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## Phenol Derivatives: Modern Electrophiles in Cross-Coupling Reactions

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### Abstract

In recent years, C–O electrophiles have emerged as powerful alternatives to organic halides, common counterparts in metal-catalyzed cross-coupling reactions. Among their advantages are their low toxicity, ready availability, the natural abundance of phenols and their pivotal role as synthons in organic synthesis, which makes them particularly attractive vehicles for further functionalization. This review summarizes the most important developments in cross-coupling reactions via catalytic C–O bond activation of particularly unreactive aryl esters, carbamates and aryl ethers, providing a general overview of the current state of the art and including mechanistic implications as well as future aspects, when appropriate.

### Keywords

phenol derivatives, C-O bond cleavage, nickel, homogeneous catalysis, alcohols, ethers, esters, carbamates

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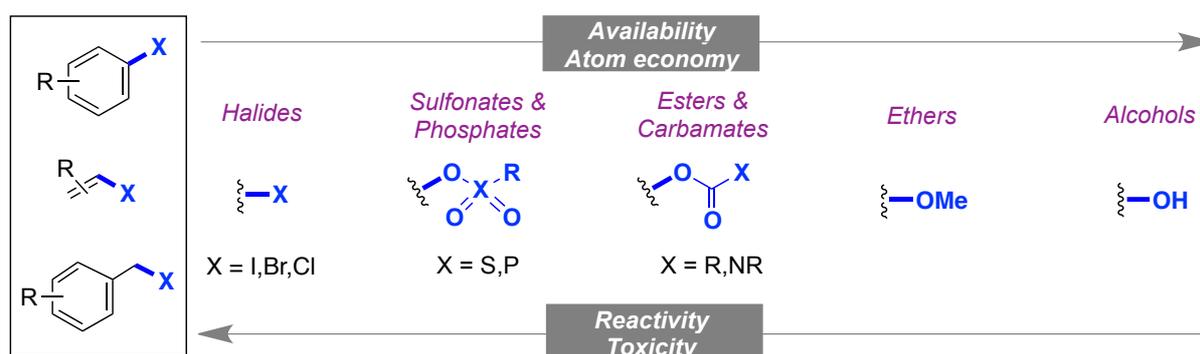
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Acknowledgments

## 1. Introduction

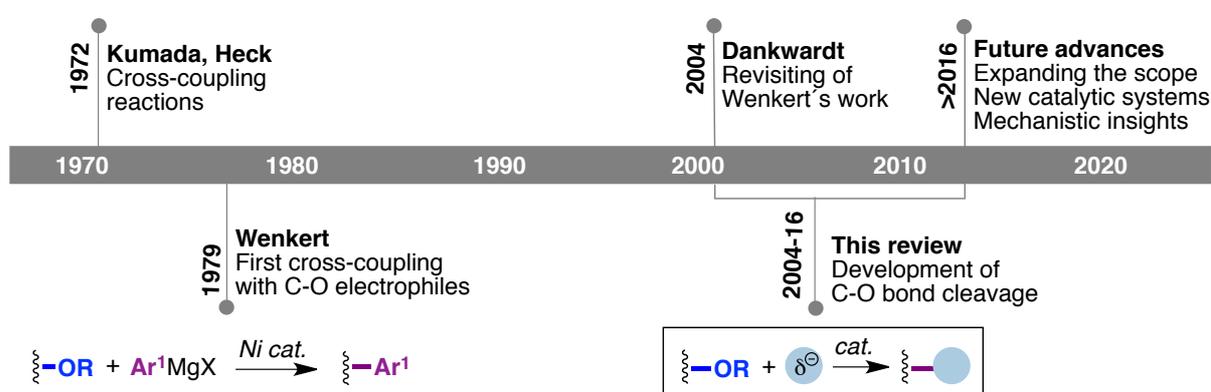
Metal-catalyzed cross-coupling reactions have evolved from mere curiosities to mature and indispensable tools in our synthetic arsenal.<sup>1</sup> The tremendous impact of these methodologies is illustrated by the fact that it is rather difficult to find an advanced total synthesis that does not take recourse to this methodology. Not surprisingly, these techniques have found widespread use in both pharmaceutical and academic laboratories. Although remarkable levels of sophistication have been reached, the vast majority of these processes are still conducted with organic halide counterparts. The difficulties encountered in accessing organic halides in a both chemo- and regioselective manner, particularly in advanced synthetic intermediates, together with the inevitable generation of toxic halogenated waste still constitute serious drawbacks when designing cross-coupling reactions, particularly for late-stage diversification. To this end, chemists have embarked on a quest to find alternate cross-coupling counterparts with improved flexibility, generality and practicality. Among these alternatives, phenol derivatives are particularly appealing as these are naturally abundant, non-toxic, readily available, and unique reaction intermediates in organic synthesis.<sup>2</sup> Additionally, their implementation in cross-coupling reactions would be particularly attractive for the design of orthogonal cross-coupling strategies in the presence of organic halides.



**Scheme 1.** C–O electrophiles in cross-coupling reactions

The means to utilize C–O electrophiles has undoubtedly gained considerable momentum, and these compounds have emerged as powerful and environmentally friendly coupling partners in the cross-coupling arena.<sup>3</sup> Despite the obvious advantages posed by the use of phenol derivatives, the vast majority of catalytic C–O functionalization reactions are based on particularly activated phenol derivatives possessing rather weak C–O bonds such as aryl

tosylates, triflates, mesylates or nonaflates (Scheme 1). Ironically, the success of these reactions has contributed to the perception that phenol derivatives with high bond-dissociation energies, such as aryl esters, carbamates or aryl ethers, could not be employed as coupling partners via C–O bond cleavage (Scheme 1). In 1979, Wenkert discovered that catalytic Kumada-Tamao-Corriu (KTC) reactions could be applied to aryl methyl ethers via counterintuitive C(sp<sup>2</sup>)–OMe cleavage (Scheme 2).<sup>4</sup> Although no doubt an incredible step forward, this reactivity remained dormant for 25 years, probably due to the success of Pd-catalyzed Suzuki-Miyaura, Negishi and Stille-type cross-coupling reactions.<sup>1</sup> Fortunately, inspiration is oftentimes in the eye of the beholder, and Dankwardt revisited Wenkert's work in 2004 by discovering that electron-rich ligands are particularly suited to catalytic C–O bond cleavage scenarios (Scheme 2).<sup>5</sup>



**Scheme 2.** Evolution of the metal-catalyzed functionalization of C–O bonds

As judged by the wealth of literature data reported in the last 10 years, it is evident that significant advances have been realized in the C–O functionalization of aryl ethers, as well as aryl esters or aryl carbamates that could result in site-selectivity issues in the presence of multiple C–O reaction sites.<sup>3</sup> Taking into consideration that the catalytic functionalization of relatively unreactive C–O bonds is still relatively unexplored terrain, we identified the need to review the current state of the art for the utilization of aryl esters, carbamates and aryl ethers as surrogates for organic halides in *homogeneous* cross-coupling reactions. Therefore, the utilization of particularly activated allyl, propargyl, allenyl derivatives, or phenol derivatives with particularly weak C–O bonds such as aryl sulfates, phosphates or sulfonates is beyond the scope of this review. Likewise, stoichiometric reactions and heterogeneous C–O bond-functionalization reactions will not be treated in detail. This review is organized in three sections according to the type of transformation, and includes mechanistic considerations and future avenues, when applicable.

## 2. Carbon-Carbon Bond-Formation

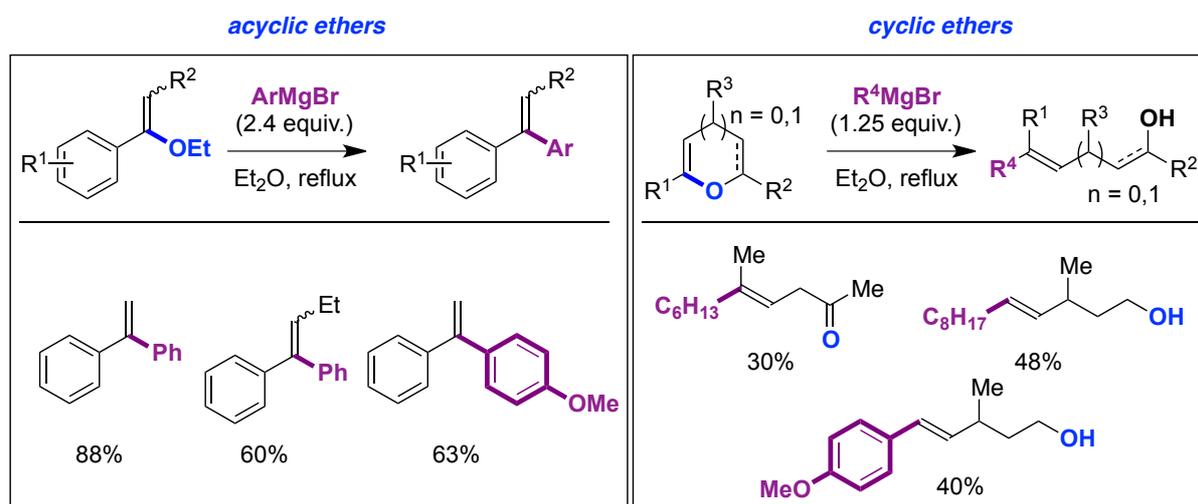
### 2.1. Kumada-Tamao-Corriu-Type Coupling Reactions

Amongst all cross-coupling reactions involving the activation of C–O bonds, the KTC reaction has been studied most intensively. This can probably be attributed to the high reactivity of Grignard reagents, which renders the activation of the C–O bond particularly

facile when compared with less-reactive nucleophilic components. Indeed, the utilization of Grignard reagents in C–O bond cleavage can be traced back to a number of non-catalyzed reactions reported in the 1950s<sup>6</sup> with vinyl ether motifs. Undoubtedly, these initial findings set the scene for the implementation of a variety of challenging catalytic C–O bond-functionalization techniques.

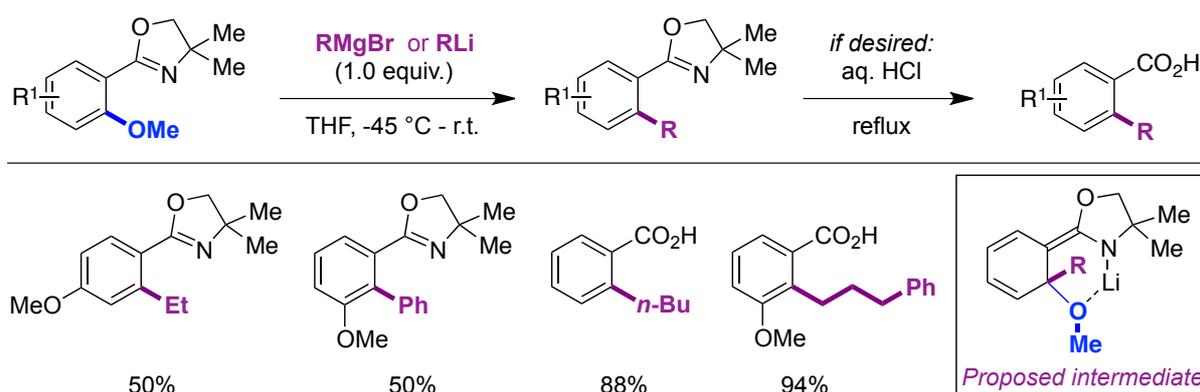
### 2.1.1. Historical Background: Uncatalyzed Reactions and Stoichiometric Experiments

In 1951, Hill reported that activated 1-aryl substituted vinyl ethers reacted rapidly with aryl Grignard reagents to give access to 1,1-diaryl substituted olefins in moderate to good yields (Scheme 3, *left*).<sup>6</sup> Subsequently, the same group demonstrated that an otherwise analogous reactivity could be found when cyclic vinyl ethers such as 3,4-dihydro-2H-pyran or furan derivatives were employed, affording alcohol backbones possessing appropriately substituted alkenes on the side chain or ketone derivatives, respectively (Scheme 3, *right*).<sup>7</sup>



**Scheme 3.** Uncatalyzed reactions of Grignard reagents with acyclic and cyclic ethers

Some years later, Meyers and colleagues described analogous reactivity for aryl methyl ethers bearing an oxazoline directing group at the *ortho* position (Scheme 4).<sup>8</sup> Such substrates were reported to react with both Grignard reagents and organolithium species to give the substitution products in moderate to high yields. Importantly, ether functions other than methoxy motifs could be utilized, invariably leading to functionalization at the *ortho* position to the directing group. The authors proposed that the reaction occurs via nucleophilic aromatic substitution, with the Li<sup>+</sup> or Mg<sup>2+</sup> ions coordinated to the oxazoline nitrogen atom and the ethereal oxygen atom. The formation of this type of intermediate nicely explains both the increased reactivity and the selectivity for *ortho* over *para* ether groups, which would not be expected if the oxazoline serves as a simple electron-withdrawing group stabilizing a Meisenheimer-type complex. Later, the use of other directing groups in similar substitution reactions was reported.<sup>9</sup>



**Scheme 4.** Uncatalyzed reactions of aryl methyl ethers with either Grignard reagents or aryl lithium reagents induced by an oxazoline directing group

Yamamoto and colleagues studied the reactivity of Ni complexes supported by phosphines or bipyridine ligands with ester groups in a stoichiometric fashion in order to determine the factors influencing the site-selectivity of the C–O bond cleavage (Scheme 5).<sup>10</sup> These investigations revealed that aryl or enol esters follow a different selectivity profile; while phenol-derived esters undergo  $C_{\text{carbonyl}}\text{--O}$  cleavage (Scheme 5, type A), structurally-related enol-derived esters resulted in  $C_{\text{vinyl}}\text{--O}$  functionalization (Scheme 5, type B).



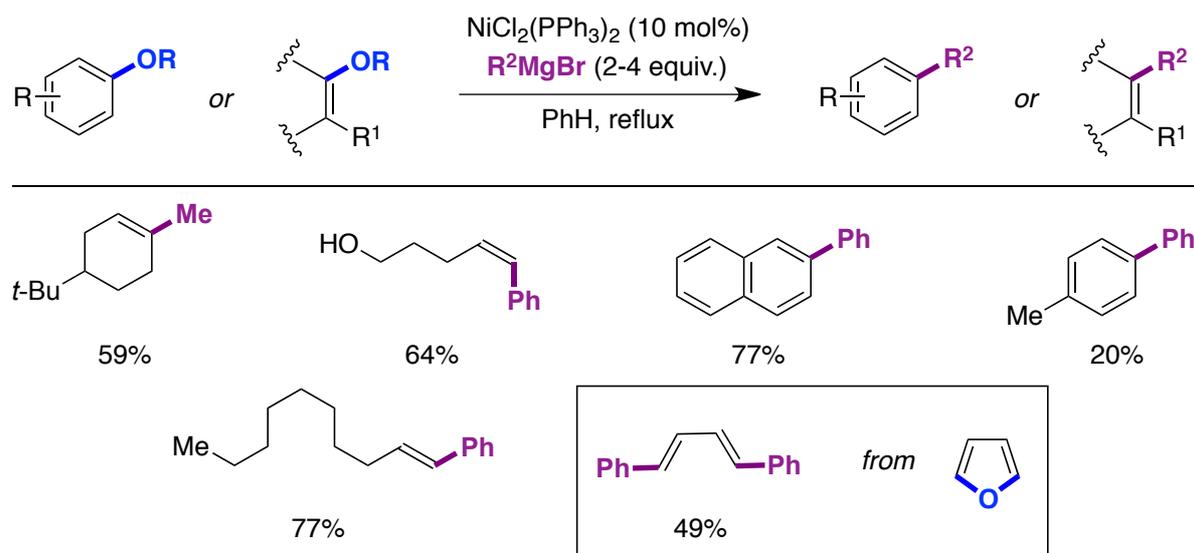
**Scheme 5.** Regioselectivity studies on the cleavage of C–O bonds in ester derivatives by Ni(0)

According to these seminal studies employing ester derivatives, similar site-selectivity could be achieved between the  $C_{\text{alkyl}}\text{--O}$  or  $C_{\text{aryl}}\text{--O}$  bonds of aryl alkyl ethers. To this end, Milstein and co-workers found that pincer ligands containing an appropriate methoxy residue on the aryl backbone followed an intriguing selectivity profile depending on the metal used.<sup>11</sup> While rhodium complexes selectively activated the  $C_{\text{aryl}}\text{--O}$  bond, nickel species triggered  $C_{\text{alkyl}}\text{--O}$  scission, a rather surprising finding considering the ability of Ni catalysts to cleanly promote the  $C_{\text{aryl}}\text{--O}$  bond cleavage in anisole-type derivatives. This discrepancy can be explained by the inherent nature of the pincer ligand backbone, as it is able to favor activation of the  $C_{\text{alkyl}}\text{--O}$  bond by facilitating pre-coordination of the nickel center while preventing its binding to the  $\pi$ -system.

### 2.1.2. Ethers

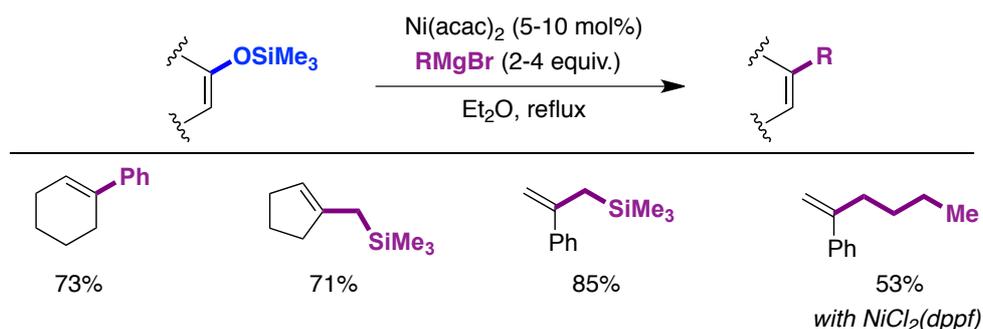
In 1979, Wenkert reported that aryl and vinyl ethers are suitable counterparts in KTC cross-coupling reactions with Grignard reagents (Scheme 6).<sup>4</sup> The scope of these reactions included the coupling of either PhMgBr or MeMgBr with  $\text{NiCl}_2(\text{PPh}_3)_2$  as precatalyst;

however, the use of alkyl Grignard reagents possessing  $\beta$ -hydrogens led to unproductive reduction events, and low yields were systematically observed for non- $\pi$ -extended aromatic rings, a recurrent drawback that continues to be observed years later. It was found that enol ethers reacted at a considerably faster rate than simple aryl ethers, an observation that is in line with the stoichiometric studies reported by Hill.<sup>6</sup> Interestingly, the use of furan as the coupling partner gave 1,3-dienes in which both C–O bonds could be activated with equal ease.



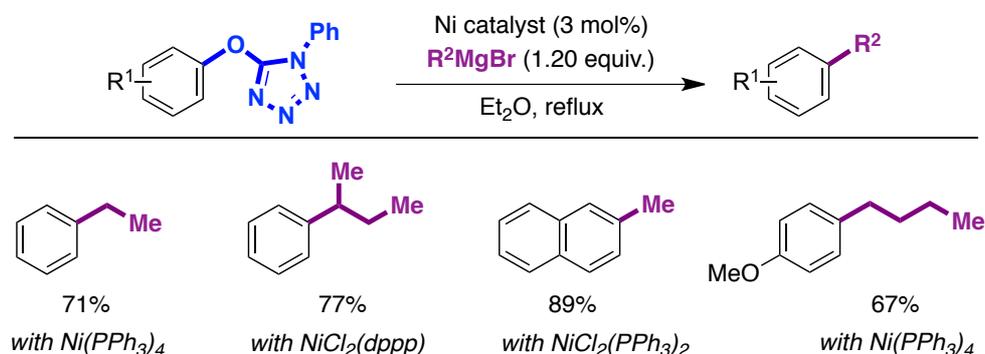
**Scheme 6.** Ni-catalyzed KTC reactions of aryl and vinyl ethers.

Despite the considerable potential of Wenkert's work,<sup>4</sup> these findings were unfortunately overlooked by the success of Pd-catalyzed cross-coupling reactions of organic halides that were reported in the mid 1970's. However, this pioneering work has been the basis of the use of C–O electrophiles in cross-coupling reactions via C–O bond cleavage, triggering the development of many new catalytic transformations that can seem counterintuitive at first sight. Following up on Wenkert's studies, Kumada demonstrated that silyl enol ethers are competent counterparts in Ni-catalyzed cross-coupling reactions with Grignard reagents (Scheme 7).<sup>12</sup> Intriguingly, the reaction took place under ligand-free conditions using simple  $\text{Ni}(\text{acac})_2$  as the precatalyst. Unfortunately, the coupling of otherwise related aryl silyl ethers was not reported, an observation that is in line with the demonstration by both Wenkert<sup>4</sup> and Hill's<sup>6</sup> —that unbiased aryl C–O electrophiles are considerably less reactive. Unlike Wenkert's work, the use of silyl enol ethers and dppf as the ligand allowed, for the first time, the coupling of aliphatic Grignard reagents possessing  $\beta$ -hydrogens, albeit in lower yields.



