Recent developments in nickel–catalyzed cross-coupling reactions via C–O functionalization
Nous avenços en reaccions d'acoblament creuat catalitzades per níquel mitjançant la funcionalització d'enllaços C–O

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Abstract: The use of phenol and carboxylic acid derivatives as electrophiles in nickel–catalyzed cross-coupling reactions has undergone exponential growth in the last two decades, becoming a powerful synthetic tool for forging C–C and C–heteroatom bonds. This review summarizes the most recent developments in the utilization of non–particularly activated C–O electrophiles such as carbamates, pivalates, methyl ethers and aryl methyl esters.

Keywords: Cross-coupling reactions, nickel catalysis, C–O bond cleavage.

Resum: L'ús de derivats del fenol i d'àcids carboxílics com a electròfils en reaccions d'acoblament creuat catalitzades per níquel ha experimentat un creixement exponencial en les últimes dues dècades, i s'ha convertit en una eina sintètica important per a forjar enllaços C–C i C–heteroàtom. Aquest treball recopila els desenvolupaments més recents en la utilització d'electròfils C–O particularment no activats, com els carbamats, els pivalats, els metil èters i els aril metil èsters.

Paraules clau: Reaccions d'acoblament creuat, catàlisi mitjançant níquel, trencament d'enllaços C–O.

Introduction

Metal-catalyzed cross-coupling reactions are one of the cornerstones of modern organic chemistry for rapidly and reliably building up molecular complexity by forging new C–C and C–heteroatom bonds. As judged by the wealth of data in literature since the seminal work of Kumada, Tamao and Corriu [1], this area of expertise has revolutionized the way chemists assemble complex molecules, reaching remarkable levels of sophistication that would, *a priori*, have otherwise been difficult to achieve. Indeed, the impact of these protocols was recognized with the 2010 Nobel Prize in Chemistry to Heck, Negishi and Suzuki for their contributions to Pd-catalyzed cross-coupling reactions [2].

While organic halides have traditionally been the electrophiles of choice in the cross-coupling arena, their toxicity and the inevitable halide waste generated in these processes prompted chemists to find more environmentally-friendly and cost-effective alternatives. Among these, C–O electrophiles have gained considerable momentum as organic halide surrogates in cross-coupling reactions due to the prevalence of alcohols in nature, pharmaceuticals, agrochemicals and material science. The first disclosure on the utilization of C–O electrophiles in cross-coupling reactions can be traced back to the seminal work of Wenkert in 1979, demonstrating that simple aryl or vinyl methyl ethers can be employed as counterparts in Ni-catalyzed Kumada-Tamao-Corriu reactions [3]. While such technology tacitly showed the potential applicability that not only C–O electrophiles or nickel catalysts might have in synthetic organic endeavors, it is worth noting that Wenkert's discovery was disclosed simultaneously with Suzuki and Miyaura's work on the Pd-catalyzed cross-coupling of aryl boron reagents with aryl/vinyl halides [4]. The popularity of the latter and the establishment of Pd as the catalyst of choice in the cross-coupling arena were probably the reasons why Wenkert's findings were overlooked and why the utilization of simple aryl ethers as C–O electrophiles remained dormant for nearly 25 years.

Among all phenol derivatives, aryl sulfonates are known to possess the lowest activation barrier for C–O bond-cleavage, even comparable to the functionalization of C–halide bonds when utilizing aryl halide counterparts [5]. However, the

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atom-economy of the reaction, and the generation of stochio-metric amounts of sulfur-containing byproducts prompted the discovery of new C−O counterparts with improved flexibility and modularity. These factors culminated in the development of a series of metal-catalyzed cross-coupling reactions of less-activated and more atom-economical alternatives such as aryl carbamates, aryl esters and aryl methyl ethers. Unlike their sulfonate counterparts, it is worth noting that these C−O alternatives offer the possibility of using these building blocks as *temporary* directing groups, thus allowing the establishment of orthogonal cross-coupling techniques with improved flexibility when building up molecular complexity from simple precursors. In 1992, Snieckus reported the first Ni-catalyzed cross-coupling of aryl carbamates with Grignard reagents [6]. Subsequently, Danwardt revisited Wenkert's work on the activation of aryl ethers and extended the scope to anisole derivatives [7]. Following up the interest for C−O electrophiles, Garg and Shi reported independently in 2008 the utilization of aryl pivalates as coupling partners in Suzuki-Miyaura-type reactions [8, 9].

In addition to the utilization of phenol derivatives as C−O electrophiles, it is worth noting that recent years have witnessed the employment of carboxylic acid derivatives as powerful alternatives in the C−O functionalization arena. As for the corresponding phenols, the attractiveness of these protocols is based on the ubiquity of carboxylic acids and their prevalence in a myriad of natural products and biologically-relevant molecules, making them particularly attractive as precursors to forge C−C and C−heteroatom bonds. Indeed, recent advances have showed that not only aryl phenyl esters [10] but also more atom-economical aryl methyl esters can be employed as coupling partners by carefully adjusting the reaction conditions, thus enabling the establishment of de-carbonylative transformations of the utmost synthetic relevance as alternatives to commonly employed organic halides or phenol derivatives [11].

A close inspection of the data in literature reveals that elegant authoritative reviews on the utilization of C−O electrophiles in the cross-coupling arena have already been presented in recent years [12]. The purpose of this account is to focus on the most significant and recent developments in nickel catalyzed cross-coupling reactions of less-activated C−O electrophiles since 2016, leaving aside the utilization of more activated aryl sulfonate or aryl phenyl ester counterparts.

