologies at the Community.

Undoubtedly, Wenkert´s discovery provided a technological push for the development of new knowledge in C–O bond-cleavage reactions. Unfortunately, the vast majority of the methods recently reported using aryl ethers as counterparts are entirely based upon empirical discoveries and the mechanism from which these reactions operate still remains rather elusive and speculative. Prompted by the perception that science must have originated in the feeling that something was wrong, some isolated mechanistic reports are starting to shed some light into this area by showing how metal complexes are capable of undergoing the cleavage of aryl ethers in certain substrate combinations. We have little doubt that the understanding of the mechanisms on a fundamental level will in turn lay the foundation for future aspects of this chemistry. In order to face such challenge, a combined effort from both theoretical and methodological chemists will be required.

History has demonstrated that the most successful chemists encountered unimaginable obstacles before they triumphed and that there are no invincible projects. The new generation of chemists are encouraged to believe that scepticism is indeed a virtue, that curiosity is a driver for innovation, and to think imaginatively instead of using traditional or preconceived ideas in order to seek new chemical knowledge in the C–O bond-cleavage arena. We speculate that such discipline is in the midst of a transition to a much broader role with impact in many different areas of research. Most certainly, the future in this field cannot be a simple extrapolation of past developments and we believe that spectacular developments will be likely arising in this vibrant and intellectually rewarding area of expertise.

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