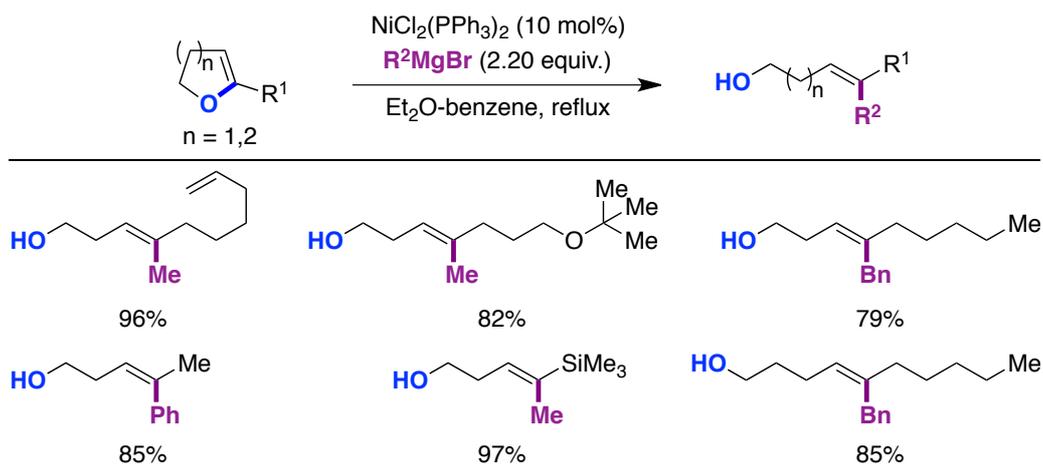
**Scheme 7.** Ni-catalyzed KTC reactions of silyl enol ethers

Johnstone and colleagues developed a Ni-catalyzed KTC cross-coupling reaction of aryl phenyltetrazole ethers with Grignard reagents (Scheme 8).<sup>13</sup> Although the substrates were rather sophisticated, the ability to couple alkyl organometallic species that could otherwise undergo parasitic  $\beta$ -hydride elimination is particularly noteworthy. In contrast to Wenkert's work,<sup>4</sup> non- $\pi$ -extended phenol derivatives posed no problems, thus increasing the synthetic utility of this method. Surprisingly, different catalysts were found to be optimal depending on the substrate used, a testament to the sensitivity of this methodology towards subtle changes in the electronic and steric properties of the corresponding coupling partners. Later investigations showed that other heteroaromatic ether motifs could be used with both Grignard reagents and organolithium species.<sup>14</sup>

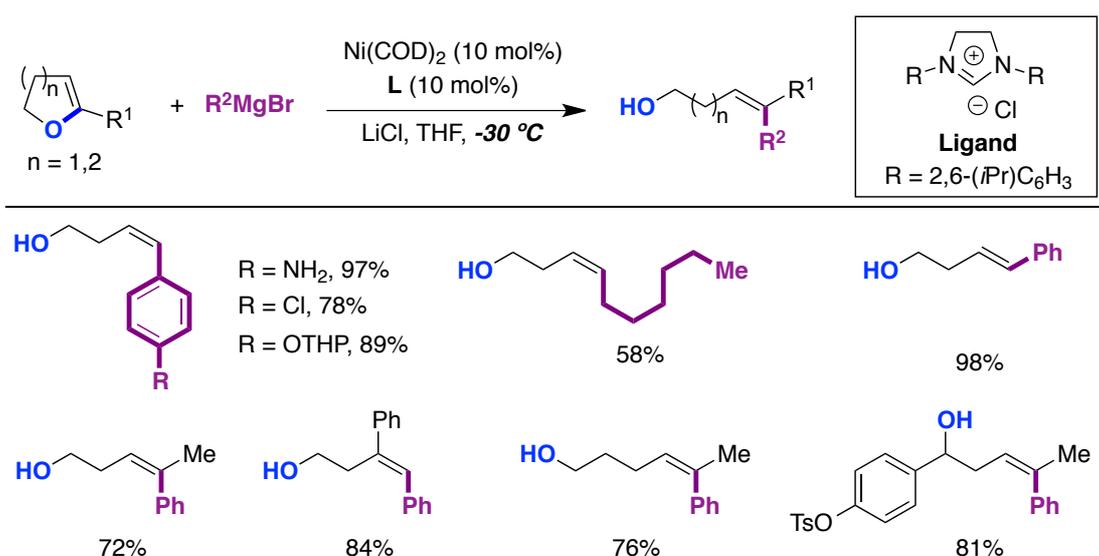


**Scheme 8.** Ni-catalyzed KTC reactions of aryl heteroaryl ethers

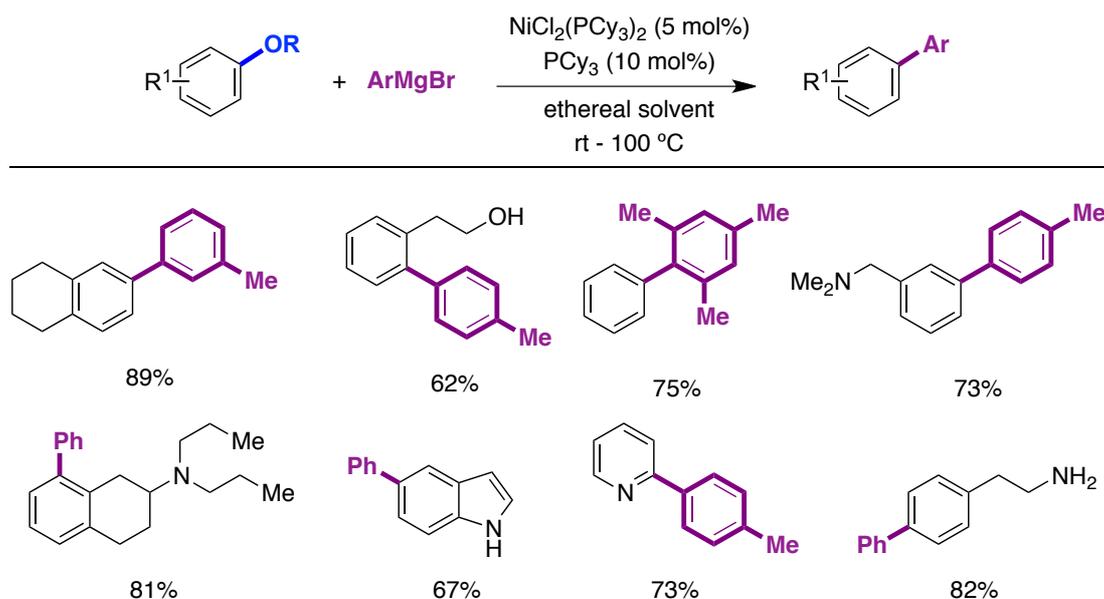
Aiming at the synthesis of selectively substituted alkenol derivatives, Kocienski studied the KTC reaction of 5-alkyl substituted 2,3-dihydrofurans and analogous pyrans (Scheme 9).<sup>15</sup> In these studies, homoallylic alcohols were obtained in high yields from 2,3-dihydrofurans in a stereospecific fashion, and a number of functional groups on the alkyl side chain could be tolerated. Although lower rates were found for analogous 2,3-dihydropyrans, the desired products could still be obtained in good yields. Importantly, the authors demonstrated that silyl and stannyl substituents could be accommodated at C5, thus giving access to valuable stereodefined vinyl silanes and/or stannanes. Unfortunately, significant amounts of reduced products were invariably observed when employing alkyl Grignard reagents possessing  $\beta$ -hydrogens.



In 2013, Martin utilized an NHC-Ni catalyst system to enable the Ni-catalyzed KTC cross-coupling reactions of dihydrofurans with aryl and alkyl Grignard reagents under exceptionally mild conditions at temperatures as low as  $-30\text{ }^\circ\text{C}$  (Scheme 10).<sup>16</sup> The authors found a marked increase in catalytic activity when using *N*-heterocyclic carbenes (NHC) as ligands in combination with LiCl. Under these conditions, more reactive functional groups such as aryl tosylates, pivalates or methyl ethers were tolerated. Likewise, good yields were obtained for alkyl Grignard reagents possessing  $\beta$ -hydrogens. The authors tacitly demonstrated the intermediacy of nickel  $\pi$ -allyl complexes by observing a stereoselectivity switch at  $40\text{ }^\circ\text{C}$  via *Z/E* isomerization. Strikingly, whereas RMgBr consistently provided high yields, the utilization of RMgCl failed to provide the corresponding coupling products. These observations were found to contradict a “classical” oxidative addition pathway, suggesting the involvement of Lewis acid assistance by the  $\text{Mg}^{2+}$  cation on the Grignard reagent and the intermediacy of Ni(0)-ate complexes.



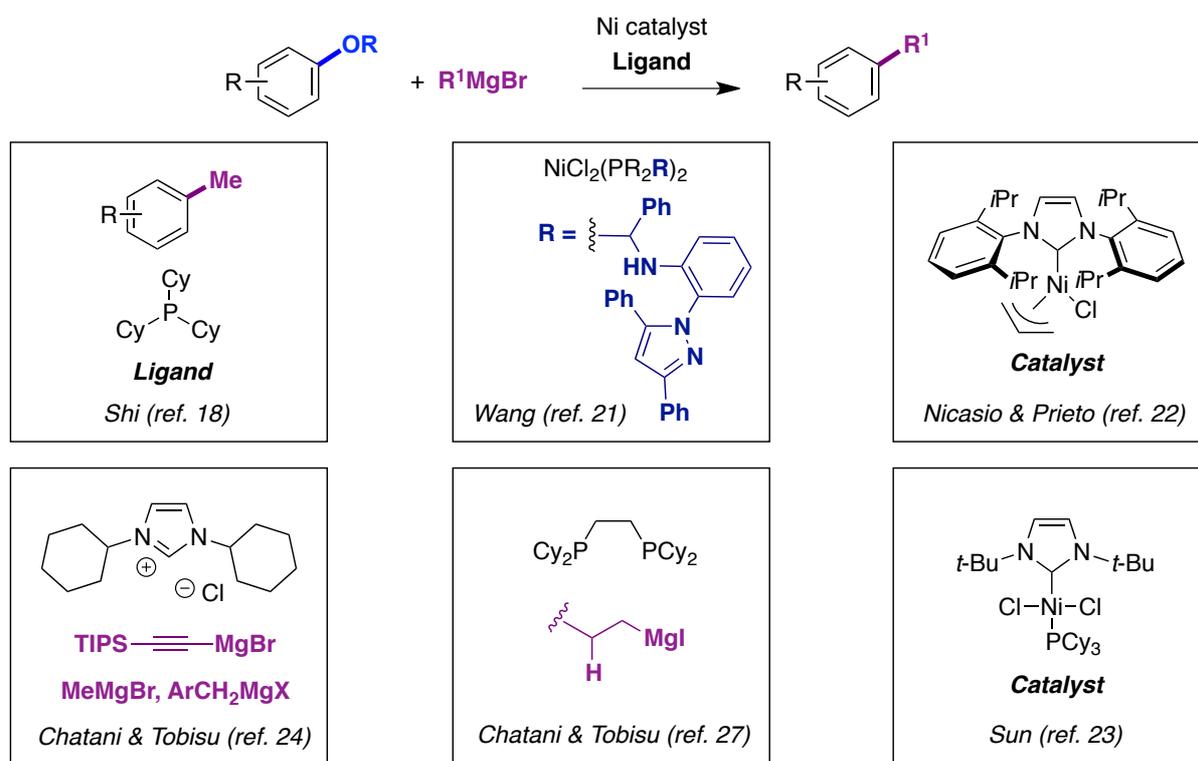
Although previous studies demonstrated that regular anisole derivatives were—~~were~~ are considerably less reactive than the corresponding  $\pi$ -extended aryl ethers, Dankwardt reported that the use of certain electron-rich phosphines could be used to address this problem, obtaining in all cases high yields, even for challenging substrate combinations.<sup>17</sup> The influence of the ligand backbone was examined and  $\text{PCy}_3$  and  $\text{PhPCy}_2$  were identified as the most promising candidates to promote the C–OMe cleavage in combination with a Ni(II) precatalyst. Under these conditions, a wide number of aryl alkyl ethers could be employed with equal ease, including silyl ethers (Scheme 11).



**Scheme 11.** Ni-catalyzed KTC coupling reactions of anisoles using  $\text{PCy}_3$  as the ligand (given percentages correspond to conversions)

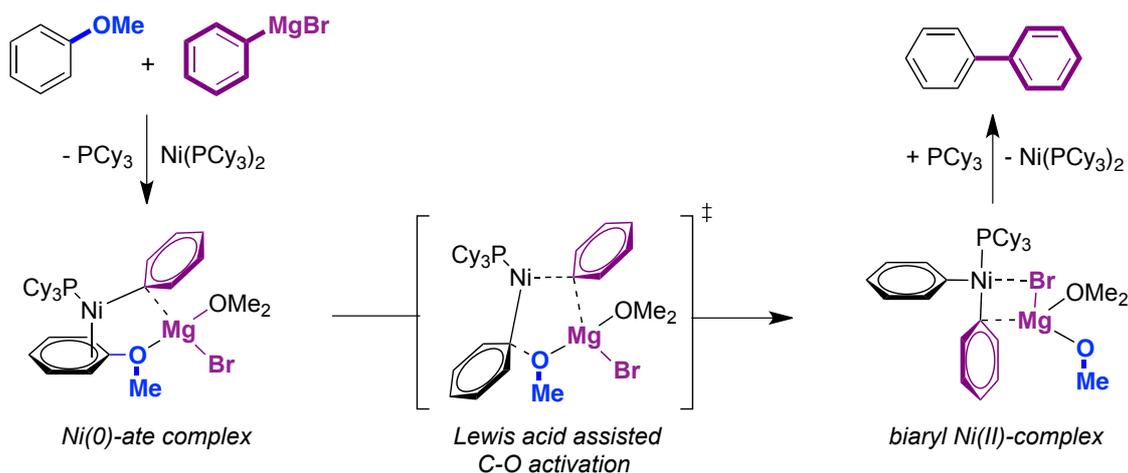
Dankwardt's report inspired others to expand the substrate scope of this reaction by fine-tuning the ligand backbone and/or the substrate (Scheme 12). For example, in 2008 Shi described the methylation of anisole derivatives using only 1.2 equivalents of  $\text{MeMgBr}$  under conditions closely resembling to those reported by Dankwardt.<sup>18</sup> The same group then employed the knowledge acquired from developing this reaction to effect sequential  $\text{C}(\text{sp}^2)$ –O bond activation of differently substituted aryl ether<sup>19</sup> and aryl silyl ether motifs.<sup>20</sup> In 2011, Wang and Xie developed modified alkyldicyclohexylphosphine ligands for effecting KTC reactions of aryl and vinyl ethers, allowing for the significant reduction in the quantity of Grignard reagents utilized when compared to Dankwardt's original report.<sup>21</sup> Prompted by the high reactivity of electron-rich trialkylphosphines towards C–O bond cleavage, Nicasio demonstrated the utilization of *N*-heterocyclic carbenes (NHCs) in the KTC reactions of anisole derivatives.<sup>22</sup> Subsequently, Sun reported a mixed catalytic system involving both phosphine and NHC ligands.<sup>23</sup> Tobisu and Chatani significantly expanded the scope of the KTC reactions of aryl ethers by using alkynyl<sup>24</sup> or alkyl Grignard reagents lacking  $\beta$ -hydrogens and NHC ligands.<sup>25</sup> This allowed the synthesis of organic semiconductors in a straightforward fashion.<sup>26</sup> More recently, Tobisu and Chatani described a rather intriguing cross-coupling reaction of simple aryl methyl ethers with alkyl Grignard reagents possessing  $\beta$ -hydrogens

using dcype as the ligand.<sup>27</sup> The reactions occurred in high yields regardless of whether anisoles,  $\pi$ -extended systems or vinyl ethers were used. Of particular importance was the finding that the reactivity was highly dependent on the counterion utilized in the corresponding Grignard reagent, an observation that is reminiscent of the work developed by Martin in 2013 that dealt with the KTC reaction of cyclic vinyl ethers employing NHC ligands (Scheme 10).<sup>16</sup>



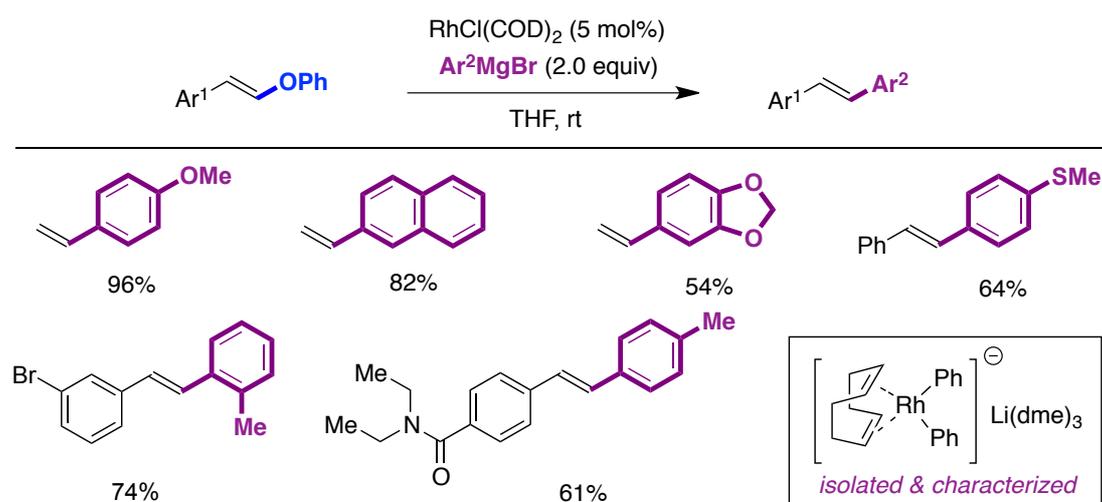
**Scheme 12.** Ni-catalyzed KTC coupling reactions of aryl methyl ethers using phosphine or NHC ligands

The non-innocent behavior of the counterion in KTC reactions, which was discovered by Martin<sup>16</sup> and recently corroborated by Tobisu and Chatani,<sup>27</sup> suggested that C–O bond cleavage in either aryl or vinyl ethers might not occur via “classical” oxidative addition but rather through the formation of Ni(0)-ate intermediates (Schemes 10 and 12). Motivated by this perception, Wang and Uchiyama carried out a computational study on the Ni-catalyzed arylation of anisole and reinforced the notion that C<sub>aryl</sub>–O bond cleavage does not occur via “classical” oxidative addition (Scheme 13).<sup>28</sup> The energetically most favorable pathway found by the authors involved the formation of a Ni(0)-ate complex by coordination of the Grignard reagent and the *in situ* generated [Ni(PCy<sub>3</sub>)<sub>2</sub>] to the anisole derivative. This nickelate complex participates in the subsequent Lewis acid assisted C<sub>aryl</sub>–O bond activation, which leads to the formation of a biaryl Ni(II)-complex, while at the same time transferring the methoxide anion to the magnesium center. Although further experimental evidence is required to confirm these findings, they are in line with the hydrogenolysis mechanism reported by the Martin group, which invokes pathways other than generally proposed C–O bond-oxidative addition.<sup>29</sup>



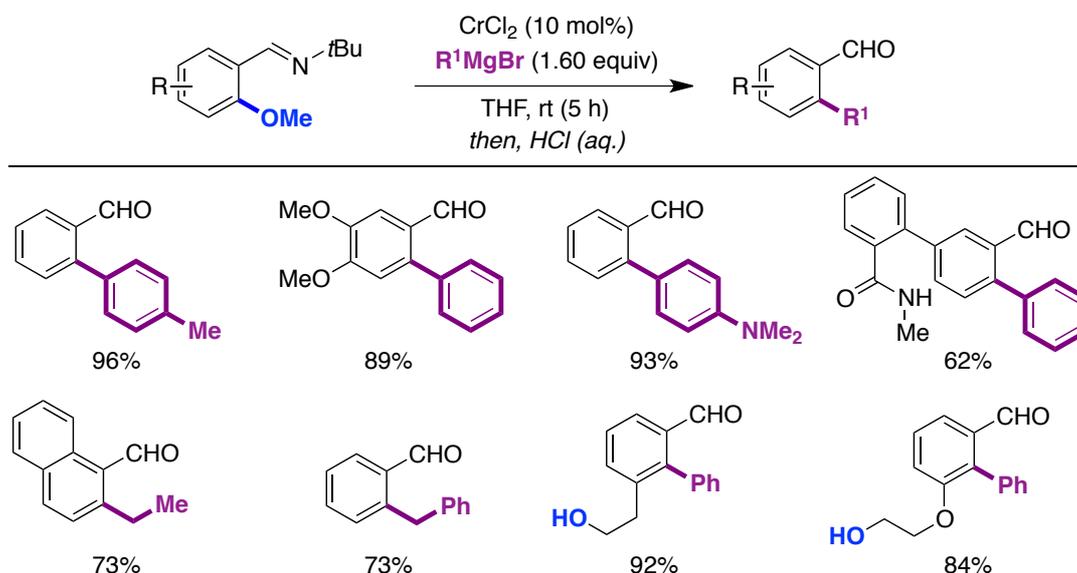
**Scheme 13.** Theoretical study on the C(sp<sup>2</sup>)-OMe cleavage in KTC reactions

Although nickel catalysts have been shown to be particularly efficient in the KTC reactions of aryl ethers, several studies have demonstrated the viability of using other metal catalysts. For example, in 2014 Kambe disclosed a ligand-free Rh-catalyzed cross-coupling reactions of aryl vinyl ethers with aryl Grignard reagents en route to styrene-type derivatives, and observed that the C<sub>vinyl</sub>-O bonds were selectively activated (Scheme 14).<sup>30</sup> The authors also demonstrated that the optimized conditions could be successfully applied to silyl ethers. Experiments towards understanding the mechanism of this reaction gave strong support for the involvement of diarylrhodate intermediates, as analytically pure [RhAr<sub>2</sub>(COD)]<sup>-</sup>[Li(dme)<sub>3</sub>]<sup>+</sup> could be isolated and characterized. Taking this into consideration, the authors proposed that a Rh(I)-ate species triggered an initial carbometalation that was followed by β-alkoxy elimination to deliver the coupling product. At the same time, an ArRh(I) species would be formed that would react rapidly with the corresponding Grignard reagent to form the active Rh(I)-ate species.



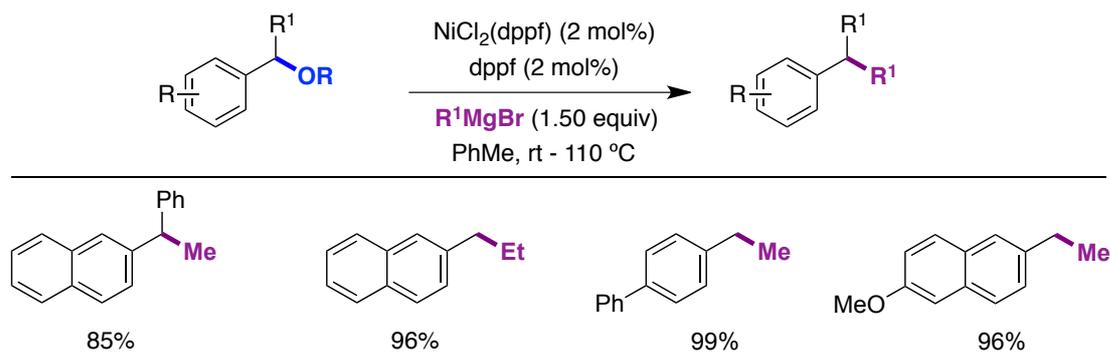
**Scheme 14.** Rh-catalyzed KTC reactions of vinyl aryl ethers (given percentages correspond to conversions)

Recently, Zeng and co-workers reported that simple chromium salts, in the absence of ligand, could be employed as catalysts in the KTC reactions of either aryl or alkyl Grignard reagents with aryl ethers bearing a *tert*-butyl imine directing group at the *ortho* position (Scheme 15).<sup>31</sup> Although the prerequisite for a directing group significantly limits the applicability of this reaction, its inclusion allows for site-selectivity in the presence of methoxy groups located at either *meta* or *para* positions.