Phenol derivatives

Aryl carbamates

C−C bond-forming reactions

Although a myriad of elegant Ni-catalyzed cross-coupling reactions of aryl carbamates have been described in the literature, the vast majority of these remain confined to particularly activated π-extended substrates [13]. In 2017, Wang and Uchiyama carried out a systematic study of organoaluminium-mediated cross-coupling reactions via functionalization of C−O, C−N and C−F bonds (figure 1, top) [14]. Notably, the method was found to be broadly applicable to non-π-extended phenol derivatives, including the utilization of organoaluminium reagents bearing electron-withdrawing groups or sterically-demanding precursors. Unfortunately, the authors did not include a mechanistic proposal that explained the results observed.
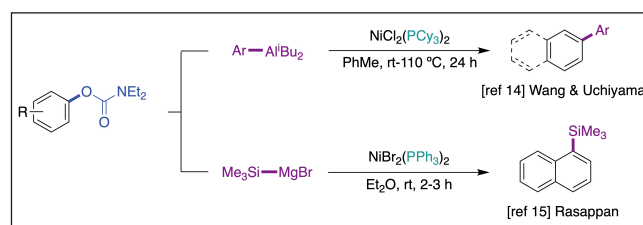

FIGURE 1.   Ni-catalyzed cross-coupling reactions of aryl carbamates. Source: Prepared by the authors.

C−heteroatom bond-forming reactions

While borylation and amination protocols were described prior to 2016 [13c, 13d], three years later Rasappan reported the catalytic silylation of aryl carbamates with silylmagnesium reagents (figure 1, bottom) [15]. The protocol operates under mild reaction conditions using inexpensive, bench-stable $NiBr_2(PPh_3)_2$ in Et_2O at room temperature. Interestingly, good yields were achieved when conducting the reaction at large scale with only 1 mol% catalyst loading. Both electron-rich and electron-deficient groups on carbamates were compatible and aryl, alkenyl and benzyl carbamates could be coupled with equal ease. Notably, the authors performed preliminary mechanistic studies, which supported a mechanistic pathway consisting of in situ formation of $Ni(0)L_n$ species that undergo a canonical catalytic cycle based on oxidative addition, transmetallation and reductive elimination pathways.

Aryl pivalates

C–C bond-forming reactions

The construction of biaryl motifs via nickel-catalyzed cross-coupling of aryl pivalates with aryl zinc reagents was first reported by Shi and co-workers in 2008 [16]. However, it was not until a decade later when Rueping described an analogous transformation with alkylzinc reagents (figure 2, top) [10c]. Interestingly, the authors were able to perform the selective functionalization of phenyl carboxylic acids, either via decarbonylative pathways or C–O bond cleavage. Unfortunately, however, no mechanistic investigations were performed to delineate the intrinsic features of these transformations.

Inspired by the work of Uemura [17] and Martin [18] on the Pd-catalyzed coupling of aryl halides with tert-cyclobutanols, Liu and co-workers have recently described the means to forge γ-arylated ketones by Ni-catalyzed cross-coupling of aryl pivalates with tert-cyclobutanols under mild reaction conditions (50-80 °C) (figure 2, bottom) [19]. Unlike most of C(sp²)–OPiv functionalization strategies, the utilization of bidentate phosphine ligands (such as dcype, dppb or dppf) was ineffective in promoting the desired transformation [20, 21]. Although the relatively more challenging anisole derivatives proved to be effective as coupling partners in this transformation, the presence of acetyl groups or ortho substituents resulted in lower yields. Unfortunately, the authors did not perform mechanistic studies to unravel the intricacies of the transformation. Still, a similar pathway was proposed to that shown by Uemura [17], based on an initial oxidative addition of the C–O electrophile to Ni(0)L$_n$, followed by ligand exchange, setting the stage for β-carbon elimination and final reductive elimination.
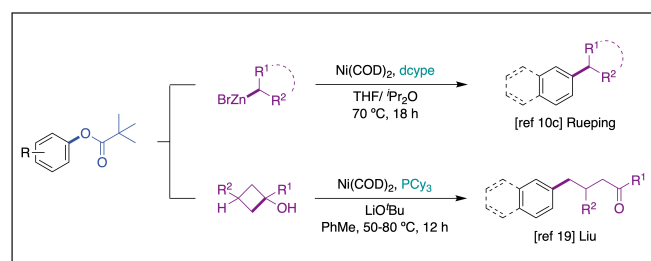
C–heteroatom bond-forming reactions

Although catalytic amination protocols via C–O bond-cleavage were already described prior to 2016 [22], these protocols were predominantly restricted to the formation of secondary and tertiary amines. Aiming at overcoming these limitations, Rueping and co-workers reported a broadly general Ni-catalyzed amination protocol with aryl pivalates (figure 3, top) [23], phenyl esters and amides as starting materials, the latter via decarbonylative pathways [10a]. Although fairly similar conditions were used in both methods, lower temperatures were needed when using pivalates, suggesting that C–O scission is probably easier than that of the corresponding phenyl ester and amide counterparts. Unfortunately, the scope of the reaction when utilizing aryl pivalates remained confined to particularly activated π-extended systems. In addition, no mechanistic investigations were conducted, leaving a reasonable doubt as to how the reaction proceeded at the molecular level.

Aiming at increasing the repertoire of C–O functionalization reactions, Martin and co-workers reported a catalytic stannylation reaction of aryl esters and SnBu$_3$SiMe$_3$ reagents (figure 3, middle) [24]. Interestingly, this methodology converts electrophilic aryl esters into nucleophilic organotin reagents, which can be further functionalized via C–Sn cleavage in a similar way to that shown previously by the same group when forging otherwise related silylation reagents via C–O cleavage [25]. Notably, non-π-extended arenes or heterocyclic moieties could also be employed as substrates. It is worth noting that the authors showed that the oxidative addition complex I (figure 3, middle) arising from reaction of the aryl pivalate to Ni(0)L$_n$ [26] turned out to be catalytically competent as a

FIGURE 2. Ni-catalyzed C–C bond-forming cross-coupling reactions of aryl pivalates. Source: Prepared by the authors.
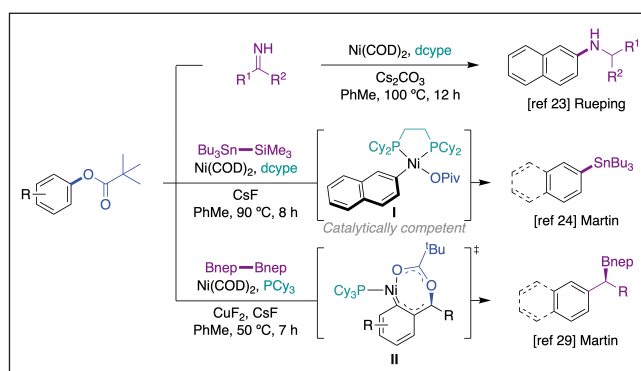

FIGURE 3. Ni-catalyzed C–heteroatom bond-forming cross-coupling reactions of aryl pivalates. Source: Prepared by the authors.

reaction intermediate, thus suggesting a classical catalytic cycle consisting of a transmetallation mediated by fluoride source followed by reductive elimination to forge the targeted C−C bond while releasing the propagating Ni(0)L$_n$ species.

A considerable step-forward in the C−O functionalization arena was the ability to extend these protocols to stereospecific transformations, allowing the transfer of the inherent chirality of the substrates into the targeted products without the need to use particularly expensive chiral ligands [12f]. The first stereospecific C−C bond-forming reaction using nickel catalysis and benzyl pivalates was independently described by both Jarvo [27] and Watson [28] in 2013. However, it was not until 2017 when Martin and co-workers reported a Ni-catalyzed stereospecific C−heteroatom bond-forming protocol for generating organoboronic esters from the corresponding benzyl pivalates (figure 3, bottom) [29]. Although the reaction was limited to π-extended systems and ortho substituents could not be accommodated, the reaction was equally effective regardless of whether electron-rich or electron-poor arenes were utilized. Unlike other stereospecific protocols, the reaction proceeded with retention of configuration, an observation that suggests the intervention of an S$_N$2'-type oxidative addition that generates a putative π-benzyl nickel(II) intermediate II (figure 3, bottom).

As described in this section, there is ample consensus that C(sp^2)−O bond activation might occur via oxidative addition of the C−O linkage to Ni(0)L$_n$. However, experimental evidence for such a seemingly innocent pathway with monodentate phosphine ligands was altogether absent in the literature. In 2018, Gómez-Bengoa, Burés and Martin reported a combined experimental and computational study on the C−O silylation of aryl esters, where the role of an unorthodox dinickel oxidative addition complexes III (figure 4) in C−O cleavage was demonstrated for the first time [30]. Aiming at highlighting the importance of the dimetallic species in the C−O cleavage of aryl esters, the authors studied in detail the Ni/Cu-catalyzed silylation previously reported by the same group (figure 4, top) [25]. Spectroscopic data, stochiometric experiments and kinetic studies provided a detailed picture of dinickel complexes as off-cycle reservoirs of the active mononickel oxidative addition complex via disproportionation.

Following up on their interest in shedding light on C−O bond-cleavage at the molecular level, early this year Martin
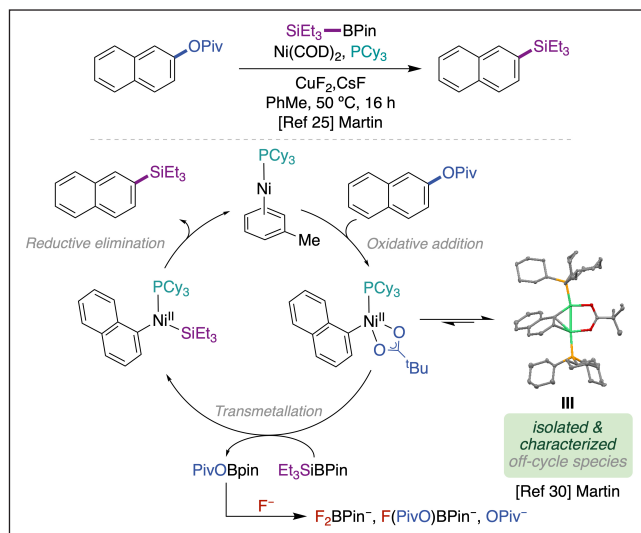
FIGURE 4. Mechanistic studies on the C−O silylation of aryl esters. Source: Prepared by the authors.