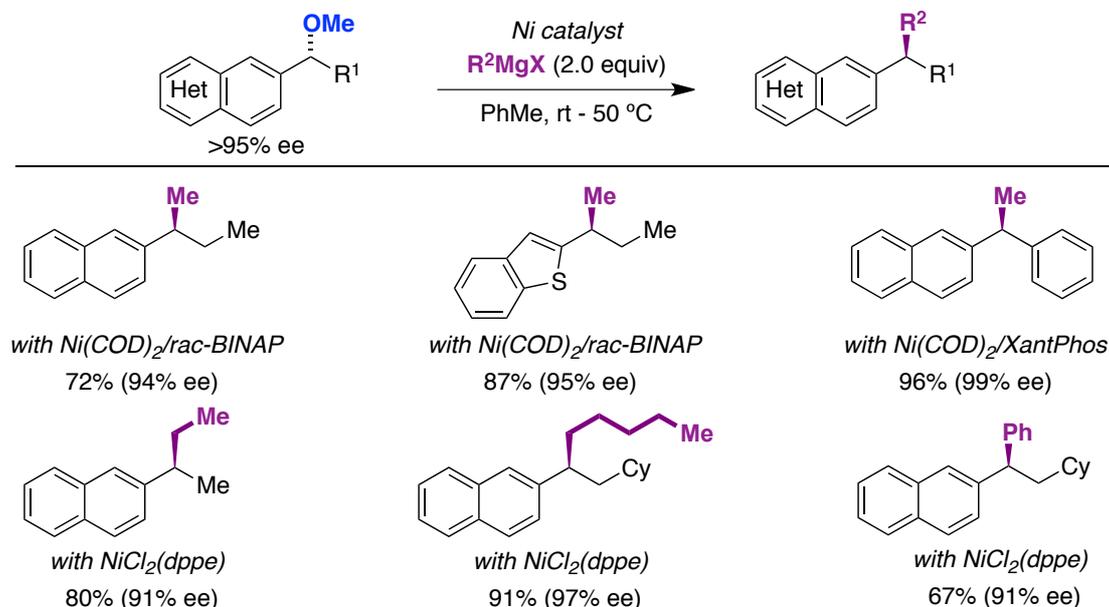
**Scheme 15.** Cr-catalyzed *ortho*-directed KTC reactions of aryl ethers

In addition to the studies focussing on the activation of  $\text{C}(\text{sp}^2)\text{-O}$  bonds in aryl ether derivatives, significant efforts have also been directed towards the activation of less reactive  $\text{C}(\text{sp}^3)\text{-O}$  bonds. The group of Shi disclosed the first KTC reactions of a variety of benzyl ethers using  $\text{NiCl}_2(\text{dppf})$  as the catalyst and  $\text{MeMgBr}$  as the coupling partner (Scheme 16).<sup>32</sup> Although the scope of these reactions allowed for the coupling of benzyl derivatives without the need for  $\pi$ -extended systems, the reaction remained limited to alkyl Grignard reagents. Interestingly, the authors found that their methodology is complementary to the KTC cross-coupling of aryl ethers; in this manner, excellent site-selective functionalization of either  $\text{C}(\text{sp}^2)\text{-O}$  or  $\text{C}(\text{sp}^3)\text{-O}$  bonds could be achieved depending on the reagents utilized. Although these reactions were limited to benzylic ethers, the Shi group subsequently reported an iron-catalyzed protocol that enables the KTC cross-coupling reaction of homobenzylic ether derivatives.<sup>33</sup> One might first assume that the iron catalysts is capable of promoting  $\text{C}(\text{sp}^3)\text{-O}$  bond cleavage; however, control experiments indicated otherwise. In particular, it was demonstrated that the basicity of the Grignard reagent triggered an initial elimination that resulted in the formation of a styrene motif. Subsequent carbometalation with an additional Grignard reagent led to a benzylic Grignard reagent that produced the final product upon aqueous workup.



**Scheme 16.** Ni-catalyzed KTC reaction of benzyl ether derivatives

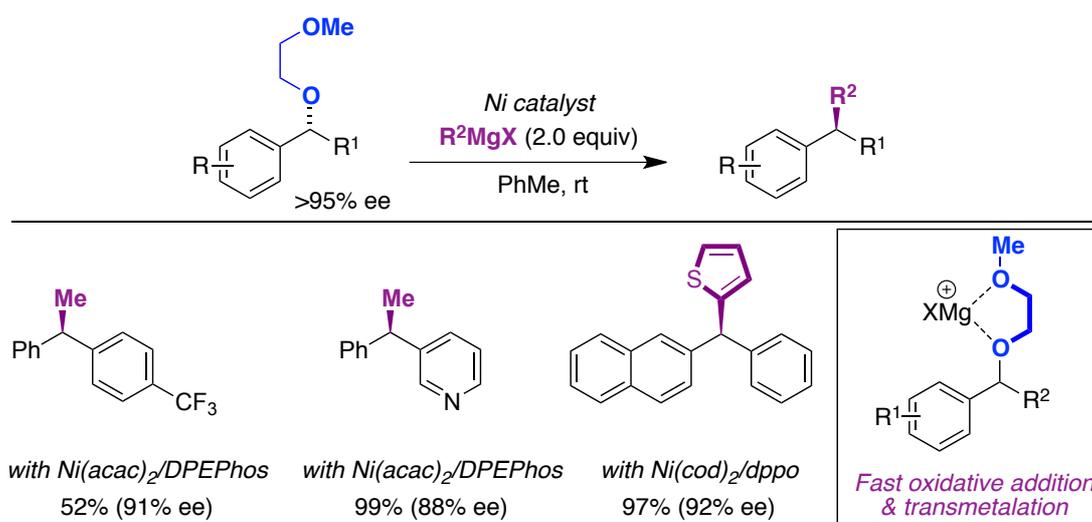
Since 2011, the Jarvo group has disclosed a series of reports detailing their studies on the Ni-catalyzed stereospecific cross-coupling reactions of benzyl ether electrophiles with a number of organometallic species.<sup>34</sup> In particular, the authors developed a Ni-catalyzed stereospecific KTC reaction of  $\pi$ -extended benzyl ethers possessing either aromatic or aliphatic substituents at the  $\alpha$ -position (Scheme 17). Interestingly, the nature of the ligand turned out to be critical, and three sets of conditions were developed depending on whether the substrate or Grignard reagent utilized possessed  $\beta$ -hydrogens or not. In particular, it was found that *dppe* was crucial for suppressing undesired  $\beta$ -hydride elimination when aliphatic nucleophilic components were employed. In all cases, the reaction proceeded with net inversion of configuration suggesting that oxidative addition probably takes place via a  $\eta^3$ -Ni(II) or via a  $\text{S}_{\text{N}}2$  mechanism followed by a stereoretentive transmetalation and reductive elimination. Unfortunately, however, the limitation to substrates with  $\pi$ -extended backbones remained a considerable drawback to be overcome.



**Scheme 17.** Stereospecific KTC reaction of benzyl methyl ethers with Grignard reagents

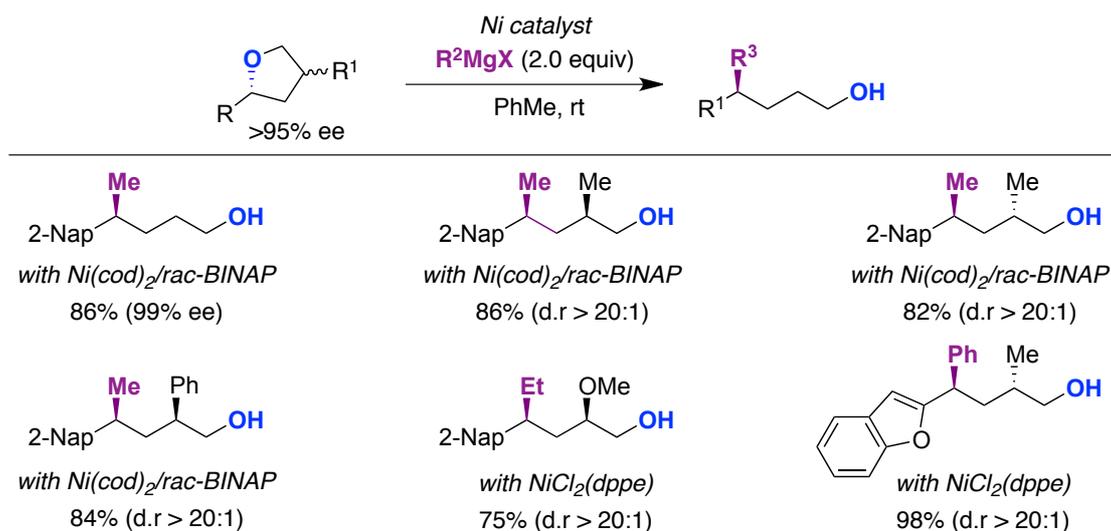
The limitation of stereospecific KTC reactions to  $\pi$ -extended backbones was addressed by the Jarvo group through a systematic study of the nature of the leaving group, revealing that methoxyethyl benzyl ethers were superior counterparts when compared to other benzyl

ethers (Scheme 18).<sup>35</sup> Prompted by an otherwise analogous effect discovered by Liebeskind when using benzyl thioethers,<sup>36</sup> Jarvo attributed the successful use of methoxyethyl benzyl ethers in KTC reactions to the ability of the magnesium cation to strongly chelate the corresponding diether-containing group, significantly weakening the benzylic C–O bond and accelerating the rate of oxidative addition and transmetalation. Two sets of conditions were developed, and whereas DPEPhos resulted in the coupling of MeMgBr, the use of dppo allowed for the coupling of heteroaryl organometallic components. In the latter case, however, a polyaromatic motif was required for the reaction to occur. In some cases, an erosion in enantioselectivity was observed, presumably due to bimolecular racemization from reaction of in situ generated Ni(II) with the oxidative addition of the Ni(0)<sub>L</sub><sub>n</sub> species.



**Scheme 18.** Stereospecific Ni-catalyzed KTC of non- $\pi$ -extended systems with benzyl methoxyethyl ethers

Recently, the same group studied the Ni-catalyzed KTC reaction of 2-aryl substituted tetrahydrofurans (Scheme 19).<sup>37</sup> As expected, the reaction resulted in selective activation of the benzylic C–O bond; unfortunately, however, the cross-coupling required the presence of a  $\pi$ -extended backbone. The study demonstrated that *cis*-substituted tetrahydrofurans afforded *syn*-configured products whereas *trans*-configured starting materials invariably provided *anti*-configured products. A variety of substituents at C3, C4, or C5 were tolerated, and in all cases good to excellent yields and high stereospecificities were obtained, even when preparing isotopically labeled materials.<sup>37b</sup>

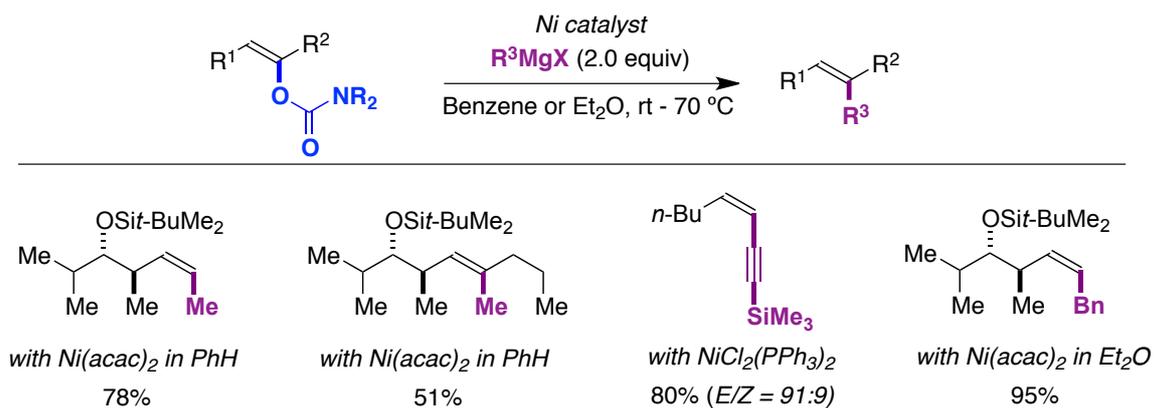


**Scheme 19.** Stereospecific Ni-catalyzed ring opening of tetrahydrofurans with Grignard reagents via benzylic C–O bond cleavage

As judged by the literature data on KTC reactions of aryl, benzyl or vinyl ethers via C–OMe cleavage, it becomes evident that remarkable levels of sophistication have been achieved. At present, a wide variety of cyclic or acyclic  $\text{C}(\text{sp}^2)\text{--}/\text{C}(\text{sp}^3)\text{--O}$  bonds can be activated with equal ease. Still, a number of challenges remain, such as: (1) finding a general solution for the lack of reactivity of substrate combinations without  $\pi$ -extended backbones; (2) addressing the inability of unactivated alkyl ethers to undergo KTC reactions; (3) the clarification of the mechanism by which these reactions operate. We anticipate that fine-tuning of ligand backbones together with in-depth mechanistic studies will allow chemists to rise to many of these challenges whilst also opening new vistas in the field.

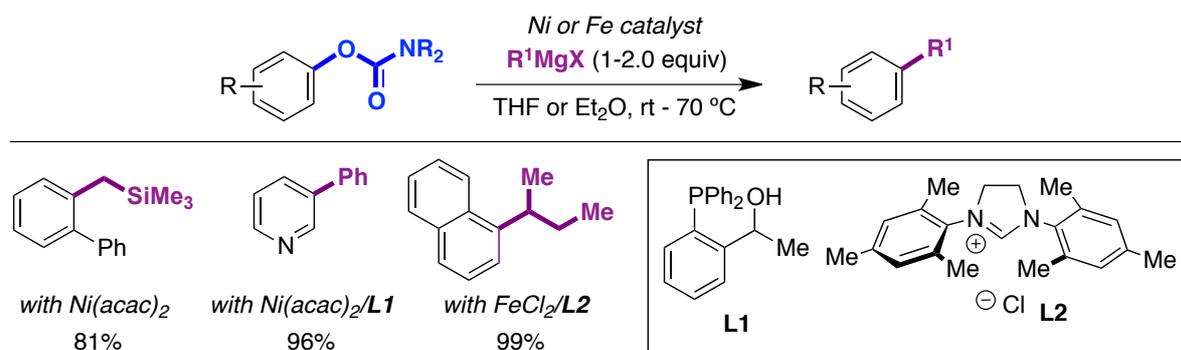
### 2.1.3. Carbamates

In 1989, Kocienski reported the first Ni-catalyzed KTC reaction of vinyl carbamates with Grignard reagents (Scheme 20).<sup>38</sup> In line with the considerable high reactivity of vinyl ethers, these reactions occurred with retention of the double bond geometry. In 1995, Férézou extended the scope of these reactions to alkynylmagnesium bromides using  $\text{PPh}_3$  as the ligand and  $\text{EtMgBr}$  as the reductant to generate *in situ* the propagating  $\text{Ni}(\text{O})\text{L}_n$  species.<sup>39</sup> Unlike Kocienski's protocol, certain substrate combinations gave products having undergone partial isomerization of the double bond. Subsequently, Betzer described a KTC protocol that allowed for expanding the scope of the Grignard reagent to alkenyl, aryl and benzyl nucleophiles.<sup>40</sup> As evident from the results compiled in Scheme 20, most of the substrates utilized in either Kocienski's, Férézou's or Betzer's protocols featured an adjacent stereodiad with a methyl substituent at the  $\alpha$ -position and a (protected) hydroxy group at the  $\beta$ -position.<sup>41</sup>



**Scheme 20.** Ni-catalyzed KTC of vinyl carbamates described by Kocienski, Férézou and Betzer

As part of a research aimed at promoting directed *ortho* metalation techniques (*DoM*), Snieckus reported the first use of aryl carbamates as C–O electrophiles in KTC reactions in 1992 (Scheme 21).<sup>42</sup> Using Ni(acac)<sub>2</sub> as precatalyst under ligand-free conditions, a wide variety of aryl carbamates could be coupled with excellent results. In 2009, Nakamura reported an improved catalytic protocol using a hydroxyphosphine ligand (**L1**) under otherwise similar reaction conditions.<sup>43</sup> Unfortunately, both protocols did not allow the coupling of Grignard reagents possessing β-hydrogens. Challenged by this limitation, Garg discovered that the combination of FeCl<sub>2</sub> with NHC precursor **L2** accommodated a diverse set of substitution patterns, including alkyl Grignard reagents possessing β-hydrogens.<sup>44</sup> The usefulness of this methodology was highlighted by the ability of carbamates to be used as directing groups to promote a directed *ortho* metalation, allowing for sequential C–C bond-forming techniques from readily available precursors.

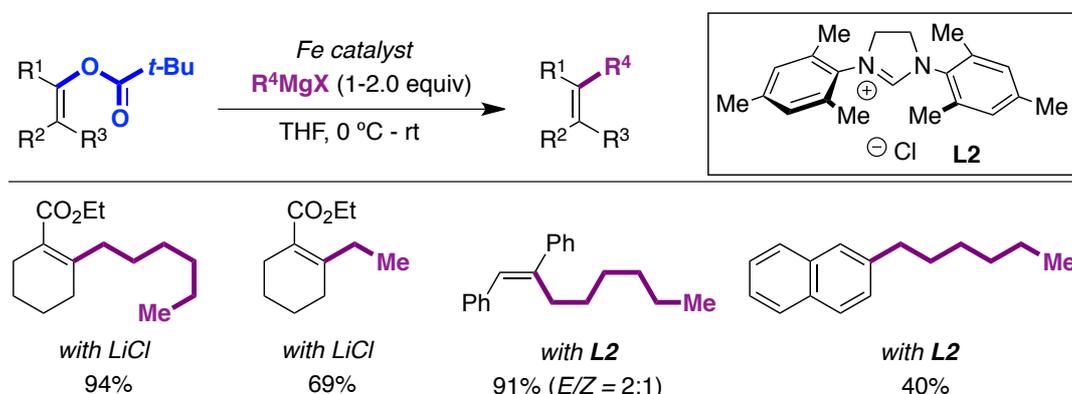


**Scheme 21.** Ni- and Fe-catalyzed KTC of aryl carbamates with Grignard reagents

### 2.1.4 Esters

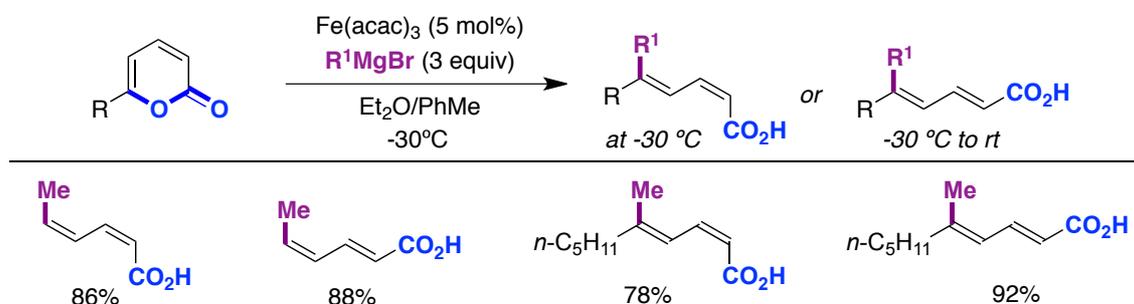
In 2009, Shi reported the first use of vinyl esters as coupling partners in KTC couplings using FeCl<sub>2</sub> as the precatalyst (Scheme 22).<sup>45</sup> The reaction could be conducted under ligand-free conditions with a variety of Grignard reagents. For substrates possessing electron-withdrawing substituents, LiCl was required for obtaining good yields. In contrast, less-activated naphthyl or styryl derivatives required the use of **L2**, a combination that was later applied by Garg for the coupling of aryl carbamates.<sup>44</sup> It is noteworthy that these reactions

could be implemented with alkyl Grignard reagents possessing  $\beta$ -hydrogens, a testament to the particularly high chemoselectivity profile of iron salts when compared with other metal catalysts used for similar means.



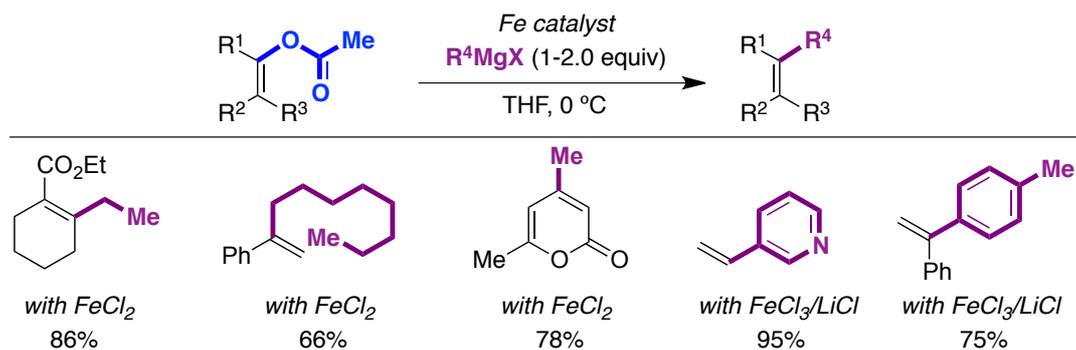
**Scheme 22.** Fe-catalyzed KTC reactions of vinyl pivalates with Grignard reagents.

As part of a program aimed at implementing Fe catalysis in cross-coupling reactions,<sup>46</sup> Fürstner extended the scope of Fe-catalyzed KTC-type reactions to 2-pyrone substrates and alkyl Grignard reagents, rapidly obtaining 2,4-dienoic acids in high yields and high stereoselectivities (Scheme 23).<sup>47</sup> The newly introduced substituent was obtained in the *cis*-relative configuration to the unsaturated motif. Notably, the reaction time and temperature dictated whether *cis* or *trans*-configured double bonds were obtained, an example of product distribution by either kinetic or thermodynamic control.



**Scheme 23.** Fe-catalyzed KTC reactions of 2-pyrones

The scope of the Fe-catalyzed KTC reaction of vinyl esters, originally described by Shi,<sup>45</sup> was recently extended by von Wangelin to acetate coupling partners and NMP as additive under ligand-free conditions (Scheme 24).<sup>48</sup> The authors found that the use of  $\text{FeCl}_3$  as the precatalyst and *in situ* formed  $\text{ArMgBr}\cdot\text{LiCl}$  reagents allowed for the coupling of less-sterically demanding substrate combinations. From a mechanistic standpoint, the authors proposed rate-determining olefin coordination prior to oxidative addition. Although control experiments ruled out the involvement of heterogeneous catalysis, an alternative radical mechanism could not be excluded with absolute certainty.

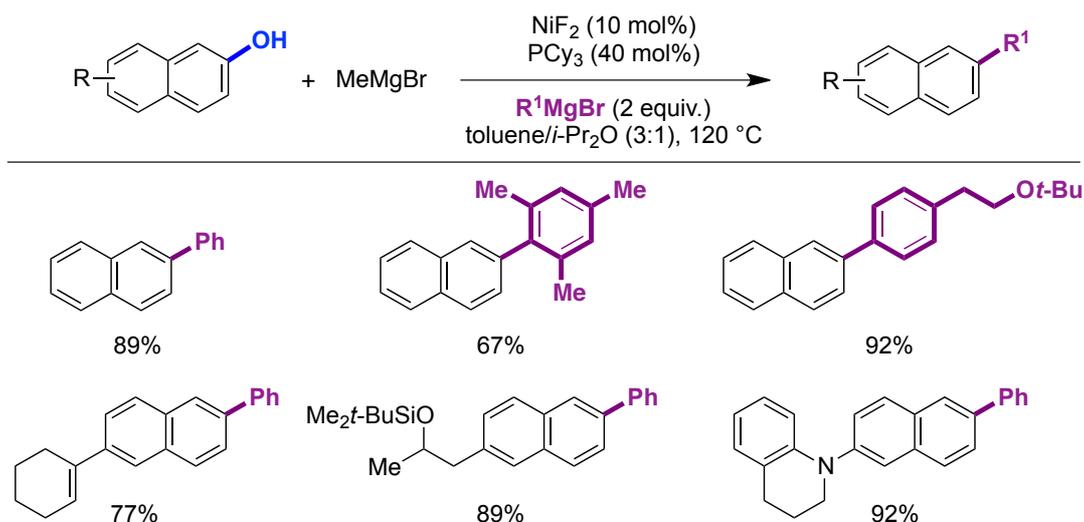


**Scheme 24.** Fe-catalyzed KTC reactions of vinyl acetates

A comparison of the KTC methodologies presented above indicates that the use of carbamates as coupling partners is more general than the corresponding ester derivatives, as both aryl and vinyl counterparts can be utilized with equal ease regardless of whether alkyl or aryl Grignard reagents are employed. Indeed, the use of aryl ester derivatives in KTC reactions is still problematic due to the difficulties encountered in selectively activating the C(sp<sup>2</sup>)-O bond over the C(carbonyl)-O bond. Additionally, the use of aryl Grignard reagents remains limited to a small set of vinyl acetates as electrophilic partners, thus constituting new opportunities for chemists in the years to come.