and co-workers reported a detailed investigation on how Ni catalysts enable sp^2−sp^2 bond-formation between aryl esters and arylzinc species (figure 5) [16, 31]. The authors started by demonstrating the long-presumed on-cycle oxidative addition of non-π-extended aryl ester to Ni(0) complexes bearing monodentate phosphines. These species can undergo decomposition forming off-cycle Ni(I) species via disproportionation pathways or via direct comproportionation (figure 5, bottom). Of special interest was the unraveling of the influence of the Zn(II) salts on the catalytic turnover, since they are frequently employed as additives in Ni-catalyzed cross-coupling reactions. In this regard, the authors gathered evidence that Zn salts facilitate decomposition by enabling non-desirable redox processes and ligand sequestering events. On the other hand, transmetallation of well-defined Ni(II) complexes was confirmed to be facilitated by [(PCy$_3$)Zn(Cl)(Ph)]$_2$. Finally, the
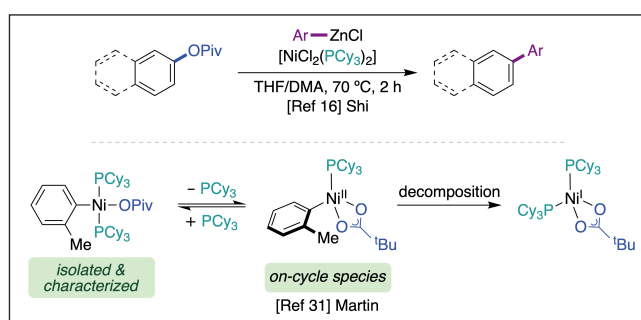
FIGURE 5. Mechanistic studies of the C−O Negishi cross-coupling reaction of aryl esters. Source: Prepared by the authors.

influence of the amide solvents was evaluated, concluding that the formation of $(DMA)ZnCl_2$ or $(PCy_3)Ni(DMA)$ adducts prevents decomposition. Interestingly, pyridine provides a similar behavior by restoring the catalytic activity when performing the catalysis in THF.

Reductive cross-coupling reactions

Prompted by a disclosure described independently by Martin, Chatani and Tobisu [32, 33], Han and co-workers reported a Ni-catalyzed reduction of aryl pivalates by using sodium formate as reductant (figure 6) [34]. Interestingly, the catalyst loading can be lowered down to 0.5 mol% without a noticeable decrease in yield. Moreover, functional groups that were not tolerated in previous methods (*e.g.*, carbonyls, nitriles, sulfides, fluorides or carbonyl groups) could all now be well accommodated [32, 33, 35]. As shown previously by Martin [24], the authors demonstrated that the aryl-Ni(II) oxidative addition complex **I** (figure 6, bottom) was competent as a reaction intermediate. In addition, isotope-labelling experiments confirmed sodium formate as a hydrogen source. Although no further mechanistic studies were performed to determine if the reaction proceeds through a Ni(0)/Ni(I) [36] or Ni(0)/Ni(II) couple, the authors favored a pathway consisting of an oxidative addition, ligand exchange with sodium formate, subsequent decarboxylation to form the nickel-hydride species, and a final reductive elimination.
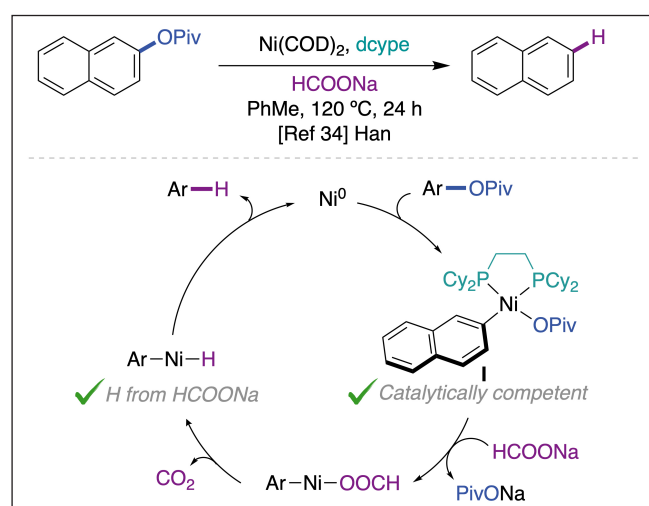

FIGURE 6. Ni-catalyzed reductive cross-coupling reaction of aryl pivalates and the corresponding mechanistic proposal. Source: Prepared by the authors.

Aryl methyl ethers

C–C bond-forming reactions

While notable developments of Kumada-Tamao-Corriu reactions using ethereal substrates with both N-heterocyclic carbenes (NHCs) and trialkylphosphine ligands have already been described in the literature [37], the utilization of carbodicarbenes (CDCs) has facilitated unique transformations previously inaccessible with related NHCs ligands [38]. Specifically, Ong and co-workers reported the utility of CDC ligands in Ni-catalyzed Kumada-Corriu reactions under exceptionally mild reaction conditions (figure 7, top) [39]. A variety of aromatic substrates featuring a broad range of electron-neutral, donating or withdrawing groups could be accommodated with equal ease. Competition experiments between naphthalene and anisole derivatives showed high selectivity for the former, indicating that π-extended backbones play a non-negligible role in reactivity. This observation is certainly not surprising given the superior reactivity of π-extended systems over regular arenes in related C–O bond-functionalization reactions [36a, 37a, 40]. Although the authors propose a transition state that shows the critical role exerted by the Lewis acidity of Mg(II) cations (**IV**) (figure 8, top), the intermediacy of Ph-Ni(II)-OMe species **V** is in sharp contrast to the reports by Uchiyama [41] and Martin [36] that suggested that the latter undergoes competitive rapid β-hydride elimination at room temperature (figure 8, bottom).

Driven by the low chemoselectivity profile of Grignard reagents, a considerable effort has been devoted to find alternate organometallic coupling partners for forging C–C bonds in the C–O bond-functionalization arena with improved gen-
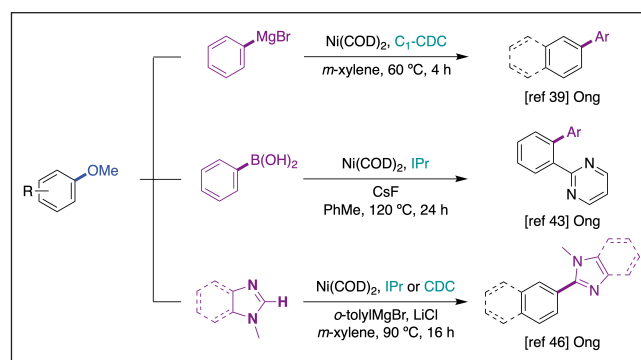

FIGURE 7. Ni-catalyzed C–C bond-forming cross-coupling reactions of aryl methyl ethers. Source: Prepared by the authors.
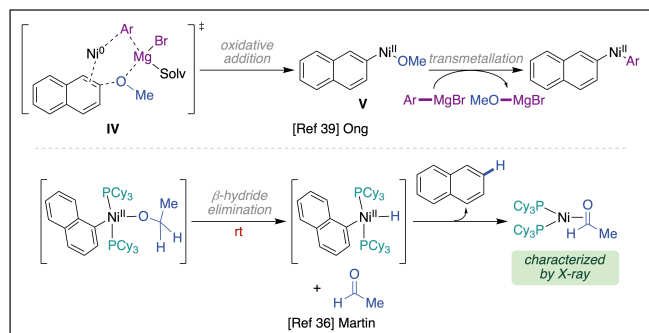
Figure 8. Mechanistic proposal of the reactivity of Ph–Ni(II)–OMe species. Source: Prepared by the authors.

erality, modularity and chemoselectivity profile. To this end, Tobisu and Chatani reported an elegant nickel-catalyzed Suzuki-Miyaura coupling of aryl methyl ethers with sterically bulky organoboron reagents (B_2nep_2) [42]. As for a myriad of C–OMe bond-functionalization reactions, however, the method was primarily restricted to π-extended aromatics. Subsequently, Ong and co-workers reported a directing group strategy to facilitate the activation of more challenging C–O linkages with regular arene derivatives by using both NHC and CDC ligands (figure 7, middle) [43]. In analogy with Chatani and Tobisu's work [42, 44], the authors propose that the energy barrier for C–OMe cleavage can be lowered by interaction of CsF and the corresponding aryl boronic esters with the in situ generated Ni(II) intermediates.

While the means to enable cross-coupling reactions of aryl methyl ethers with well-defined organometallic reagents provided a considerable push in chemical innovation, the use of the latter constituted an inherent limitation to the exploration of the full potential of these technologies in the scientific community. Prompted by this observation, chemists were challenged to merge the activation of C–OMe bonds with the ability to trigger C–H functionalization. Although considerable progress was made with related aryl pivalates [45] and aryl carbamates [13g] as C–O electrophiles, it was not until 2018 when Ong reported the first strategy using aryl methyl ethers as coupling partners (figure 7, bottom) [46]. The protocol demonstrates the viability of conducting a cross-coupling reaction of aryl methyl ethers and heteroarene derivatives based on a tandem strategy using Ni(COD)$_2$/IPr and o-tolylMgBr. Although the incorporation of the latter lowered the functional group tolerance, the scope included π-extended backbones as well as regular anisole derivatives. Preliminary mechanistic studies suggested that Grignard reagents

assisted the C–O bond activation via the Lewis acidity of Mg(II) whereas sterically-demanding RMgBr reagents were critical to avoid Kumada-Corriu type side-reactions. In this case, the authors did not require the use of Cs$_2$CO$_3$ as an additive to aid in the formation of the Ni–C bond through the formation of a Cs$^+$ cluster, as proposed by Itami, Musaev and co-workers [45b].

C–heteroatom formation

Despite the significant progress in the C–OMe functionalization arena when forging C–C bonds [37,39-46], it is somewhat intriguing that C–heteroatom bond-forming reactions have found comparatively little echo. The first efforts towards this goal involved elegant studies describing the ability to enable borylation [47] or amination [48] protocols via C–OMe bond-cleavage. It is worth noting, however, that these techniques require particularly electron-rich, yet expensive, phosphine or NHC ligands at considerable high temperatures. Driven by these precedents, Martin and co-workers described a ligand-free C–Si bond formation via Ni-catalyzed C(sp^2)–OMe cleavage that operated at room temperature with silylborane reagents (figure 9, top) [49]. In contrast to prior reports, this protocol could be extended to non-π-extended systems or arenes lacking activating groups in the vicinity. In addition, the coupling of benzyl methyl ethers posed no problems. Interestingly, mono or bis-silylation could be enabled by carefully adjusting the stoichiometry of the reaction. The authors propose that the reaction proceeds via ate complex **VI** (figure 9, top) where the non-coordinating escorting potassium counterion facilitates binding of the OMe motif, thus facilitating a formal nucleophilic aromatic substitution at the C–OMe linkage [50].
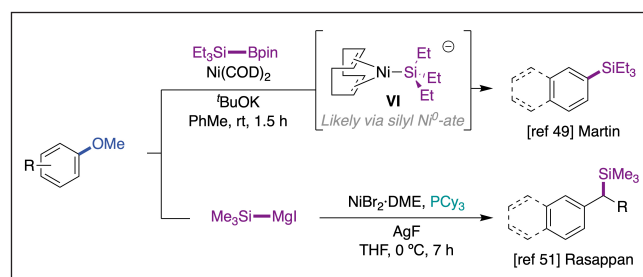

Figure 9. Ni-catalyzed C–heteroatom bond-forming cross-coupling reactions of aryl methyl ethers. Source: Prepared by the authors.