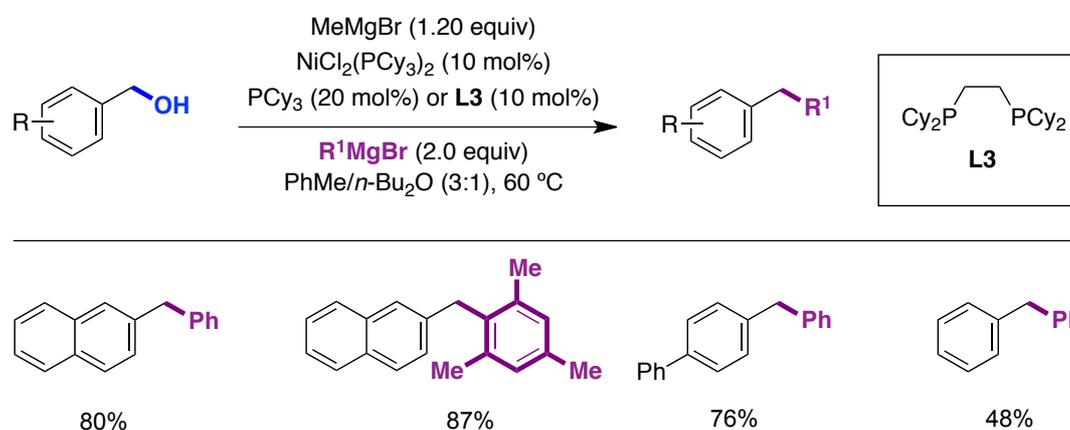
#### 2.1.4 Benzyl Alcohols

Prompted by the use of allylic alcohols in cross-coupling reactions,<sup>49</sup> Shi studied the possibility of using naphthols as coupling partners in KTC reactions without the need for protecting group manipulations (Scheme 25).<sup>50</sup> The key strategy for achieving this goal was the conversion of naphthols to the corresponding magnesium naphtholates under the reaction conditions. Taking this into consideration, the authors discovered a protocol using methylmagnesium bromide to promote the initial formation of a magnesium naphthoate followed by treatment with a nickel catalyst and the corresponding Grignard reagent, thus triggering the targeted C-C bond-forming event via formal C(sp<sup>2</sup>)-OH cleavage. Such naphthoate formation could be corroborated by X-ray crystallographic analysis of  $[\text{NiOMgBr}(\text{THF})_2]_2$ . In these species, the naphtholate oxygen is coordinated to two magnesium ions, which provide sufficient Lewis acidity to enable the oxide anion to act as a leaving group. While no doubt an enormous step-forward in the area of C-O bond cleavage, this method is unfortunately limited to  $\pi$ -extended backbones.



**Scheme 25.** Ni-catalyzed KTC reaction of naphthols

Subsequently, Shi extended the scope of the Ni-catalyzed KTC reactions to benzyl alcohols via formal C(sp<sup>3</sup>)–OH bond cleavage by utilizing a protocol based on PCy<sub>3</sub> or dcype (**L3**) as ligand (Scheme 26).<sup>51</sup> Unlike the functionalization of C(sp<sup>2</sup>)–OH bonds,<sup>50</sup> these reactions could accommodate non- $\pi$ -extended backbones, although superior results were found for naphthyl-type substrates. Unfortunately, these processes were found to be limited to aryl or benzyl Grignard reagents, as alkyl organometallic species possessing  $\beta$ -hydrogens predominantly resulted in reduced products.



**Scheme 26.** Ni-catalyzed KTC reaction of benzyl alcohols

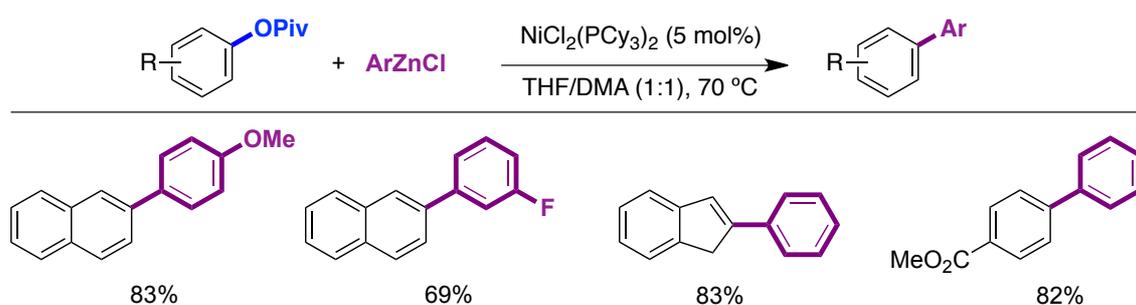
Undoubtedly, the ability to use free alcohols as counterparts holds promise to revolutionize the C–O bond cleavage arena as no prefunctionalization would be required. Although the strategy of salt formation represents a proof of concept for effecting the targeted C–OH bond cleavage, the scope of these reactions remains rather limited. Given the acidity of free alcohols and basicity of Grignard reagents, it is evident that innovative strategies will be required to widen the scope of the coupling partners utilized in KTC reactions.

## 2.2. Negishi-Type Coupling Reactions

Although considerably less reactive than Grignard or organolithium reagents, organozinc derivatives have become privileged synthons in catalytic C–C bond-forming reactions. In light of the remarkable advances that have been made involving the use of Grignard reagents for activating C(sp<sup>2</sup>)– or C(sp<sup>3</sup>)–O bonds, it comes as no surprise that there is considerable interest in realizing the potential of organozinc compounds in these reactions.

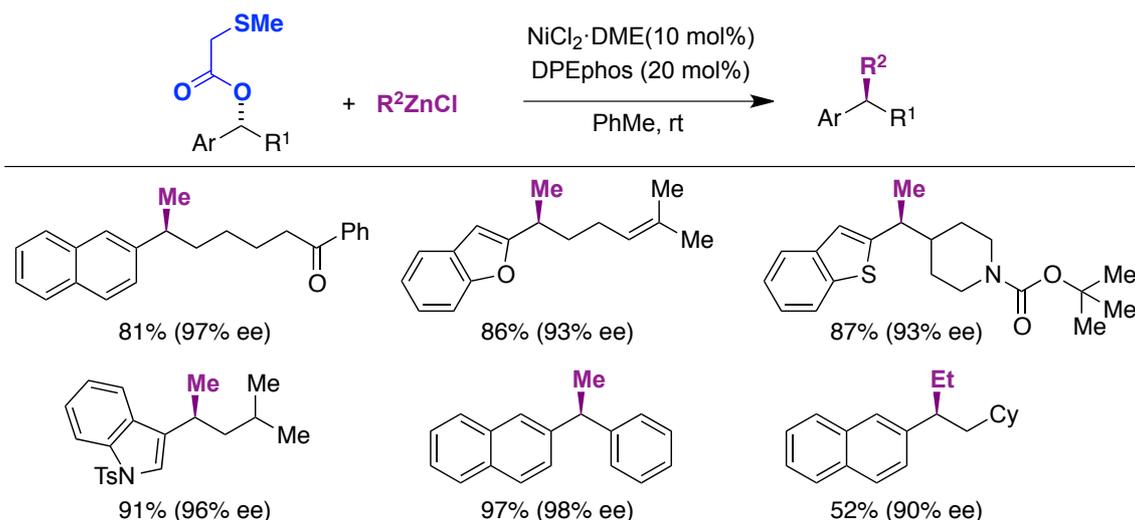
### 2.2.1. Esters

In 2008, Shi reported the Ni-catalyzed cross-coupling reaction of aryl pivalates and in situ generated arylzinc chlorides (Scheme 27).<sup>52</sup> As for the KTC reaction of aryl esters,  $\pi$ -extended systems were considerably more reactive than their phenyl congeners. With this in mind, good yields could still be obtained for electron-poor aryl esters or indene backbones. The authors proposed a “classical” organometallic pathway involving the oxidative addition of aryl pivalates to Ni(0) species followed by a transmetalation and a final reductive elimination to deliver the expected biaryl motifs.



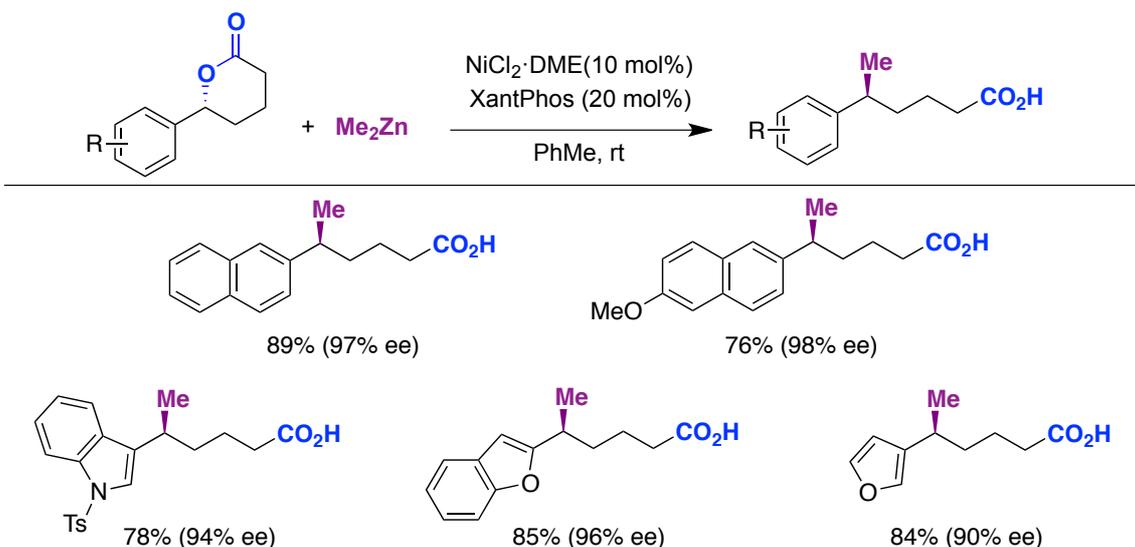
**Scheme 27.** Ni-catalyzed Negishi-type coupling reactions of aryl pivalates

Continuing their research into stereospecific KTC reactions via C(sp<sup>3</sup>)–O bond cleavage, the Jarvo group reported the Ni-catalyzed Negishi-type reaction of organozinc derivatives with enantioenriched secondary benzyl ester derivatives (Scheme 28).<sup>53</sup> The use of less-reactive organozinc compounds was expected to be problematic due to the propensity of alkyl organometallic species towards destructive  $\beta$ -hydride elimination or radical-type pathways that could ultimately erode the enantiopurity of the products. These challenges were addressed through the systematic optimization of the leaving group, leading to the identification of (methylthio)acetates as the optimal substrates. This is presumably due to the chelating effect in these species. Thus, a number of enantioenriched secondary benzyl alcohol derivatives bearing 2-naphthyl or heteroaryl substituents could be coupled in good to excellent yields and with essentially perfect stereospecificity. Even substrates prone to racemization, such as 3-indoyle substituted species or benzhydryl derivatives, could be employed with equal success, highlighting the ability of this approach to suppress epimerization pathways. Notably, this methodology is particularly sensitive to the nature of the organometallic species employed, as Et<sub>2</sub>Zn requires a different set of reaction conditions.



**Scheme 28.** Stereospecific Ni-catalyzed Negishi coupling reactions of benzyl ester derivatives

In 2014, Jarvo reported an expansion of their previous methodology to the stereospecific ring opening of 6-aryl substituted enantioenriched  $\delta$ -valerolactone derivatives with  $\text{Me}_2\text{Zn}$  (Scheme 29).<sup>54</sup> These reactions also proceeded with exceptional stereospecificities; however, the protocol is primarily restricted to naphthyl- and heteroaryl-substituted substrates, a recurring limitation in catalytic C–O bond cleavage reactions.

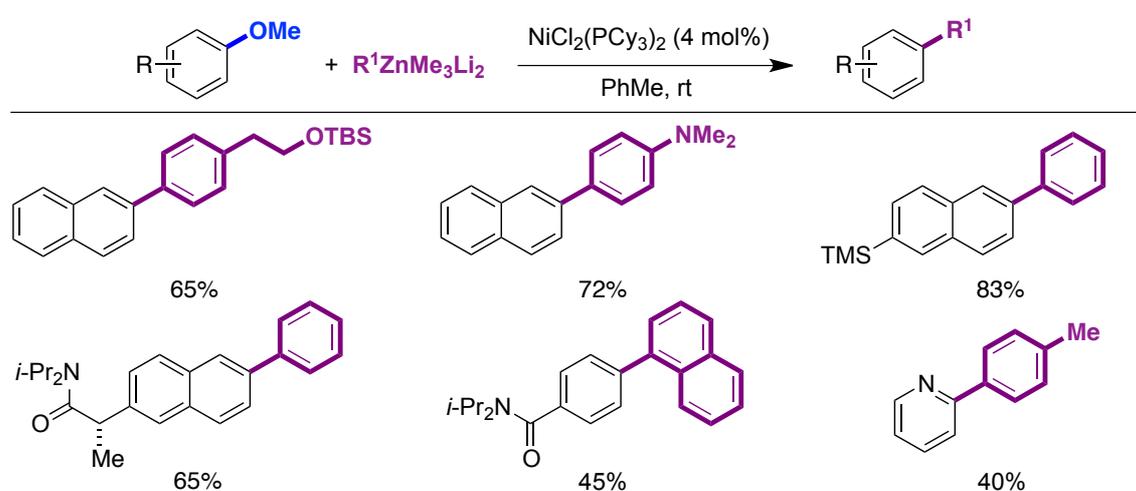


**Scheme 29.** Stereospecific Ni-catalyzed coupling of  $\text{Me}_2\text{Zn}$  with 6-aryl  $\delta$ -valerolactone

### 2.2.2. Ethers

Due to the exceptional bond-dissociation energy required for effecting  $\text{C}(\text{sp}^2)\text{--OMe}$  cleavage, one might wonder whether cross-coupling reactions of aryl ethers with less-reactive organozinc derivatives could ever be implemented. This challenge was met by Uchiyama and Wang, who used dianion-type organozincates  $\text{ArZnMe}_3\text{Li}_2$  that were generated in situ from  $\text{Me}_4\text{ZnLi}_2$  (prepared by exposing  $\text{ZnCl}_2$  to an excess of  $\text{MeLi}$  in  $\text{THF}/\text{Et}_2\text{O}$ ), and appropriately substituted aryl iodides (Scheme 30).<sup>55</sup> As for other C–O bond

cleavage processes, a significant preference for  $\pi$ -extended substrates was observed regardless of the identity of the nucleophilic component. Notably, these conditions could be even be applied to with substrates prone to racemization without any apparent erosion of enantiopurity. Intriguingly, aryl pivalate substrates provided inferior results to aryl methyl ethers, which contrasts with the prevailing dogma that the lower the bond-dissociation energy, the higher the reactivity of the C–O electrophile. The authors rationalized these results on the basis of the competitive addition of the nucleophilic aryl zinc species to the carbonyl group of the pivaloyl motif. Although the authors favored a catalytic cycle involving an oxidative addition, transmetalation and reductive elimination, no mechanistic experiments were conducted, thus leaving ample room for the proposal of alternative scenarios.



**Scheme 30.** Ni-catalyzed Negishi coupling of dianion-type organozincates with aryl ethers

As judged by the available literature data, the development of Negishi-type cross-coupling reactions via C–O bond cleavage is still in its infancy compared to the KTC reactions. Indeed, a rather limited set of substrates can be employed in these methodologies. The considerably lower reactivity of organozinc derivatives when compared with Grignard reagents may hamper the implementation of these processes for C–O functionalization. However, we anticipate that further efforts would be highly rewarding given the excellent functional group tolerance of organozinc derivatives. To this end, recent reports on the use of metal salts capable of dramatically modulating the reactivity of organozinc compounds hold promise as a way of enhancing the synthetic applicability of Negishi cross-coupling reactions with C–O electrophiles.

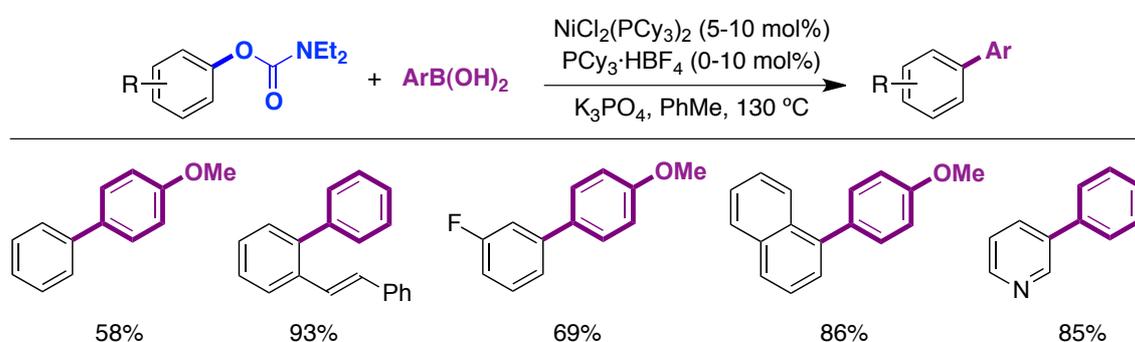
### 2.3. Suzuki-Miyaura-Type Couplings

Although significant advances have been reported in metal-catalyzed cross-coupling reactions using Grignard reagents or organozinc derivatives, the air- and moisture-sensitivity of these coupling partners may still represent a drawback that limits the synthetic applicability of these protocols. Chemists have therefore investigated alternate counterparts with increased flexibility, practicality and generality. Among these, boronic acids or esters

have shown to be viable alternatives to commonly employed Grignard reagents or organozinc derivatives in a variety of C–C bond-forming reactions. Their air-stability and commercial availability have been crucial to their widespread use in both academic and pharmaceutical laboratories. Not surprisingly, a number of Suzuki-Miyaura-type cross-coupling reactions involving C–O bond cleavage have been designed.

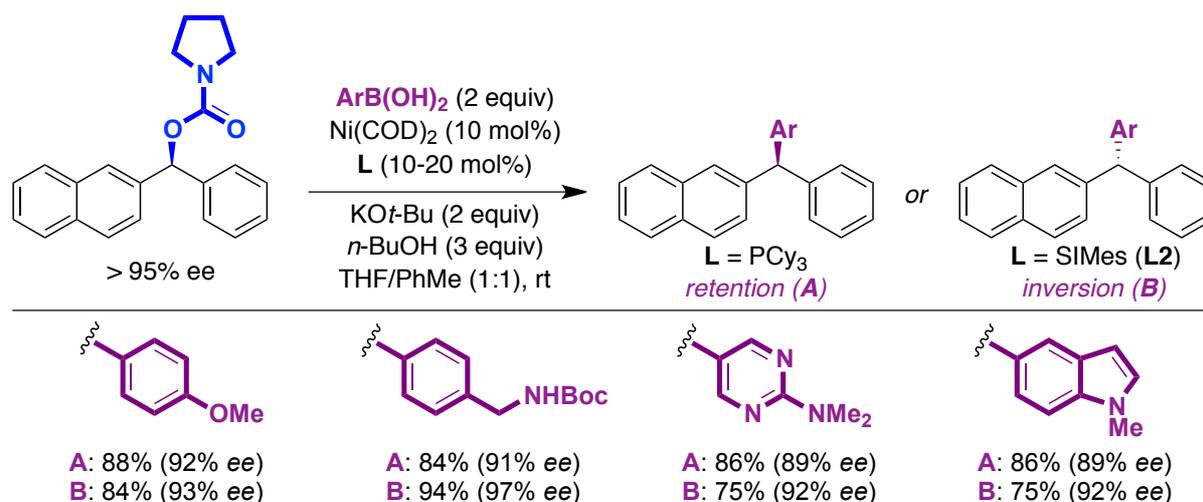
### 2.3.1. Carbamates

In 2009, the groups of Garg and Snieckus independently reported the first Suzuki-Miyaura-type cross-coupling reactions of aryl carbamates (Scheme 31).<sup>56</sup> Intriguingly, Snieckus *et al.* found that the water liberated by the boroxine/boronic acid equilibrium had a non-negligible impact on reactivity, and found that a 10:1 ratio of these compounds gives optimal results. The authors hypothesized that this ratio was critical for forming the intermediate boronates involved in the transmetalation step. This behavior cannot be extrapolated to Garg's protocol due to the presence of significantly larger amounts of potassium carbonate that could serve both as a drying agent and as the promoter of borate formation within the catalytic cycle. Later, the groups of Garg, Snieckus, and Houk described a mechanistic study of the Suzuki-Miyaura-type cross-coupling of aryl carbamates and concluded that the reactions proceed through a sequence of oxidative addition, transmetalation and reductive elimination steps, with transmetalation being the rate-limiting.<sup>57</sup> The authors suggested that the selectivity between the cleavage of the C<sub>aryl</sub>-O bond and the weaker C<sub>carbonyl</sub>-O bond can be explained by a switch between a five-membered transition state (aided by the carbonyl C=O bond) in the former and a three-membered transition state in the latter case. In 2010, Shi and colleagues broadened the applicability of the reaction by including both vinyl and aryl carbamate substrates. Boroxines were used as the nucleophilic entities and stoichiometric water was required.<sup>58</sup> In 2011, Kappe reported that microwave irradiation significantly increases the reaction efficiency of the Ni-catalyzed Suzuki-Miyaura coupling of aryl carbamates, with complete conversions obtained after only 10 minutes.<sup>59</sup> More recently, Tobisu and Chatani demonstrated that the cross-coupling of boronic acids or boronic esters with aryl or vinyl carbamates is not limited to Ni-based catalysts, and that Rh precatalysts can be used with similar efficiencies and selectivities.<sup>60</sup>



**Scheme 31.** Ni-catalyzed Suzuki-Miyaura-type arylation of aryl carbamates

Continuing their research into stereospecific Ni-catalyzed benzylic C(sp<sup>3</sup>)-O functionalization reactions, the Jarvo group described a set of conditions that promote the stereospecific Suzuki-Miyaura arylation of benzyl carbamates (Scheme 32).<sup>61</sup> Although all previous literature data on stereospecific transformations via C-O bond cleavage proceeded via inversion of configuration, the authors found that the nature of the ligand dictated the selectivity pattern when using a particular carbamate motif: whereas the use of SIMes (**L2**) resulted in inversion of configuration, the use of PCy<sub>3</sub> yielded the corresponding arylated product with retention of configuration. Although mechanistic experiments were not performed to understand the origin of this intriguing observation, the authors propose that chelation of the carbamate motif to a Ni catalyst based on PCy<sub>3</sub> results in an oxidative addition with retention of configuration. In contrast, when SIMes (**L2**) is present, oxidative addition is thought to proceed through the common pathway in which inversion of configuration occurs. In both cases, oxidative addition is proposed to take place via a η<sup>3</sup>-Ni(II) intermediate, thus resembling the oxidative addition step of an allylic system. Presumably, this η<sup>3</sup>-coordination explains the lower reactivity observed for non-π-extended backbones, a recurrent drawback observed in a wide variety of C-O functionalization techniques. In a related report, the group of Lu recently described the synthesis of biarylmethanes in water, starting from simple benzylic carbamates and utilizing a Pd-NHC catalyst.<sup>62</sup>

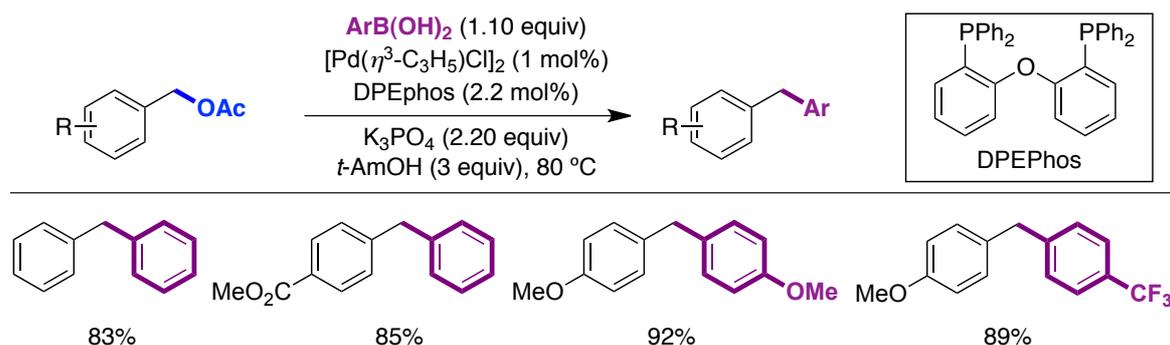


**Scheme 32.** Stereospecific Ni-catalyzed Suzuki-Miyaura arylation of benzyl carbamates

Rueping and coworkers have recently reported the first Suzuki-Miyaura-type coupling of aryl carbamates and pivalates with (9-BBN)-alkyl species possessing β-hydrogens. Although this discovery no doubt constitutes a step-forward, the method is limited to particularly activated naphthyl and biphenyl systems as well as linear alkyl boranes.<sup>63</sup>

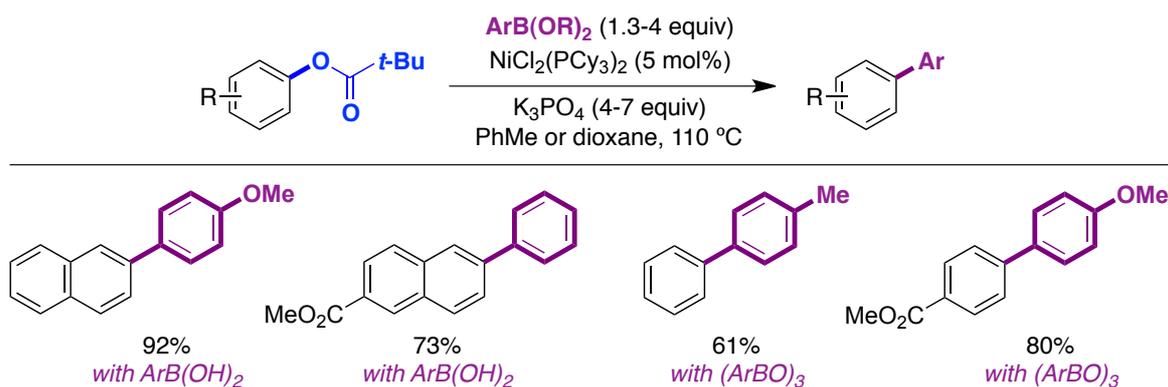
### 2.3.2. Esters

The first Suzuki-Miyaura cross-coupling reaction of boronic acids and ester derivatives was reported by Kuwano and Yokogi using benzyl derivatives and Pd(II) precatalysts (Scheme 33).<sup>64</sup> The alcoholic solvent employed in this transformation was suggested to facilitate the transmetalation step prior to the final reductive elimination.



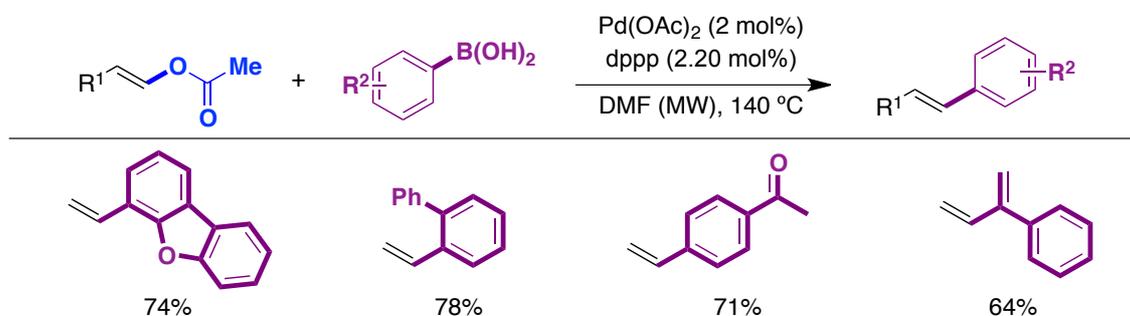
**Scheme 33.** Suzuki-Miyaura-type arylation of benzyl acetates

In 2008, the groups of Garg and Shi independently developed Ni-catalyzed protocols for the Suzuki-Miyaura-type cross-coupling of aryl ester derivatives (Scheme 34).<sup>65</sup> It is worth noting that these reactions are highly reminiscent of the use of aryl carbamates for similar purposes reported by Garg and Snieckus.<sup>56</sup> Whereas Garg utilized aryl boronic acids with aryl pivalates as coupling partners, Shi employed the corresponding boroxines in the presence of stoichiometric amounts of water and a wide variety of different aryl ester motifs. Both groups highlighted the synthetic utility of the newly developed protocols in the context of multistep syntheses. Shi proposed a “classical” cross-coupling mechanism consisting of a Ni(0)/Ni(II) couple and oxidative addition, transmetalation, and reductive elimination. Such a scenario was later corroborated by Liu in a computational study of the reaction of aryl acetates with aryl boronic acids.<sup>66</sup> Based on the stoichiometric studies by Yamamoto and colleagues in the context of Kumada-Tamao-Corriu-type reactions,<sup>10</sup> aryl acetates would be expected to undergo undesirable  $\text{C}_{\text{carbonyl}}\text{-O}$  bond cleavage with reasonable ease. Indeed, theoretical calculations revealed a considerably lower activation barrier for  $\text{C}_{\text{carbonyl}}\text{-O}$  bond cleavage than the desired  $\text{C}_{\text{aryl}}\text{-O}$  functionalization. However,  $\text{C}_{\text{carbonyl}}\text{-O}$  activation was found to be reversible, with the resulting Ni(II) acyl complex not able to undergo easy transmetalation. This can therefore be considered a prototypical Curtin-Hammett situation in which selectivity arises from two interconverting isomers, one of which leads to the desired the  $\text{C}_{\text{aryl}}\text{-O}$  bond cleavage product due to its lower kinetic energy barrier. Molander subsequently disclosed a related protocol using potassium heteroaryltrifluoroborates as the nucleophilic component and a limited set of  $\pi$ -extended aryl pivalate substrates.<sup>67</sup> The synthetic applicability of the Suzuki-Miyaura arylation of aryl esters was demonstrated by Tu and co-workers by preparing fluorescent (hetero)-aryl substituted anthracene derivatives using a pyridine-bridged pincer NHC Ni complex supported by  $\text{PCy}_3$ .<sup>68</sup>



**Scheme 34.** Ni-catalyzed Suzuki-Miyaura-type arylations of aryl esters

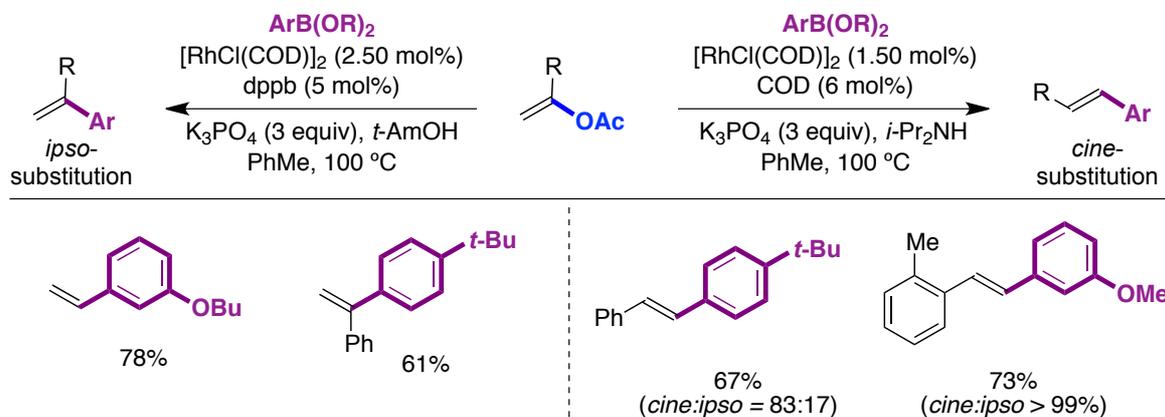
The use of vinyl acetate derivatives as coupling partners in Suzuki-Miyaura-type reactions has been reported using Pd, Rh and Ni catalysts. Specifically, Larhed and co-workers described a Pd-based protocol using boronic acids as nucleophilic entities that gave the corresponding vinylated compounds (Scheme 34).<sup>69</sup> The authors considered two possible pathways: (1) initial transmetalation of the Pd(II) precatalyst and boronic acid to form an aryl palladium(II) species, followed by carbometalation of the vinyl acetate, and final  $\beta$ -elimination to release the target vinylated arene; (2) Initial hydropalladation of vinyl acetate, followed by  $\beta$ -elimination to deliver ethylene, then carbometalation with the in situ generated aryl palladium(II) species, and a final  $\beta$ -hydride elimination. While it is difficult to distinguish both pathways, mass spectrometry measurements allowed for the detection of some of the putative reaction intermediates, which supported pathway (2).



**Scheme 35.** Pd-catalyzed Suzuki-Miyaura-type arylations with vinyl acetate

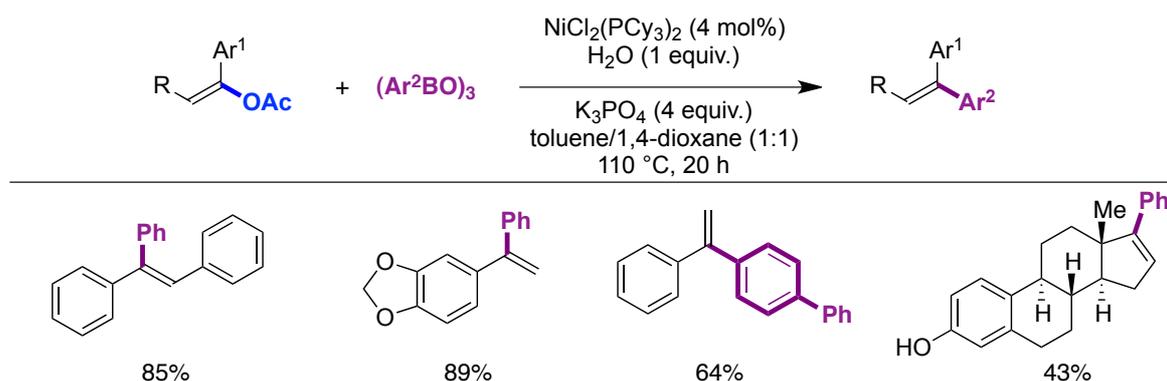
In 2009, Lee and Kwong disclosed a Rh-catalyzed protocol displaying a similarly broad scope of boronic acids using vinyl acetate as coupling partner. The authors proposed a mechanism consisting of oxidative addition, transmetalation and reductive elimination.<sup>70</sup> Kuwano subsequently described two complementary Rh-based catalytic systems (Scheme 36).<sup>71</sup> In the earlier system,<sup>71a</sup> the combination of a Rh-catalyst and dppb as the ligand was found to give *ipso*-substitution selectively. Stereochemical studies suggested a mechanistic scenario based on an oxidative addition, transmetalation and reductive elimination. In their subsequent report,<sup>71b</sup> a catalyst system containing COD as the ligand was found to yield the products of *cine*-substitution with 1-substituted vinyl acetates. The authors proposed a mechanism involving an initial transmetalation to Rh(I) followed by carbometalation and  $\beta$ -

hydride elimination. Hydrorhodation with reversed regioselectivity followed by elimination of Rh acetate would close the catalytic cycle and explain the observed *cine*-substitution. Minor amounts of the *ipso*-substitution product would either form by the mechanism proposed in their previous communication or by imperfections in the regioselectivity of the carbometalation step.



**Scheme 36.** Complementary *ipso*- or *cine*-Suzuki-Miyaura arylation of vinyl acetates

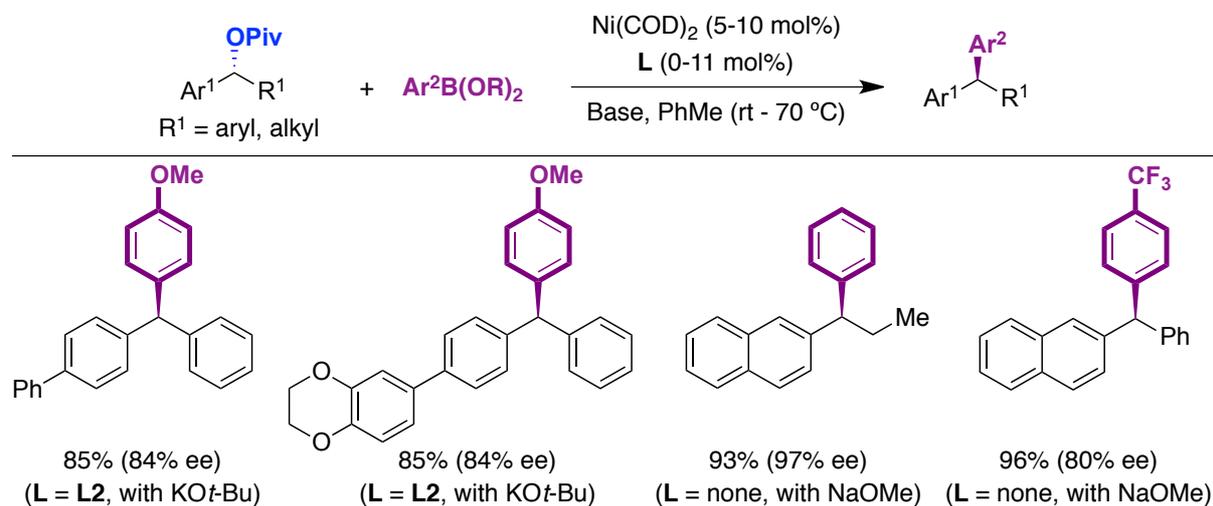
In 2010, Shi disclosed a Ni-catalyzed protocol allowing that allows for the coupling of diversely substituted vinyl acetate derivatives with boroxine coupling partners (Scheme 37).<sup>72</sup> Although no mechanistic studies were reported, the authors favor a “classical” mechanistic scenario consisting of oxidative addition, transmetalation and reductive elimination. Interestingly, the reaction occurs in the presence of an aryl acetate, representing a testament to the higher reactivity of vinylic motifs when compared with aryl acetate backbones



**Scheme 37.** Ni-catalyzed Suzuki-Miyaura-type arylation of vinyl acetates

Taking into consideration the inherent interest of enantioenriched triarylmethane derivatives,<sup>73</sup> Jarvo and Watson independently developed stereospecific Suzuki-Miyaura-type cross-couplings of benzyl pivalate derivatives (Scheme 38).<sup>61,74</sup> Whereas Jarvo employed a catalytic system that is analogous to the one previously described for carbamate substrates,<sup>61</sup> Watson employed a ligand-free  $\text{Ni}(\text{COD})_2$  protocol using boroxines as coupling partners.<sup>74</sup> As expected, inversion of configuration was obtained regardless of whether

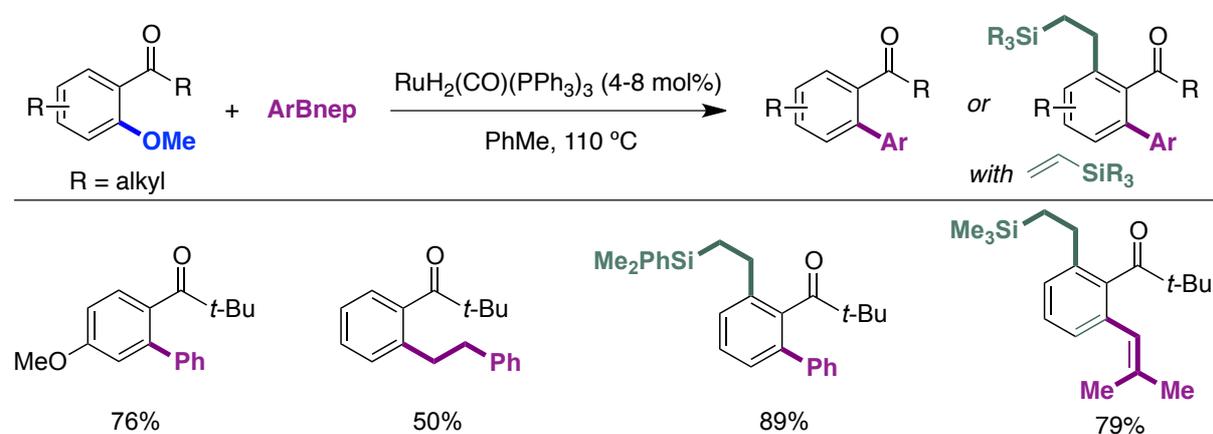
boronates or boroxines were employed as the nucleophilic component. Preliminary mechanistic investigations by Watson concluded that the stereochemical outcome is determined by an inversion of configuration during the oxidative addition step, which is followed by stereoretentive transmetalation and reductive elimination. More recently, Fan and Yang described a catalytic system employing an air-stable Ni(II)-precatalyst, providing good yields for the arylation of racemic and achiral benzyl pivalates.<sup>75</sup>



**Scheme 38.** Stereospecific Ni-catalyzed Suzuki-Miyaura-type arylations of benzyl pivalates

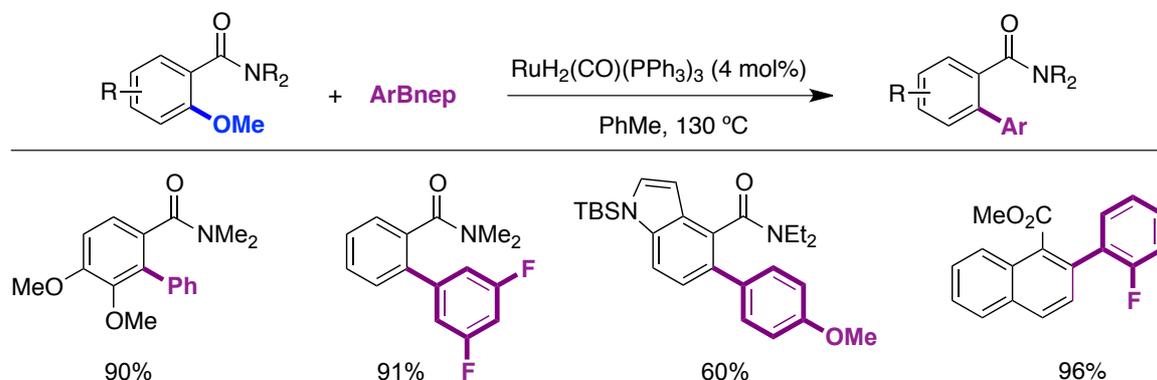
### 2.3.3. Ethers

In 2004, Kakiuchi reported the first Ru-catalyzed Suzuki-Miyaura cross-coupling reactions of aryl neopentyl boronic esters and aryl ethers possessing alkyl ketones located at the *ortho* position (Scheme 39).<sup>76a</sup> Notably, alkenyl and alkyl boronates provided acceptable yields when the catalyst loading was increased to 10 mol%. Intrigued by these results, Kakiuchi studied the metalation of a model substrate, and demonstrated that C–H functionalization is kinetically favored, and that equilibration allows for the thermodynamically favoured C–O bond cleavage.<sup>76b</sup> Based on this observation, a sequential C–H functionalization/C(sp<sup>2</sup>)–OMe arylation reaction was designed, resulting in double functionalization of the substrate.



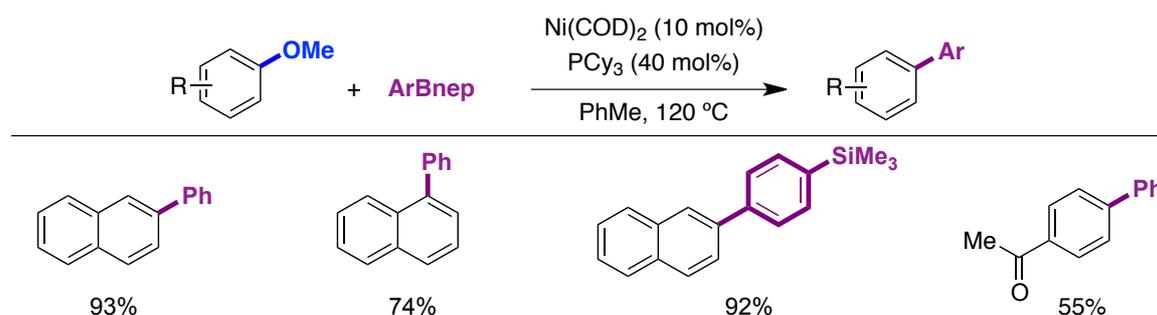
**Scheme 39.** Ketone -directed Ru-catalyzed Suzuki-Miyaura coupling reaction with aryl ethers

Prompted by the work of Kakiuchi, Zhao and Snieckus used the same catalytic protocol but extended the directing group strategy by using amides located at the *ortho* position (Scheme 40).<sup>77</sup> The methodology displayed a broad scope for both the aryl ether and the boronic ester, but unfortunately required the need for a directing group to effect the transformation.



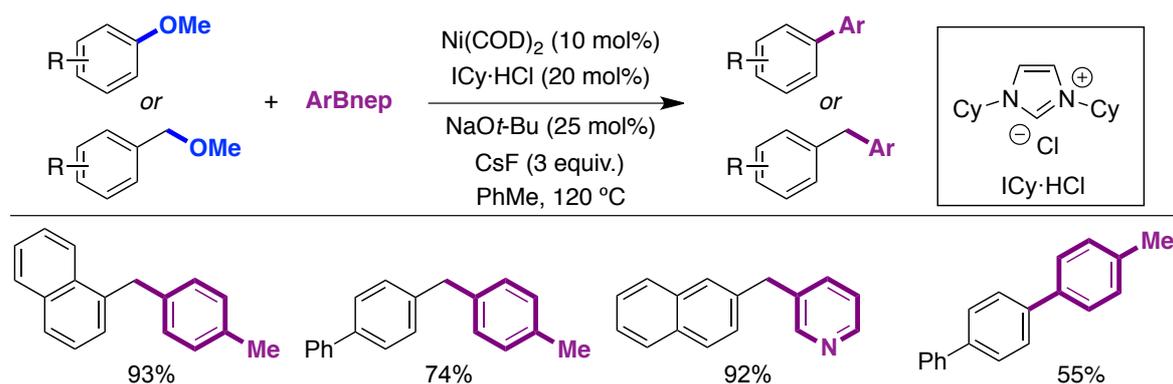
**Scheme 40.** Amide-directed Ru-catalyzed Suzuki-Miyaura coupling of aryl ethers.