Early this year, Rasappan extended the methodology by promoting a silylation of benzylic C(sp^3)–OMe bonds using Me$_3$SiMgI instead of the above-mentioned silylborane (figure 9, bottom) [51]. Interestingly, while Ni(COD)$_2$ completely shut down the reactivity, NiBr$_2$·glyme and NiBr$_2$·diglyme provided the best results when using AgF in THF at 0 °C. Moreover, the strategy could be extended to an enantiospecific silylation with inversion of stereochemistry using enantiopure benzyl alcohol derivatives. Likewise, benzylic C(sp^3)–OMe bonds were significantly more reactive than their corresponding C(sp^2)–OMe motifs, an observation already made by Martin in 2010 on enabling a formal hydrogenolysis reaction [32]. Unfortunately, however, no in-depth mechanistic studies were performed to unravel the role that AgF might play in the reaction outcome.

Reductive cross-coupling reactions

As previously mentioned, the catalytic reductive cleavage of C–O bonds in phenol derivatives has received significant attention in recent years. In this regard, Martin [32], Chatani [33] and Hartwig [35] made important advances towards this end. However, π-extended systems were considerably more reactive than their simple arene congeners, thus constituting a limitation for further developments. In 2018, Chatani and Tobisu extended the methodology to simple anisole derivatives using diisopropylamino boranes as reducing agents (figure 10) [52], showing that such a system outperformed previously developed protocols aimed to achieve the same goal. Although high temperatures were still required to activate anisole derivatives, biphenyl compounds could be reductively cleaved under milder conditions (180 vs. 100 °C). The authors noticed, however, that an excess of the boron source was needed for the reaction to occur, as parasitic borylation of the solvent
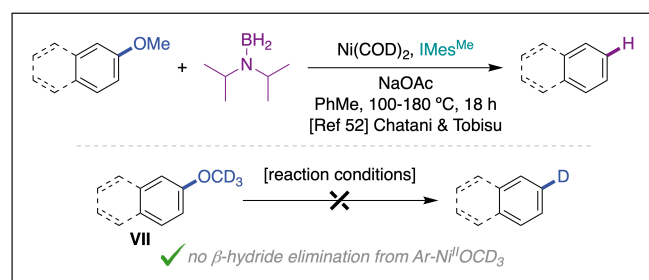
was observed in the crude reaction mixtures. Several experiments to unravel the origin of the hydride source were performed by the authors: (1) the use of the isotopically-labelled ArOCD$_3$ **VII** resulted in no deuterium incorporation into the arene, tacitly suggesting that a pathway consisting of β-hydride elimination from in situ generated Ar-Ni(II)OCD$_3$ was not coming into play (figure 10, bottom); (2) intriguingly, significant deuterium incorporation into all arene C–H bonds was found when utilizing either labelled aminoborane, toluene-d_8 or dioxane-d_8. Putting all the pieces together, it was not evident how the reaction operates at the molecular level; however, there is little doubt that this contribution might offer new avenues in the years to come, from both the methodological and mechanistic standpoints.

Carboxylic acid derivatives – aryl methyl esters

Non-decarbonylative reactions

C–heteroatom bond-forming reactions

In 2016, Garg and co-workers [53] reported the first example of the utilization of aryl methyl esters (ArCO$_2$Me) as C–O electrophiles, culminating in the development of a catalytic amidation with aniline derivatives based on a Ni(COD)$_2$/SIPr regime (figure 11, top). Although π-extended systems were considerably more reactive than their regular arene congeners, it is worth noting that the reaction could take place at considerably lower temperatures than those observed previously in related C–O functionalization reactions. This can be explained by the use of stoichiometric Al(O^{t}Bu)$_3$ as a media-

FIGURE 10. Ni-catalyzed reductive cross-coupling reaction of aryl methyl ethers. Source: Prepared by the authors.
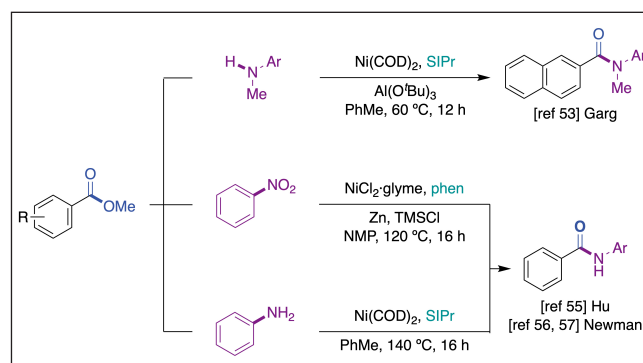

FIGURE 11. Non-decarbonylative Ni-catalyzed C–heteroatom bond-forming cross-coupling reactions of aryl methyl esters. Source: Prepared by the authors.

tor, which affects both the kinetics and the thermodynamics of the reaction [54]. Computational studies supported a mechanistic pathway consisting of an oxidative addition, ligand exchange and reductive elimination (figure 12, left). Moreover, decarbonylation was found to be less favored from the corresponding acyl-Ni(II) intermediates.