Although no doubt a tremendous step forward, the need for an appropriate *ortho*-directing group prevented the application of these reactions to other substrates. Tobisu and Chatani demonstrated the ability of nickel catalysts to effect the Suzuki-Miyaura coupling of aryl methyl ethers *in the absence* of directing groups (Scheme 41).<sup>78</sup> As for other cross-coupling reactions carried out with aryl methyl ether substrates, this reaction is suited to  $\pi$ -extended systems. Under the optimized reaction conditions, a limited set of anisole derivatives bearing electron-withdrawing substituents at the *para*-position could be employed, albeit in considerably lower yields. The authors speculated that a “classical” cross-coupling mechanism involving oxidative addition, transmetalation and reductive elimination might be operative. They also proposed the intermediacy of Meisenheimer-type complexes that are formed via partial dearomatization of the aromatic ring, an observation that might correlate well with the higher reactivity found for  $\pi$ -extended aromatic backbones. Tobisu and Chatani subsequently reported the expansion to vinyl alkyl ethers, thereby broadening the applicability of their initial catalytic system.<sup>79</sup> Interestingly, the configurations of the double bonds involved were found to equilibrate under the reaction conditions. The authors concluded that the products underwent equilibration, as the starting materials were found to be configurationally stable under the reaction conditions



**Scheme 41.** Ni-catalyzed Suzuki-Miyaura reaction of boronic esters with aryl methyl ethers

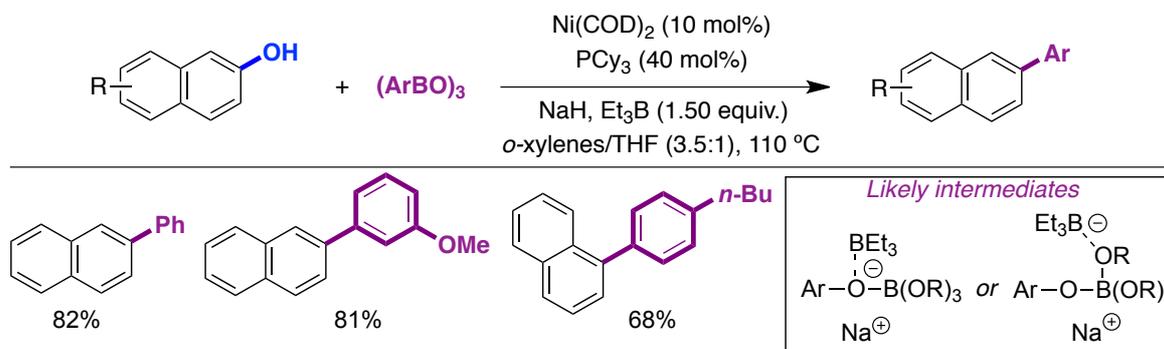
In 2014, Tobisu and Chatani reported a catalytic system based on ICy·HCl that is capable of promoting the cross-coupling reactions of both benzyl methyl ethers and simple anisole derivatives, a limitation encountered on the previous protocol based on PCy<sub>3</sub> (Scheme 42).<sup>78,80</sup> The same authors recently reported a homocoupling protocol of  $\pi$ -extended methoxyarenes using B<sub>2</sub>(nep)<sub>2</sub>.<sup>81</sup> This transformation is based on the ability of the Ni(COD)<sub>2</sub>/ICy catalytic system to undergo an initial C-OMe bond borylation followed by a Suzuki-Miyaura-type coupling between the *in situ* generated aryl boronate and the remaining aryl methyl ether.



**Scheme 42.** Ni-catalyzed Suzuki-Miyaura reactions of aryl and benzyl methyl ethers.

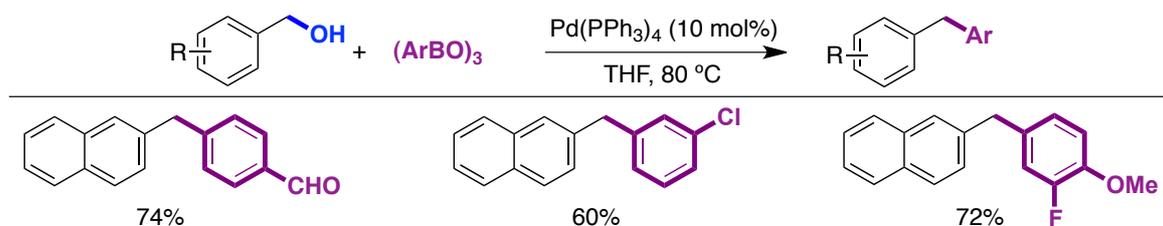
#### 2.3.4. Alcohols

Following their initial work on Ni-catalyzed KTC reactions of simple phenols,<sup>50,51</sup> the Shi group reported a direct Suzuki-Miyaura-type cross coupling reaction via formal Pd-catalyzed C(sp<sup>2</sup>)-OH bond cleavage (Scheme 43).<sup>82</sup> The authors argued that the phenolate derivative generated upon treatment of the substrate with an appropriate base might facilitate the corresponding transmetalation step. The coordination to the Lewis-acidic boron center would substantially increase the leaving group capabilities of the alcoholate oxygen. In line with this notion, the authors found that triethyl borane as additive had a beneficial effect on reactivity. These results gained credence by the crystallization of an analog to the putative naphtholate boronic ester adduct, demonstrating that such a compound was competent as reaction intermediate. Unfortunately, the reaction was limited to  $\pi$ -extended systems.



**Scheme 43.** Ni-catalyzed Suzuki-Miyaura cross-coupling of naphthols with boroxines

In 2015, Shi reported an extension to the mutual activation approach that encompasses benzylic C(sp<sup>3</sup>)-OH bonds (Scheme 44).<sup>83</sup> The reported methodology differs from the previously described protocol for aromatic C(sp<sup>2</sup>)-OH bonds because Pd(PPh<sub>3</sub>)<sub>4</sub> was found to be particularly competent catalyst in the absence of external additives. As for the previous study, the authors proposed a mutual activation mechanism consisting of the coordination of the alcohol functionality to the boroxine, forming an adduct that can participate in the subsequent Suzuki-Miyaura arylation.



**Scheme 44.** Pd-catalyzed Suzuki-Miyaura reactions of benzyl alcohols with boroxines

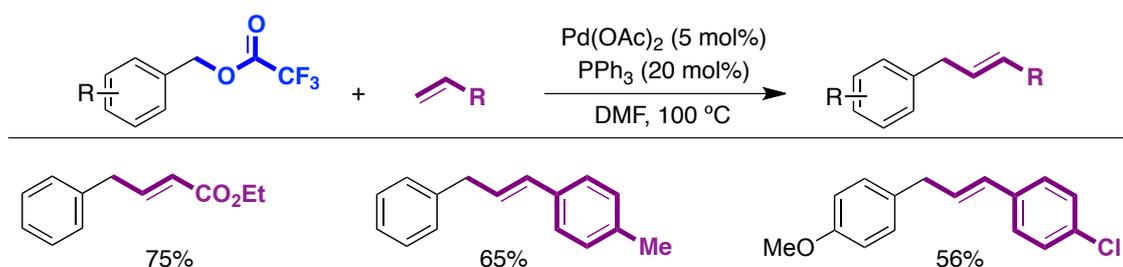
It is evident that a considerable progress has been achieved when performing C–C bond-forming reactions via C–O bond-cleavage using well-defined organometallic components. Despite the advances realized, a wide number of methodologies are still restricted to the utilization of  $\pi$ -extended systems in order to obtain satisfactory results. Unfortunately, these intriguing observations have not been correlated with a deeper mechanistic understanding, an aspect that undoubtedly could potentially lead to the discovery of conceptually new processes in the future.

## 2.4. Mizoroki-Heck-Type Coupling Reactions

Although the use of well-defined organometallic species has contributed to the perception that C–O electrophiles can successfully be employed as organic halide surrogates, a non-negligible number of these reagents are both air- and moisture-sensitive, and the use of these species generates a considerable amount of waste. Therefore, chemists have been challenged to design alternate catalytic C–C bond-forming reactions that avoid the use of organometallic compounds.

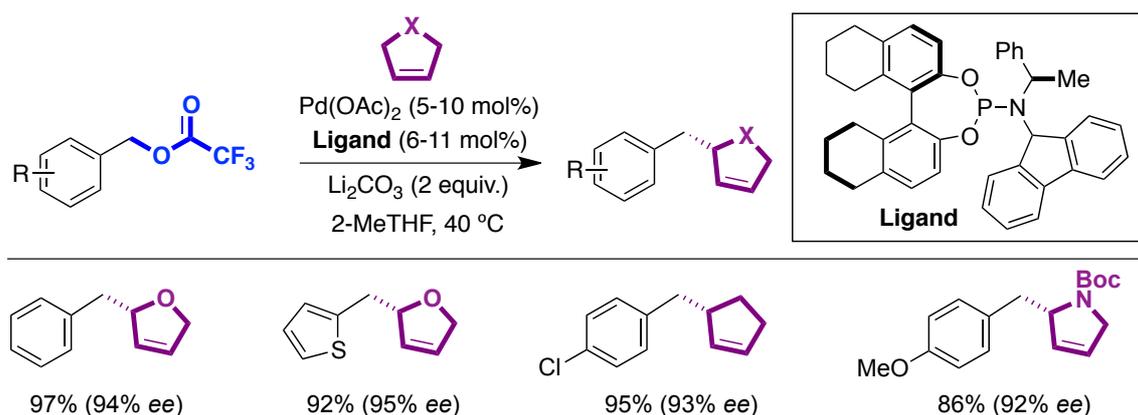
### 2.4.1. Esters

In 2004, Shimizu disclosed a Pd-catalyzed Mizoroki-Heck-type reaction of benzyl trifluoroacetates with appropriately substituted olefins (Scheme 45).<sup>84</sup> The reaction was found to be limited to trifluoroacetate derivatives and to electron-withdrawing olefins, including acrylates and styrenes. Mechanistic studies were carried out with some of the putative reaction intermediates and supplied evidence for a mechanism consisting of an oxidation of the C<sub>benzyl</sub>-O Bond to Pd(0), resulting in  $\eta^1$ -benzylic Pd(II) intermediates that likely coexist with the corresponding  $\eta^3$ -species, followed by insertion into the double bond, and a final  $\beta$ -hydride elimination.<sup>85</sup>



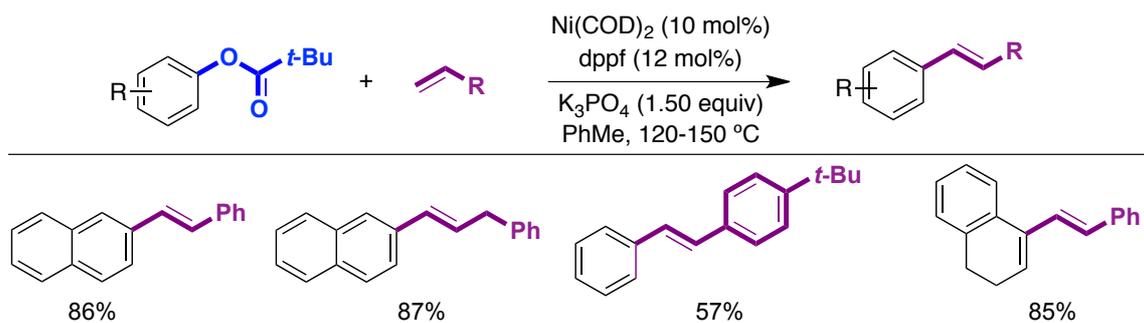
**Scheme 45.** Pd-catalyzed Mizoroki-Heck-type reactions of benzylic trifluoroacetates

Prompted by these precedents, Yang and Zhou reported an asymmetric variant of the Mizoroki-Heck-type reaction with benzyl trifluoroacetate electrophiles and cyclic olefins (Scheme 45).<sup>86</sup> Although a variety of ligands were examined, the best enantioselectivities with a wide variety of substituted benzyl trifluoroacetates were found when using finely tuned phosphoramidite ligands. As for the corresponding olefin counterpart, both 2,3- and 2,5-dihydrofurans could be used as starting materials with similar results, and N-Boc-2,3-pyrrolidine and cyclopentene could be utilized to obtain excellent enantioselectivities. Although one might expect that isomerization of the double bond within the five-membered ring could take place to give achiral products, this was not the case.



**Scheme 46.** Pd-catalyzed Enantioselective Mizoroki-Heck-type reaction of benzylic trifluoroacetates

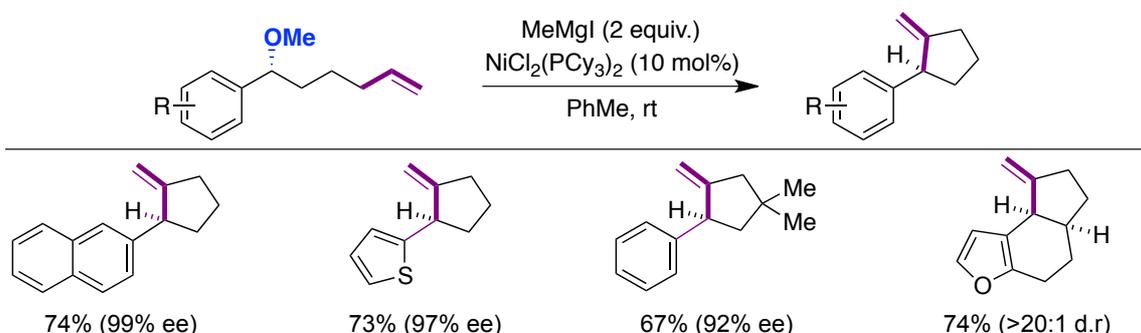
In 2012, Watson disclosed a significant step forward in Mizoroki-Heck-type reactions via C–O bond cleavage using aryl pivalates as substrates (Scheme 47).<sup>87</sup> The reaction was found to tolerate a wide range of aryl and vinyl pivalates, although harsh conditions were required for substrates not featuring extended  $\pi$ -systems. Interestingly, the authors reported an alternative protocol that avoids air-sensitive  $[\text{Ni}(\text{COD})_2]$  by using bench stable  $\text{Ni}(\text{II})\text{Cl}_2\cdot\text{DME}$  as the precatalyst and Zn dust as the reductant.



**Scheme 47.** Ni-catalyzed Mizoroki-Heck-type reaction of aryl pivalates

### 2.4.2. Ethers

Jarvo and colleagues reported a stereospecific intramolecular Mizoroki-Heck reaction of enantioenriched benzyl alkyl ethers (Scheme 48).<sup>88</sup> In general, good to excellent results were observed with naphthyl-substituted or heteroaryl-substituted backbones, and in all cases products were obtained that were derived from an inversion of configuration at the benzylic position. As for other stereospecific transformations, however, non- $\pi$ -extended systems bearing simple phenyl groups proved to be particularly challenging. The authors found that the use of a methoxyethyl ether as leaving groups is advantageous in these cases. A mechanism was proposed involving the initial coordination of the olefin to the Ni(0)-catalyst, followed by an oxidative addition with inversion of configuration. The subsequent migratory insertion and  $\beta$ -hydride elimination reactions are stereospecific, thus fixing the double bond geometry in substrates containing doubly substituted olefins.



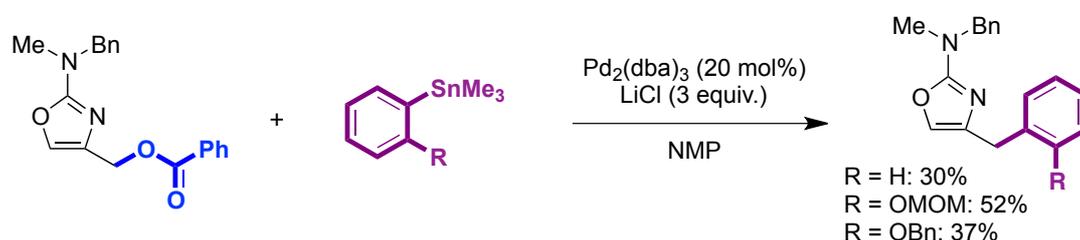
**Scheme 48.** Stereospecific intramolecular Mizoroki-Heck reactions of benzyl ethers

Despite the elegant work of Jarvo, examples of intermolecular variants of Mizoroki-Heck reactions using benzyl alkyl ethers or aryl alkyl ethers are absent in the literature. We certainly anticipate that progress along these lines will bring new knowledge in this field of expertise while dramatically expanding the efficiency and practicality of one of the less-studied reactions in the field of C–O bond cleavage.

### 2.5. Stille-Type Couplings

The only examples reported using Stille-type couplings were described by Pettus using benzoate derivatives (Scheme 49).<sup>89</sup> Unfortunately, these reactions are limited to rather

particular substrates that favor the initial oxidative addition step, and moderate yields are generally obtained, suggesting that significant improvements would be required to explore the full potential of this transformation.



**Scheme 49.** Pd-catalyzed Stille-coupling reaction using benzoate derivatives

## 2.6 Reactions Involving Other Organometallic Compounds: Organolithium and Organoaluminium Reagents

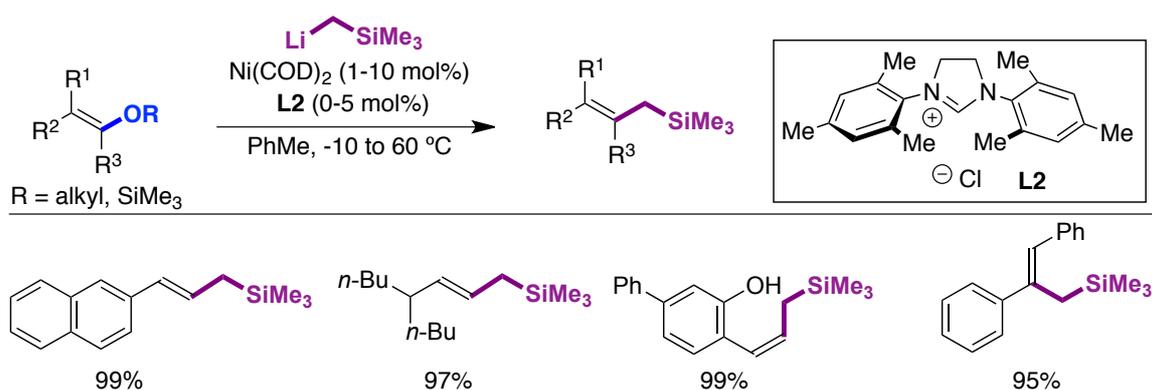
Organolithium reagents rank amongst the most used organometallic reagents in organic synthesis. Although the seminal work of Murahashi and co-workers in 1979 demonstrated the feasibility of their use in cross-coupling reactions,<sup>90</sup> their implementation in these processes has been hampered by their high reactivity, which leads to low functional group tolerance and low yields due to competitive pathways such as  $\beta$ -hydride elimination. Prompted by the seminal work of Murahashi and the work of Feringa using Pd catalysts in related endeavors,<sup>91</sup> Rueping and colleagues disclosed a Ni-catalyzed cross-coupling of aryl methyl ethers with neosilyllithium (Scheme 50).<sup>92</sup> Unlike other C–O bond-functionalizations, a variety of non- $\pi$ -extended systems could be employed with equal ease. Several synthetic applications carried out by transforming the trimethylsilyl group into other functionalized backbones highlighted the application profile of this methodology. The authors proposed a “classical” mechanism consisting of oxidative addition, transmetalation and reductive elimination; however, it is unclear how oxidative addition into a very strong C(sp<sup>2</sup>)–OMe bond could take place under ligand-free conditions. Certainly, a study focused on the mechanism of this transformation would clarify whether other scenarios come into play.



**Scheme 50.** Ni-catalyzed cross-coupling of aryl methyl ethers with neosilyllithium

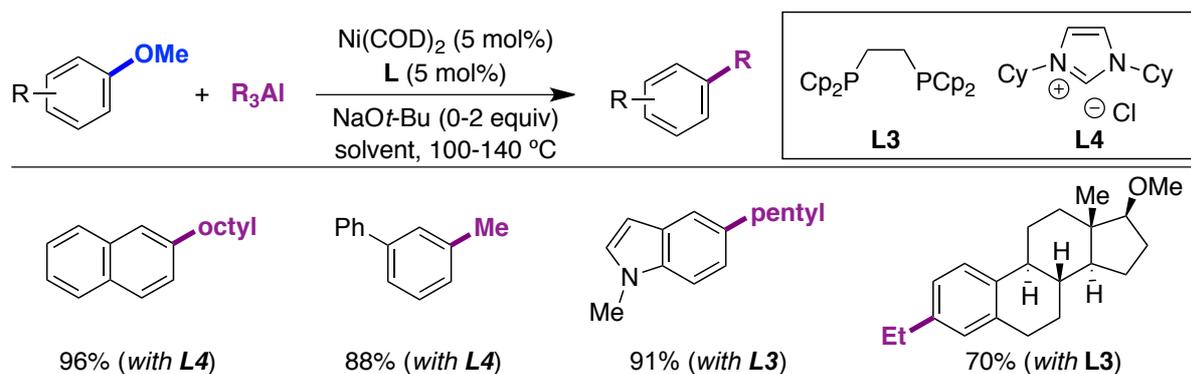
Very recently, Hornillios and Feringa reported a study on the Ni-catalyzed cross-coupling reactions of aryl and heteroaryl lithium species with a series of different leaving groups, including aryl methyl ethers.<sup>93</sup> Unfortunately, a limited number of examples was provided, so the potential of these transformations has not been fully explored. Taking into

consideration these results, Rueping reported the reaction between various vinyl ether derivatives with neosilyllithium (Scheme 51).<sup>94</sup> The protocol was shown to be suitable for vinyl methyl ethers with a diverse range of substituents, as well as for silyl enol ethers. Thus, the methodology gives access to a broad range of allyl trimethylsilane derivatives, which constitute highly valuable intermediates for organic synthesis. In all cases, high stereospecificities were observed and the reactions occurred with retention of the double bond configuration.



**Scheme 51.** Ni-catalyzed cross-coupling of vinyl alkyl and silyl ethers with neosilyllithium

Recently, Tobisu and Chatani published a Ni/NHC-catalyzed methylation of anisole derivatives using trimethylaluminum (Scheme 52).<sup>95</sup> This transformation is the first example of the cross-coupling of challenging phenol derivatives with organoaluminum reagents. Interestingly, other trialkylaluminum reagents with longer alkyl chains provided similar results. Rueping and Schoenebeck then expanded the scope of this transformation by developing a catalytic system that is partially capable of avoiding competing  $\beta$ -hydride elimination by means of a bidentate trialkylphosphine ligand (Scheme 52).<sup>96</sup> *In situ*-prepared primary trialkylaluminum reagents with different chain lengths could be coupled with several aryl methyl ethers in excellent to good yields, whereas other Li-, Mg- or Zn-based nucleophilic reagents gave worse results. Unfortunately, acyclic tertiary trialkylaluminum compounds led to a mixture of branched and linear products. As expected from the high reactivity of R<sub>3</sub>Al as well as the strongly basic conditions, a low functional group tolerance was observed in both Tobisu and Chatani's and Rueping's protocols.



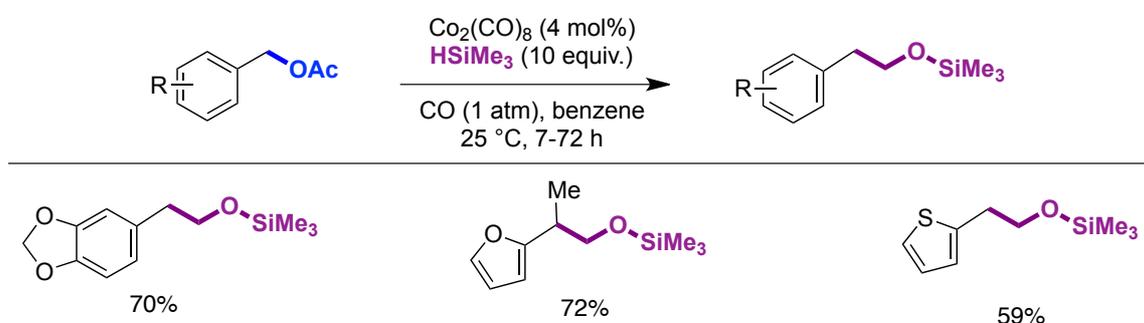
**Scheme 52.** Ni-catalyzed cross-coupling reactions of aryl methyl ethers with R<sub>3</sub>Al

The authors confirmed the presence of an interaction between the aryl methyl ether and the trialkylaluminium reagent by NMR spectroscopy, representing the first experimental proof of the previously suggested Lewis acid-anisole coordination. Computational studies also support the proposal that coordination significantly aids the C-OMe bond oxidative addition and favors the formation of [Ni(II)(OMe)(Ar)] intermediates. Moreover, the presence of a Ni(II) intermediate was underlined by the quantitative formation of product from the reaction of [LNi(II)Cl(Ar)] complex (L = dppf) and AlEt<sub>3</sub>. However, this observation should not be considered conclusive since the ligand utilized differs from that used in the catalytic conditions (dcype).

## 2.7. Miscellaneous C-C Bond-Forming Reactions

### 2.7.1. Reactions of Benzyl Esters with Various Nucleophiles

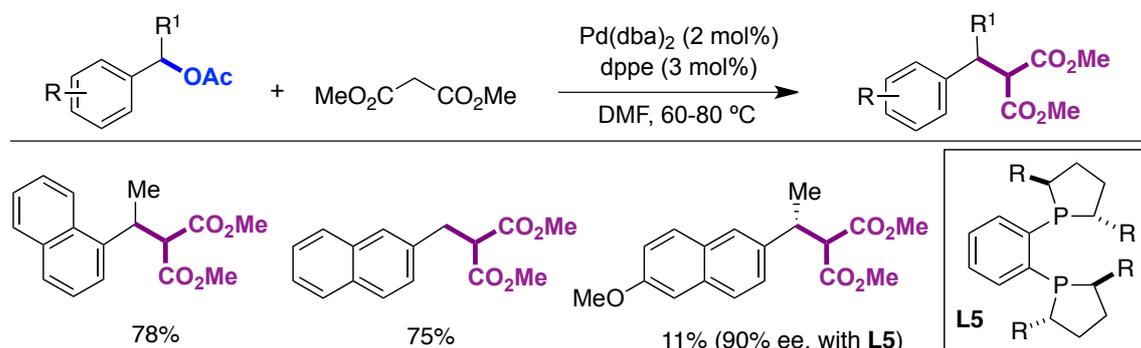
In the early 90's, Murai and co-workers reported a cobalt-catalyzed carbonylation-hydrosilylation sequence using benzyl acetate substrates (Scheme 53).<sup>97</sup> The reaction converted benzyl acetates into the corresponding homobenzylic silyl ethers using carbon monoxide and trimethylsilane. The authors proposed that the reaction proceeds through the initial formation of silyl-cobalt intermediates, which set the stage for an oxidative addition en route to trimethylsilyl acetate and benzyl cobalt species. The latter was proposed to rapidly react with CO to afford an acyl cobalt intermediate that promotes a hydrosilylation. The aldehyde that is liberated undergoes an additional hydrosilylation to deliver the silyl ether product.



**Scheme 53.** Co-catalyzed carbonylation/hydrosilylation of benzyl acetates

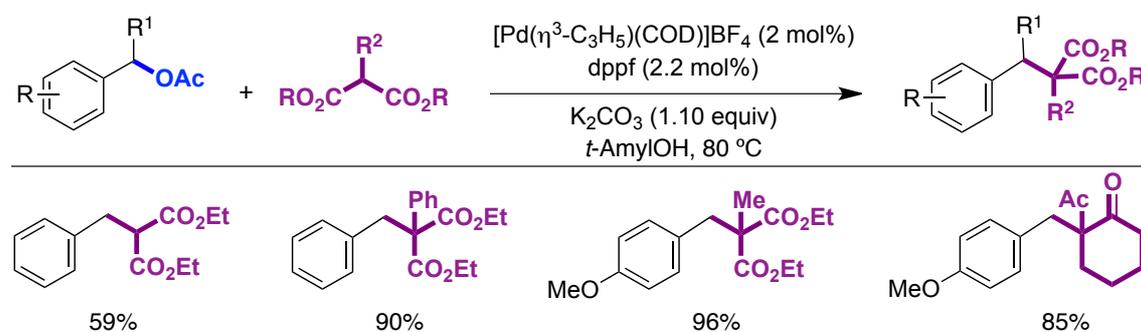
Prompted by Murai's report, Legros and Fiaud studied the possibility of promoting Pd-catalyzed C-C bond-forming reactions of benzyl acetates with dimethylmalonates (Scheme 54).<sup>98</sup> The authors found that the reaction remained limited to benzylic acetates derived from substrates with extended  $\pi$ -backbones, an observation that was attributed to the requirement for partial dearomatization via  $\pi$ -allyl-Pd-complexes. Interestingly, non-negligible stereospecificity was observed when the reaction was carried out with enantiopure secondary benzyl acetates. In all cases, products underwent net inversion of configuration. Unfortunately, however, significant amounts of styrenes were observed, probably due to competitive  $\beta$ -hydride elimination with secondary benzyl acetates. More interestingly, the authors described the use of chiral ligands in combination with racemic

secondary benzyl acetates, obtaining promising yields and stereoinductions with (*S,S*)-BDPP or (*R,R*)-*i*-Pr-DUPHOS.



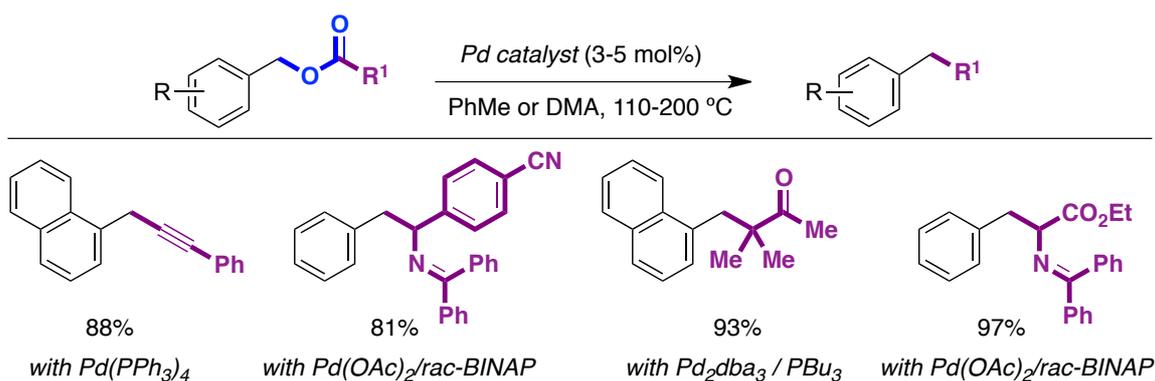
**Scheme 54.** Pd-catalyzed cross-coupling of benzyl acetates with dimethylmalonates

In 2007, Yokogi and Kuwano extended Legros's studies to substrates without extended  $\pi$ -systems using dppf as the ligand (Scheme 55).<sup>99</sup> Lower yields were obtained for unsubstituted diethylmalonates, likely due to the propensity of the substrate to undergo double substitution reactions. Subsequently, Kuwano disclosed an intramolecular protocol in which the malonate and the acetate motif were connected through a tether.<sup>100</sup> Recently, Hirano and Miura reported the successful Pd/(*R*)-H<sub>8</sub>-BINAP-catalyzed asymmetric benzylic alkylation of  $\pi$ -extended benzyl pivalates with a wide range of active methylene compounds.<sup>101</sup> Mal and Roy then described heterobimetallic Pd-Sn-catalysts capable of promoting substitution reactions of benzylic alcohol substrates, although the reactivity resembles the classical Friedel-Crafts-type reaction.<sup>102</sup>



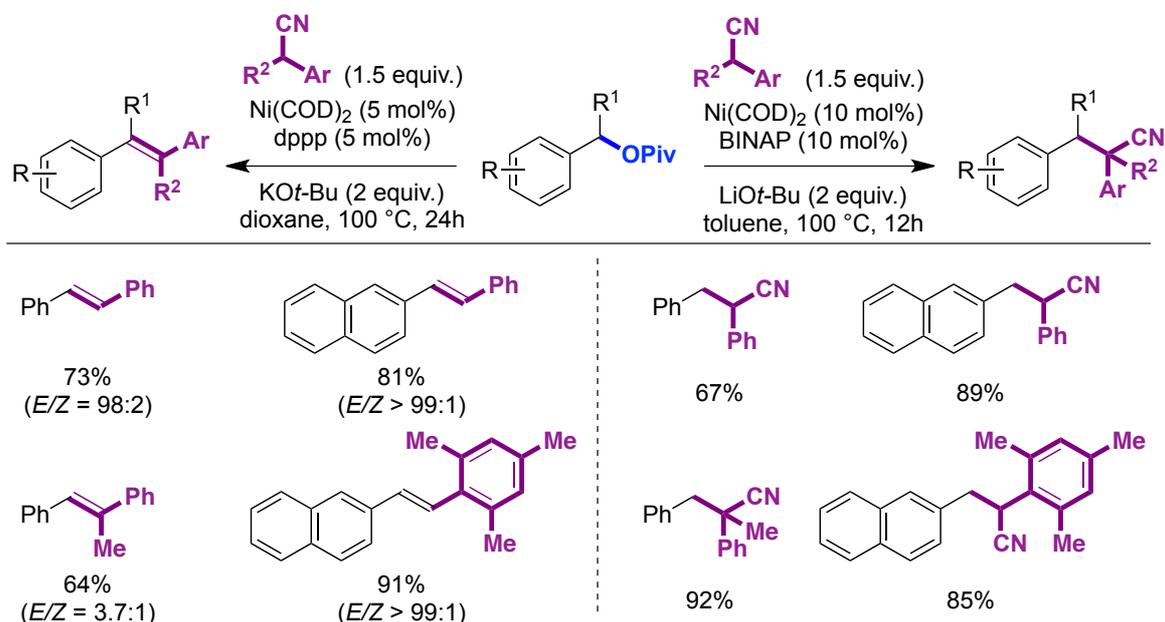
**Scheme 55.** Pd-catalyzed reaction of benzyl acetates with active methylene compounds

Tunge and Chruma have reported decarboxylative processes via C(sp<sup>3</sup>)-O cleavage for the installation of alkynes and ketones at the benzylic position (Scheme 56).<sup>103</sup> Unfortunately, the scope of these reactions is essentially limited to substrates with  $\pi$ -extended backbones. In 2010, Chruma described an otherwise similar transformation using benzyl diphenylglycinate imines; in this case, however, decarboxylation results in benzophenone imine protected amines as products.<sup>104</sup>



**Scheme 56.** Pd-catalyzed decarboxylative reactions of benzyl esters

In 2016, Chen and Han disclosed complementary protocols for the reaction between benzyl pivalates and phenyl acetonitrile derivatives giving either benzylation products or the corresponding stilbene derivatives resulting from HCN elimination (Scheme 57).<sup>105</sup> In both reports, a broad range of benzyl substrates and nucleophiles was presented, encompassing both  $\pi$ -extended backbones and phenyl-type substrates. Mechanistically, the authors propose that the reactions proceed through a “classical” sequence of oxidative addition, ligand exchange, and reductive elimination. The difference between the two protocols was attributed to a subsequent base-induced elimination of HCN occurring for the stilbene formation, favoring *trans*-configured olefins predominantly.

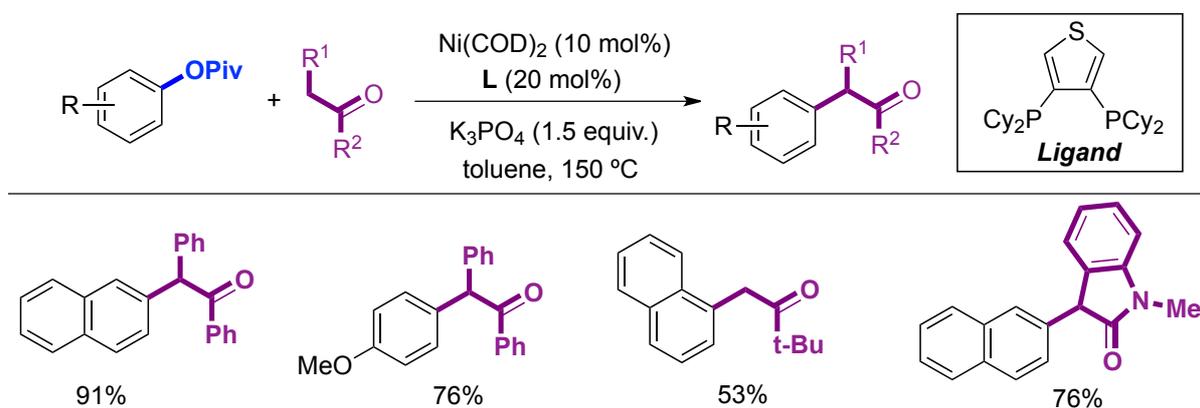


**Scheme 57.** Ni-catalyzed reactions of phenyl acetonitrile derivatives with benzyl pivalates

### 2.7.2. $\alpha$ -Arylations of Aryl Esters

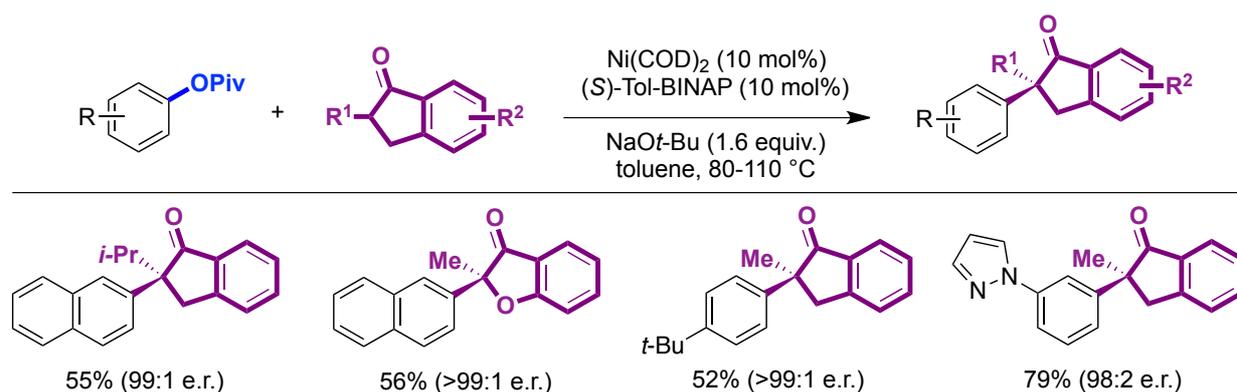
Although remarkable advances have been reported using benzyl esters with nucleophilic entities (Schemes 53-57), these methods are restricted to substrates that can rapidly undergo oxidative addition. In order to bypass this restriction, Itami and Yamaguchi initiated a research program to realise the potential of  $\alpha$ -arylation reactions of pronucleophiles with

aryl esters. Specifically, the authors described the means to promote an  $\alpha$ -arylation of ketone derivatives (Scheme 58).<sup>106</sup> Their catalytic system involved the use of a thiophene bridged bis(dicyclohexyl)phosphine ligand and enabled the reaction of various activated and non-activated aryl pivalates with differently substituted ketones. The authors succeeded in isolating the product of oxidative addition between the ligand-stabilized Ni(0)-species and the 2-naphthol-derived pivalate. The resulting Ni(II)-complex was characterized by X-ray crystallography.<sup>107</sup> Stoichiometric and catalytic experiments revealed that this compound was a competent reaction intermediate and a suitable Ni(II) precatalyst. In 2015, the same group reported an extension of the methodology to phenylacetic acid derivatives, cyclic amides, and aryl pivalates.<sup>108</sup>



**Scheme 58.** Ni-catalyzed  $\alpha$ -Arylation of ketones, esters and amides

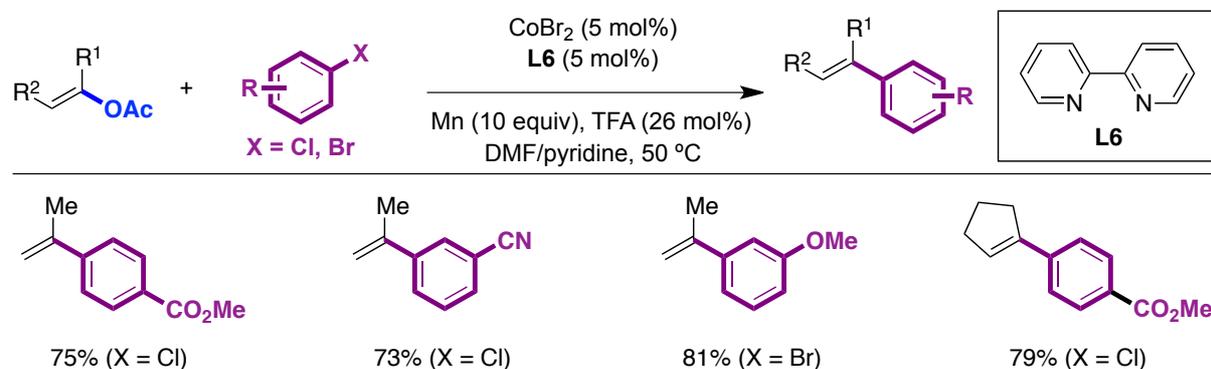
Although the work of Itami and Yamaguchi suggested that a rather electron-rich ligand was required for effecting the  $\alpha$ -arylation of aryl esters via C–O bond cleavage, Martin demonstrated that enantioselective  $\alpha$ -arylation of cyclic ketones could be conducted using chiral BINAP derivatives with cyclic ketones and high levels of enantioselectivity (Scheme 59).<sup>109</sup> Under these conditions,  $\alpha$ -branched cyclic ketones reacted with both activated and non-activated aryl pivalates to give virtually enantiopure  $\alpha$ -arylated ketones, thereby generating a quaternary stereocenter in an enantioselective fashion. Additionally, the nucleophile part could be varied to include larger substituents on the reactive site, heteroatoms on the nucleophilic carbon center, substitution on the backbone, as well as larger rings. With this study, the potential to use challenging C–O bond activations in the context of enantioselective reactions was highlighted. This is complementary to the protocols discussed above that deal with stereospecific reactions on substrates with preexisting stereocenters.



**Scheme 59.** Ni-catalyzed enantioselective  $\alpha$ -arylation of cyclic ketones with aryl esters

### 2.7.3. Reductive Coupling Reactions

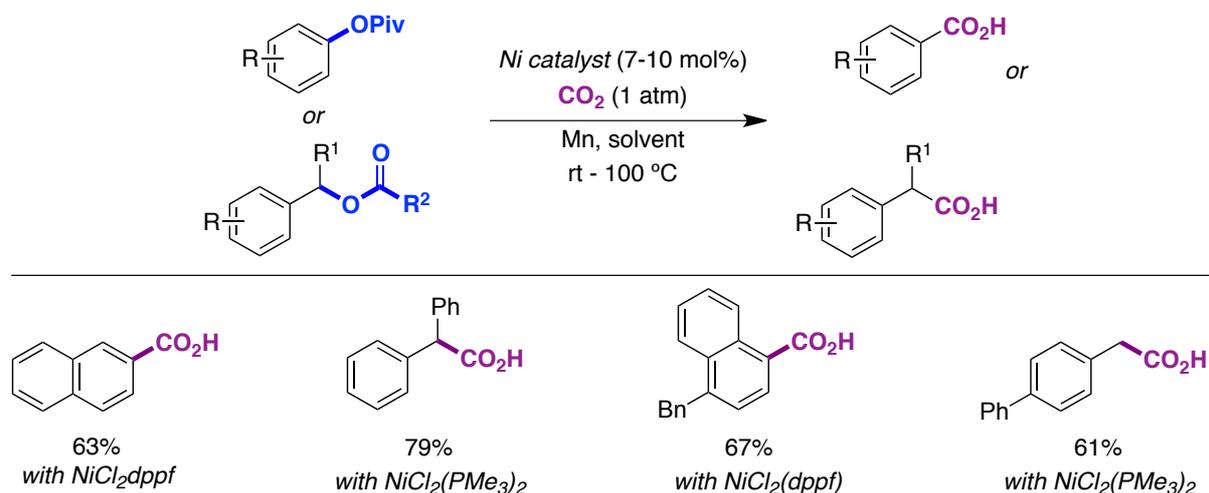
In recent years, cross-electrophile coupling reactions have become powerful alternatives to classical nucleophilic/electrophile regimes based on stoichiometric, well-defined and in many instances, air-sensitive organometallic species.<sup>110</sup> At present, the vast majority of these processes remain confined to organic halides, giving the perception that C–O electrophiles could not be employed as coupling partners in these endeavors. In 2005, Gosmini successfully implemented a Co-catalyzed reductive cross-electrophile coupling of aryl halides and vinyl acetate derivatives using bipyridine as ligand and manganese as reductant (Scheme 60).<sup>111</sup> Using bipyridine as the ligand and manganese as the reductant, a series of aryl chlorides and bromides, including heteroaryl derivatives, could be coupled with a variety of vinyl acetates.