Subsequently, Hu and co-workers [55] reported an alternative protocol for the conversion of $ArCO_2Me$ into anilides employing nitroarenes as coupling partners (figure 11, middle). The use of nitroarenes is not only more step-economical than anilines but also improves the functional group compatibility in the presence of alkyl halides or carbonyl groups that could be susceptible to activation under optimized reaction conditions. Primary alkyl esters showed greater reactivity than the corresponding secondary alkyl analogues, an observation that is consistent with steric considerations. The authors proposed a mechanistic picture that differs from that proposed by Garg [53], where an azobenzene is generated in situ by the presence of a strongly reductive medium. These species presumably react with Ni(0) to form a Ni(II) nitrene intermediate, which reacts via a yet unknown pathway en route to a Ni(II) amidate complex, which is then reduced by Zn to give a zinc amidate and regenerate the Ni(0) catalyst (figure 12, right). One year later, Newman reported a complementary protocol for the catalytic amidation of aryl methyl esters [56] that operates in the absence of stochiometric activating agents, allowing the coupling of a wide range of nucleophilic coupling partners and heterocycle motifs, even in the presence of particularly sensitive functional groups (figure 11, bottom). Subsequently, the authors reported a related contribution that made use of commercially available and air-stable IPr·HCl as the ligand. Even so, the reaction required the utilization of air-sensitive Ni(COD)$_2$ and high reaction temperatures [57].

C–C bond-forming reactions

In 2019, Newman described the development of a Ni-catalyzed domino Heck-type reaction with aryl methyl esters (figure 13, top and middle) [58]. Inspired by the work of Garg [59] and Stanley [60], the authors proposed that in situ generated acyl-Ni(II) intermediate **VIII** (figure 14, left) could be trapped intramolecularly by a tethered allyl fragment and sequential intermolecular transmetallation with an organoboron nucleophile or by a β-hydride elimination pathway. Specifically, it was found that the Ni-catalyzed Heck/Suzuki-Miyaura coupling could be enabled by Ni(COD)$_2$/SIPr and a mixture of CsF/KF in THF at 80 °C, whereas the Mizoroki-Heck reaction was achieved by Ni(COD)$_2$/ SIPr·HCl with ^{t}BuOK and K$_3$PO$_4$ in toluene at 100 °C for 16 h, and by using 1-phenylethanol as hydride source. The authors support a pathway consisting of an oxidative addition to the C(acyl)–O bond to form a Ni(II) intermediate followed by migratory insertion of the tethered olefin, ultimately triggering a transmetallation and/or reductive elimination to deliver the targeted products.

Early this year, Newman described the development of a Ni-catalyzed Suzuki-Miyaura cross-coupling of aryl methyl esters en route to phenyl ketone derivatives (figure 13, bottom) [61]. Intriguingly, an unusual NHC ligand with remote steric bulk was required for the reaction to occur. As expected, the steric bulk at the ester backbone had a non-negligible impact on reactivity. In any case, the transformation was characterized by its generality across a wide range of substrates bearing different electronic and steric environments. Interestingly, aryl boronic acids could not be employed as substrates whereas a considerable drop in yield was observed by subtle
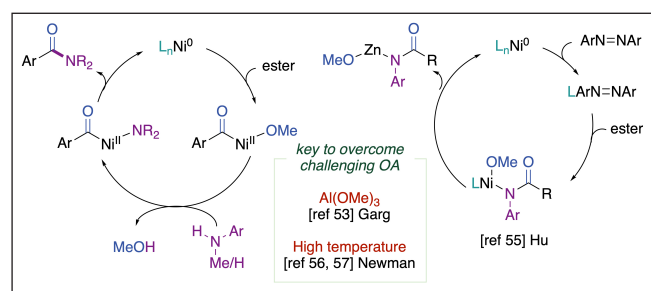
FIGURE 12. Mechanistic proposals of non–decarbonylative Ni–catalyzed C–heteroatom bond–forming cross–coupling reactions of aryl methyl esters. Source: Prepared by the authors.
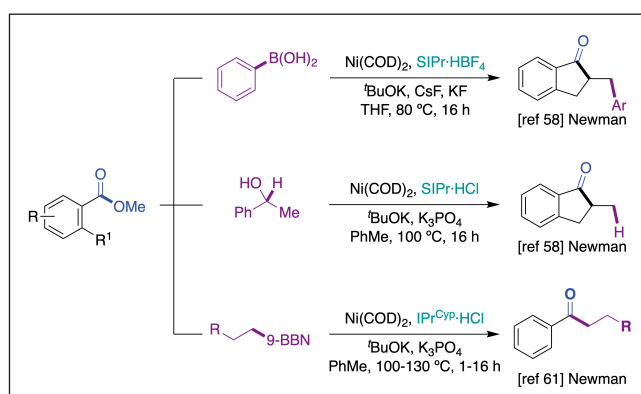
FIGURE 13. Non–decarbonylative Ni–catalyzed C–C bond–forming cross–coupling reactions of aryl methyl esters. Source: Prepared by the authors.

modification of the boronic acid, specifically the absence of aromatic rings within its structure. This observation was supported by theoretical calculations, suggesting the involvement of non-covalent interactions between the catalyst and substrate (figure 14, right). Importantly, the authors showed that the technology could be used in the presence of groups that are a priori amenable to activation with Ni catalysts, suggesting that orthogonal protocols might come into play with a judicious choice of the reaction conditions. Moreover, site-selectivity could be accomplished for substrates possessing electronically-differentiated esters, with particularly electron-poor substrates showing superior reactivity.
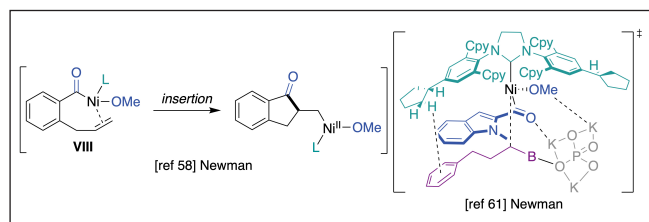

FIGURE 14. Key intermediates in non–decarbonylative Ni–catalyzed C–C bond–forming cross–coupling reactions of aryl methyl esters. Source: Prepared by the authors.

Decarbonylative reactions

C–heteroatom bond-forming reactions

Prompted by a catalytic stannylation reported by Martin when using aryl pivalates as C–O electrophiles and $Me_3SiSnBu_3$ [24], Rueping described an otherwise analogue reaction with the same silylstannyl reagent by using aryl methyl esters instead, resulting in a decarbonylative stannylation that operated at high temperatures (figure 15, top) [62]. Interestingly, a subtle change in both the Ni catalyst and the base employed allowed for the coupling of aryl esters with different steric environments. Unfortunately, the authors did not include a mechanistic proposal that explained the results observed.

C–C bond-forming reactions

In 2018, Yamaguchi described the development of a Ni-catalyzed methylation of aromatic esters by using dimethylaluminium chloride as both nucleophilic partner and Lewis acid to activate the targeted C–O bond (figure 15, middle) [63]. Not only phenyl- but also alkyl-substituted aryl esters could be used as coupling partners, albeit the technology relied pri-
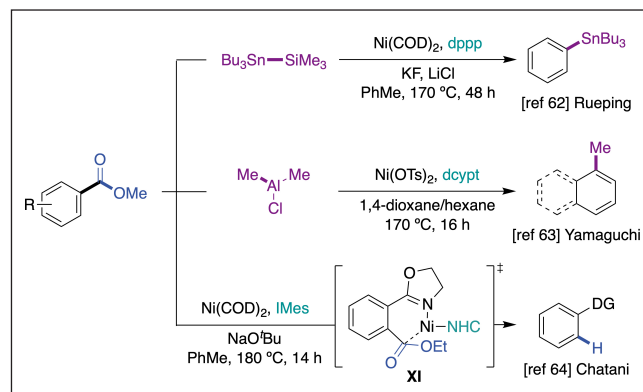

FIGURE 15. Decarbonylative Ni–catalyzed cross–coupling reactions of aryl methyl esters. Source: Prepared by the authors.

marily on the utilization of π-extended systems. As for Rueping's protocol [62], high temperatures (170 °C) and bidentate ligands (dcypt or dppp) were required for the reaction to occur; indeed, the utilization of monodentate PCy_3 and NHC ligands significantly decreased the yield of the reaction. While the activation of methyl esters required the presence of aluminium reagents, this was not the case when employing phenyl esters. Unfortunately, the authors did not include a mechanistic proposal of this rather appealing transformation, but one might tentatively anticipate that both transformations occur via a "classical" Ni(0)/Ni(II) mechanistic scenario consisting of oxidative addition, CO extrusion, transmetallation and reductive elimination.

Reductive cross-coupling reactions

In 2019, Chatani reported the nickel-catalyzed reductive defunctionalization of esters in the absence of an external reductant using the $Ni(COD)_2$/IMes couple in toluene at 180 °C (figure 15, bottom) [64]. While excellent yields were obtained for esters bearing OMe, OEt, OBu or O^iPr groups, lower results were consistently obtained for sterically encumbered ^tBu analogues. As for other cross-coupling reactions of C–O electrophiles, the present ortho N-heteroaromatic rings or carbonyl groups could be employed as directing groups to facilitate oxidative addition into the C–O bond (see IX, figure 15), thus setting the stage for triggering a decarbonylation, β-hydride elimination and reductive elimination. Preliminary mechanistic studies suggested an irreversible C–O cleavage and/or decarbonylation, whereas reversibility was proposed for the β-hydride elimination step.

Conclusions

Despite the seminal work reported by Wenkert in 1979 on the nickel-catalyzed cross-coupling of aryl and vinyl ethers with Grignard reagents, the cross-coupling arena had largely been focused on the use of organic halides as electrophilic counterparts. However, in recent years chemists have shown that simple and readily available phenol and aryl carboxylic acid derivatives can be used for similar purposes, representing a worthwhile endeavor for chemical invention. Unfortunately, however, these reactions are still in their infancy compared with the impressive preparative profile of cross-coupling reactions with organic halides. In addition, it is worth noting that little knowledge has been gathered regarding the mechanism by which these reactions operate. Isolated mechanistic studies have revealed that the functionalization of C–O bonds might follow a different rationale from that shown for organic halides, populating pathways a priori beyond reach in the latter while offering new dogmas at molecular level for designing future endeavors. It is consequently reasonable to predict a bright future for the coming years in the C–O functionalization arena, not only by expanding the range of cross-coupling partners that can be utilized in these processes, but also by understanding the mechanistic intricacies of these rather appealing transformations.

Acknowledgments

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