**Scheme 60.** Co-catalyzed reductive coupling of aryl halides and vinyl acetates

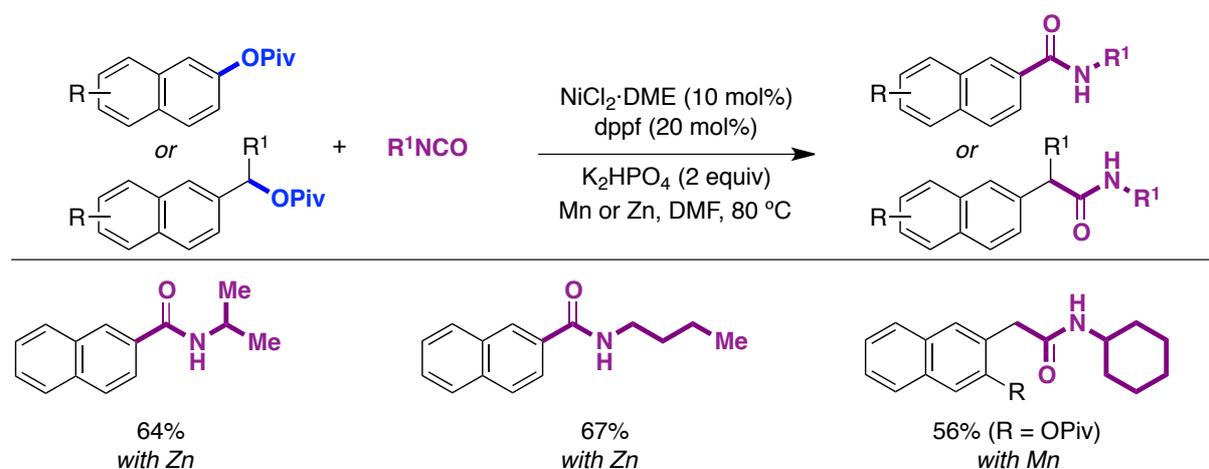
Continuing their research into catalytic reductive carboxylation reactions using carbon dioxide as a C1 synthon,<sup>112</sup> the Martin group demonstrated the viability of promoting reductive carboxylation techniques using aryl and benzyl esters as electrophiles via C–O cleavage (Scheme 61).<sup>113</sup> Although  $\pi$ -extended backbones were required when dealing with aryl ester derivatives, the use of traceless directing groups allowed for the coupling of regular aromatic motifs via C–O cleavage. It was postulated that the presence of a hemilabile directing group dramatically accelerated the rate of oxidative addition and opened coordination sites at the Ni center that facilitated the binding of CO<sub>2</sub>. The Martin group

conducted control experiments that allowed them to rule out the presence of *in situ* generated organomanganese species. This pointed to a mechanistic scenario based on the intermediacy of Ni(I) species that are able to react rapidly with carbon dioxide prior to a single-electron transfer mediated by Mn, thus regenerating the active Ni(0) catalyst while forming a manganese carboxylate that upon hydrolytic workup generates the desired carboxylic acid.



**Scheme 61.** Ni-catalyzed reductive carboxylations of aryl and benzyl esters

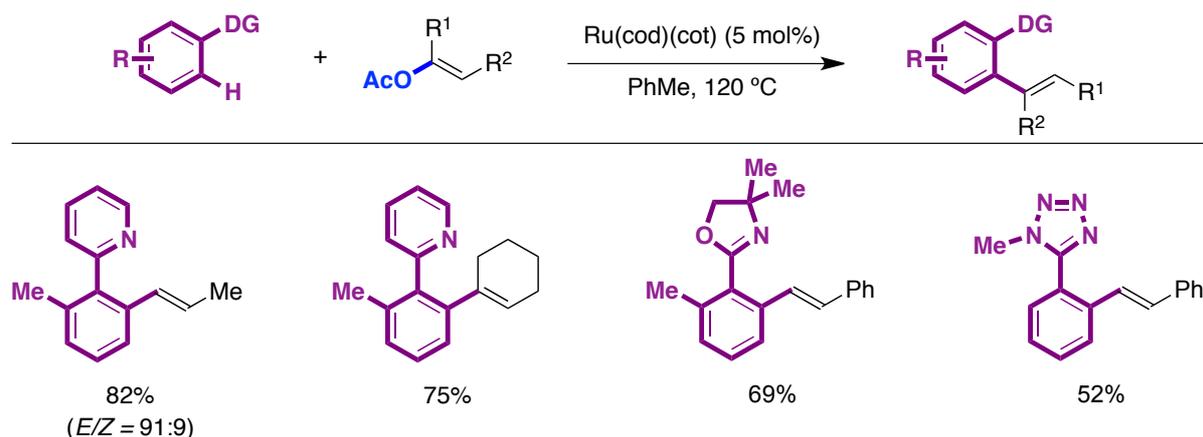
Recently, Martin reported the Ni-catalyzed reductive amidation of aryl pivalates with both alkyl and aryl isocyanates via C(sp<sup>2</sup>)- and C(sp<sup>3</sup>)-O bond cleavage (Scheme 62).<sup>114</sup> Although the C-O cleavage protocol was restricted to naphthalene derivatives, the use of aryl halides gave access to the corresponding benzamides without requiring a  $\pi$ -extended backbone. Like for other related reductive coupling protocols, benzylic C-O electrophiles were considerably more reactive than aryl C-O bonds, probably due to the higher propensity of benzylic electrophiles to undergo oxidative addition.



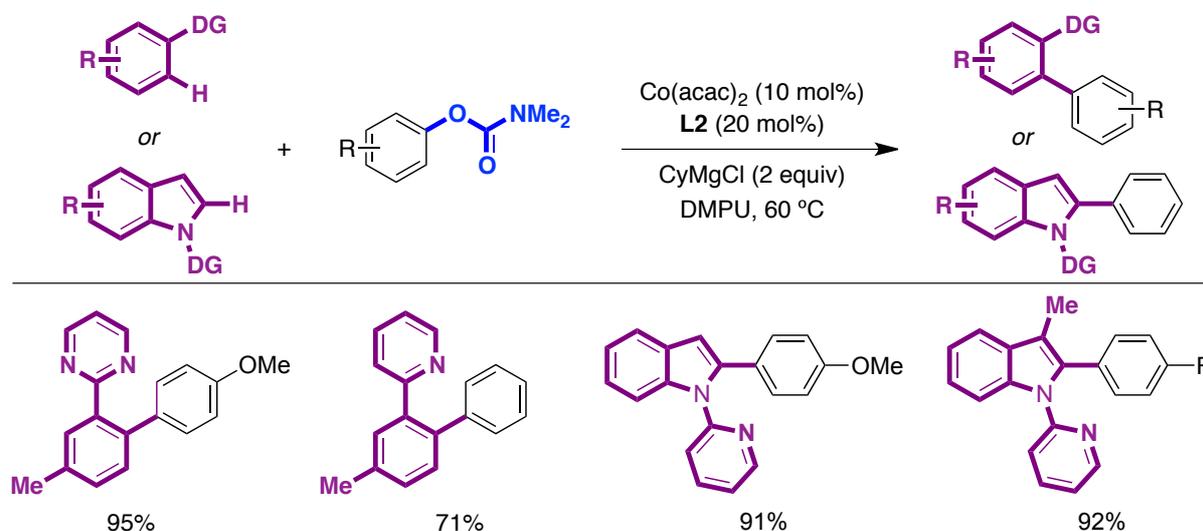
**Scheme 62.** Ni-catalyzed reductive amidation of aryl and benzyl pivalates with isocyanates

## 2.7.4. C-H/C-O Coupling Reactions

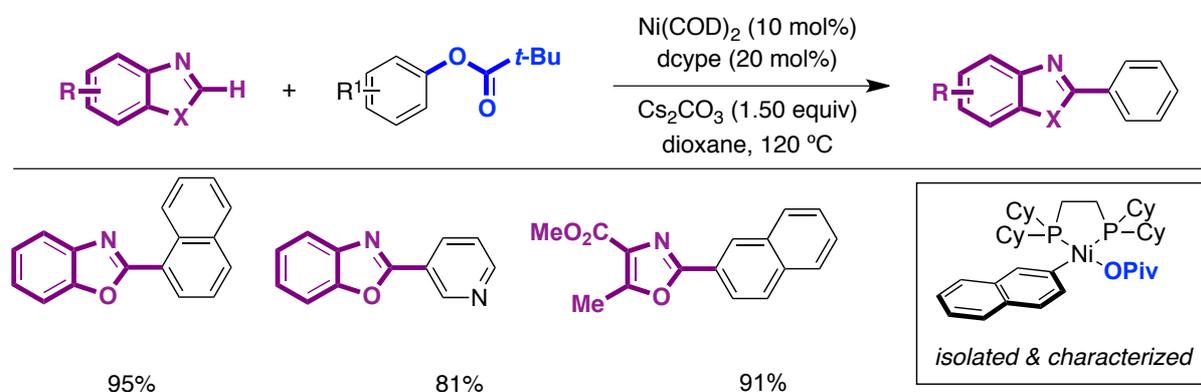
Although the means to promote cross-electrophile couplings represents a significant step towards the implementation of C–O electrophiles in cross-coupling methodologies, the need for pre-functionalization of both coupling partners still represents a limitation. To this end, Kakiuchi investigated the possibility of using vinyl acetates in combination with a ruthenium-catalyzed C–H bond-functionalization event (Scheme 63).<sup>115</sup> Using this protocol, a variety of vinyl acetates and arenes possessing *ortho*-pyridine, -oxazoline, or -tetrazole directing groups gave similar yields of the desired products.



In 2012, Song and Ackermann reported on the use of cobalt catalysis to enable the reaction of a variety of aryl carbamates with arenes possessing *ortho*-pyridyl and -pyrimidyl directing groups (Scheme 64).<sup>116</sup> Control experiments pointed towards a pathway that depends on the inherent kinetic C–H acidity of the substrates. The authors subsequently reported an extension of their protocol that includes indole derivatives, alkenyl acetates, and alkenyl carbamates.<sup>117</sup>



Itami and Yamaguchi developed a Ni-catalyzed arylation of oxazole and thiazole derivatives using aryl pivalates as counterparts (Scheme 65).<sup>118</sup> A wide range of (benz)oxazoles and thiazoles could be reacted with aryl pivalates under these conditions to give the cross coupling products in good to excellent yields, although activated aryl pivalates were required. A number of features deserve further consideration: (1) the choice of dcype (**L3**) as the ligand was found to be crucial for the reaction to proceed; (2) cesium carbonate was found to be superior to other related inorganic bases. Itami, Yamaguchi, and Lei continued the work on this catalytic system by conducting a mechanistic study. The authors provided extensive data in favor of a mechanism consisting of an oxidative addition of the aryl pivalate to Ni(0)(dcype) followed by ligand exchange, C(sp<sup>2</sup>)-H functionalization and a final reductive elimination. The nickel(II) complex resulting from oxidative addition into the C(sp<sup>2</sup>)-O bond of 2-naphthyl pivalates was isolated, constituting the first evidence that C(sp<sup>2</sup>)-O bond cleavage in aryl esters may indeed involve direct oxidative addition.<sup>107</sup>



**Scheme 65.** Ni-catalyzed C-H activation/arylation of (benz)oxazole and thiazole derivatives using aryl pivalates

In 2014, a computational study aimed at elucidating the precise role of the Cs<sub>2</sub>CO<sub>3</sub> base was reported.<sup>119</sup> The calculations confirmed that C-H functionalization is rate-determining and proceeds through a concerted-metalation-deprotonation pathway in the absence of base. Interestingly, Cs<sub>2</sub>CO<sub>3</sub> was found to react with the oxidative addition intermediate, giving an adduct of type [Ni(dcype)(naph)][PivOCs-CsCO<sub>3</sub>]. Coordination of the azole to the Ni(II) center results in a significant increase in the azole acidity and leads to a lower barrier for the C-H functionalization event. Itami and Yamaguchi subsequently disclosed a related catalytic system that enables the use of N-substituted (benz)imidazoles as substrates in otherwise analogous reactions.<sup>120</sup> Very recently, Carpentier and Kirillov reported the possibility of performing C-H/C-OMe coupling with yttrium and scandium complexes. Although these reactions occurred in a stoichiometric fashion, this report demonstrated the ability of certain early transition metals to activate C-O bonds.<sup>121</sup> Recently, Shi and coworkers have reported a Ni/Cu-catalyzed C-O/C-H coupling of aryl carbamates and polyfluoroarenes. The authors proposed polyfluoroarylcuprates(I) as the active transmetalating species to the ArNi(II)OR intermediates generated through the oxidative addition of the C-O bonds to Ni(0).<sup>122</sup>

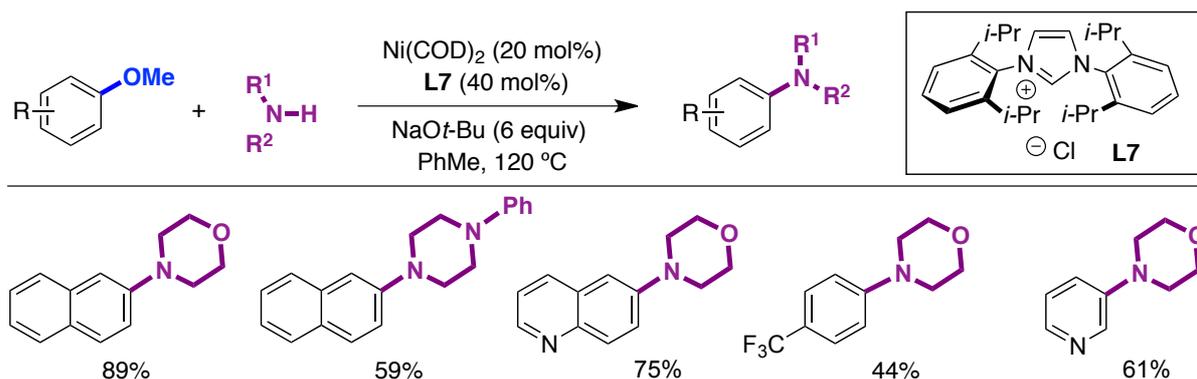
Overall, the reactions summarized in this chapter on miscellaneous reactions involving the activation of C–O bonds demonstrate the potential of C–O electrophiles in catalytic cross-coupling processes. The diversity of the reaction partners, ranging from reductive couplings with appropriate electrophilic partners to challenging nucleophilic entities, indicates that much remains to be discovered.

### 3. Carbon-Heteroatom Bond-Forming Reactions

Unlike the wealth of literature data on catalytic C–C bond-forming reactions using C–O electrophiles, the means to promote C-heteroatom bond-formation remains rather unexplored. Taking into consideration that catalytic C-heteroatom bond-formation has significantly contributed to streamlining the synthesis of many pharmaceuticals and other molecules that display significant biological properties,<sup>123</sup> chemists have been challenged to implement otherwise similar protocols via C–O bond cleavage.

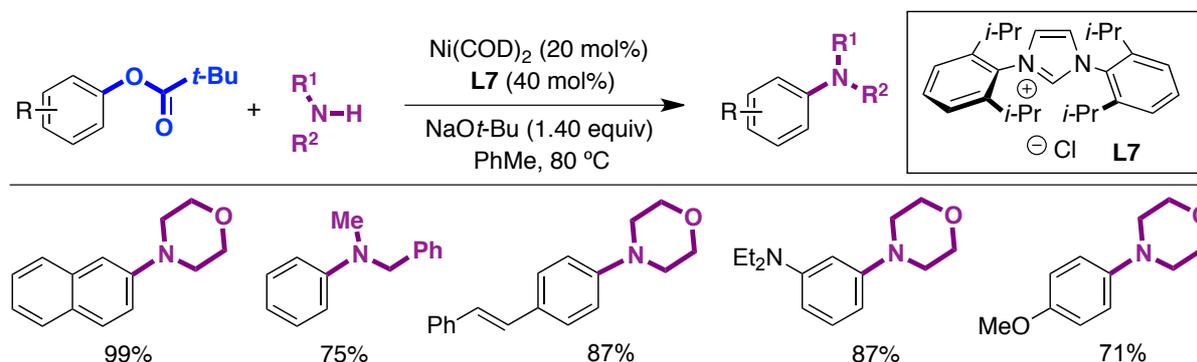
#### 3.1. C–N Bond Formation

Aromatic C–N bonds rank amongst the most ubiquitous motifs in, for example, pharmaceuticals, agrochemicals, electronic materials, polymers, or liquid crystals.<sup>124</sup> Metal-catalyzed amination of aryl, vinyl and heteroaryl (pseudo)halides has emerged as a platform for forging C–N bonds, with the Buchwald-Hartwig amination being the most established and powerful methodology used for this purpose.<sup>125</sup> Although the use of Pd<sup>125</sup> and Cu<sup>126</sup> catalysts in C(sp<sup>2</sup>)–N bond-formation has become routine, the employment of Ni catalysts in this type of reaction has received much less attention.<sup>127</sup> Unlike with organic halides, the use of C–O bond-functionalization techniques in C–N bond-formation is particularly challenging due to the inherent difficulty in promoting C–O bond oxidative addition and, when dealing with aryl esters and carbamates, the proclivity for O–C(O)R hydrolysis under basic conditions. As part of their studies on C–O bond cleavage, Tobisu and Chatani described a seminal Ni-catalyzed catalytic amination aryl methyl ethers using **L7** as the ligand (Scheme 66).<sup>128,129</sup> Interestingly, whereas *N*-heterocyclic carbenes provided the best results, PCy<sub>3</sub>, which is commonly employed in C–O functionalization, delivered the product in considerably lower yields. Unfortunately, high catalyst loadings were required, the protocol was restricted to cyclic amines, and regular anisoles were several orders of magnitude less reactive than  $\pi$ -extended systems. Still, however, promising reactivity was still observed for heteroaryl rings without a pronounced difference in reactivity between  $\pi$ -or non  $\pi$ -extended systems.<sup>130</sup> Additionally, the functional group tolerance was rather problematic due to the strongly basic conditions.



**Scheme 66.** Ni-catalyzed amination of aryl methyl ethers

Tobisu and Chatani subsequently found that the drawbacks associated with the amination of aryl methyl ethers could be overcome by using aryl pivalates or carbamates instead (Scheme 67).<sup>131</sup> Surprisingly, the strongly basic conditions do not result in competitive hydrolysis of the ester functionality. Importantly, not only  $\pi$ -extended systems but also regular arenes were competent substrates regardless of the electronics of the aromatic ring. The higher reactivity of aryl pivalates when compared to aryl methyl ethers allowed the reaction to be conducted under considerably milder reaction conditions, thus significantly improving its chemoselectivity.



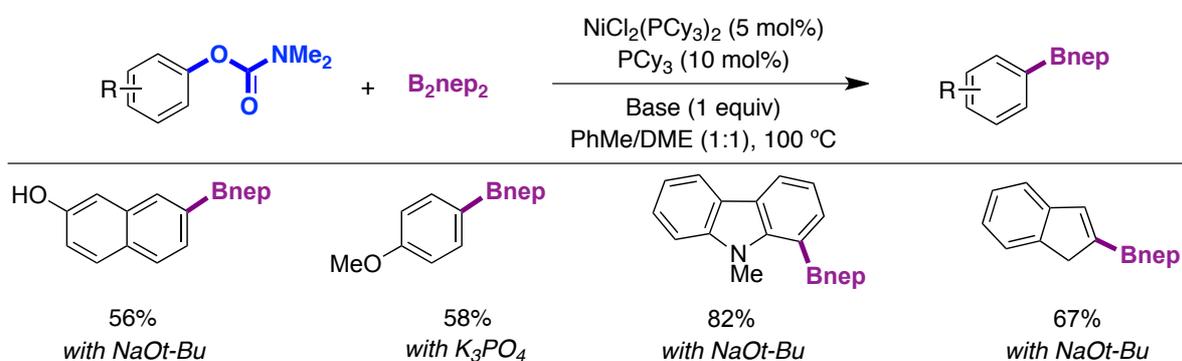
**Scheme 67.** Ni-catalyzed amination of aryl pivalates

Garg and coworkers demonstrated that a  $[\text{NiCl}_2(\text{DME})]$  precatalyst in combination with PhBpin as a mild reducing agent could efficiently catalyze the amination of aryl carbamates and sulfamates.<sup>132</sup> The air stability and lower cost of this Ni(II) precatalyst renders this amination a practical alternative to existing Ni-catalyzed amination techniques. As for the Ni-catalyzed amination of aryl pivalates reported by Tobisu and Chatani,<sup>131</sup>  $\pi$ -extended systems and regular arenes could be coupled with equal efficiency, and nitrogen-containing heterocycles such as N-methylindolyl and pyridylcarbamates could also provide the corresponding aminated products in moderate to excellent yields. It should be noted that none of the methodologies mentioned above included the amination of benzylic alcohol derivatives via  $\text{C}(\text{sp}^3)\text{-O}$  bond cleavage.

### 3.2. C-B Bond Formation

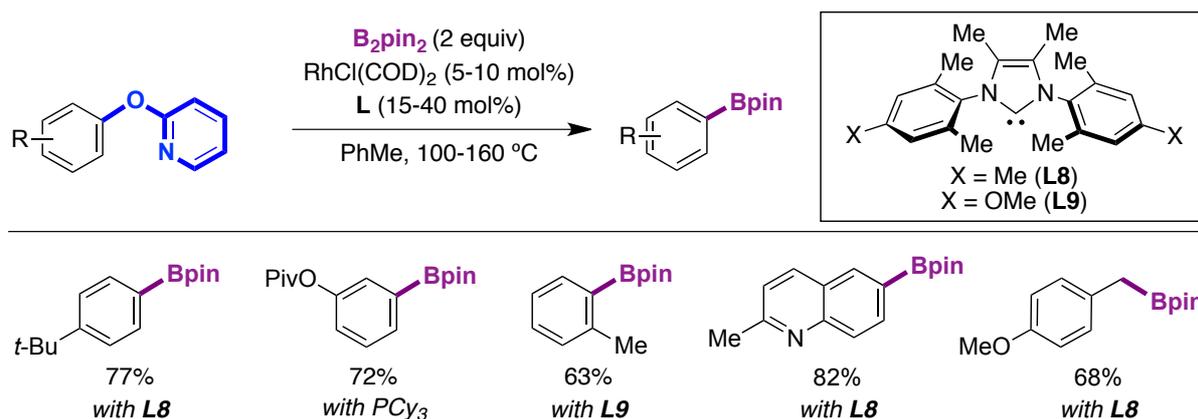
The versatility and pivotal role of organoboron compounds as synthons in organic synthesis has attracted the attention of the synthetic community, making them attractive vehicles for further applications. Although traditional synthetic methods for the preparation of aryl and benzyl boronic acids involve the use of Grignard reagents or organolithium species,<sup>133</sup> the high reactivity and air-sensitivity of these compounds required the design of alternate borylation protocols. In recent years, significant advances have been achieved via the Miyaura borylation and C–H borylation techniques.<sup>134,135</sup> Unfortunately, however, the need for organic halides as well as the lack of regioselectivity control in C–H functionalization reactions with unbiased substrate combinations are drawbacks that must be overcome. To this end, chemists have focused their attention on exploiting the opportunity of using C–O electrophiles for forging C(sp<sup>2</sup>)–B and C(sp<sup>3</sup>)–B bonds.<sup>136</sup>

In 2011, Shi and coworkers reported the borylation of (hetero)aryl carbamates via a Ni-catalyzed C(sp<sup>2</sup>)–O bond activation using [NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub>] as precatalyst and B<sub>2</sub>nep<sub>2</sub> as the boron source (Scheme 68).<sup>137</sup> Under these conditions, aryl pivalates, benzoates and carbonates could also be borylated, albeit with moderate efficiencies. Notably, N-containing heterocycles such as those in carbazole, indole, and quinoline carbamates were equally tolerated. As expected, stereoelectronic effects played a crucial role, with both electron-donating rings and substituents possessing *ortho*-substituents significantly eroding the yields. A prototypical Ni(0)/Ni(II) couple was proposed, invoking a classical oxidative addition, transmetalation and a final C–B bond-reductive elimination.



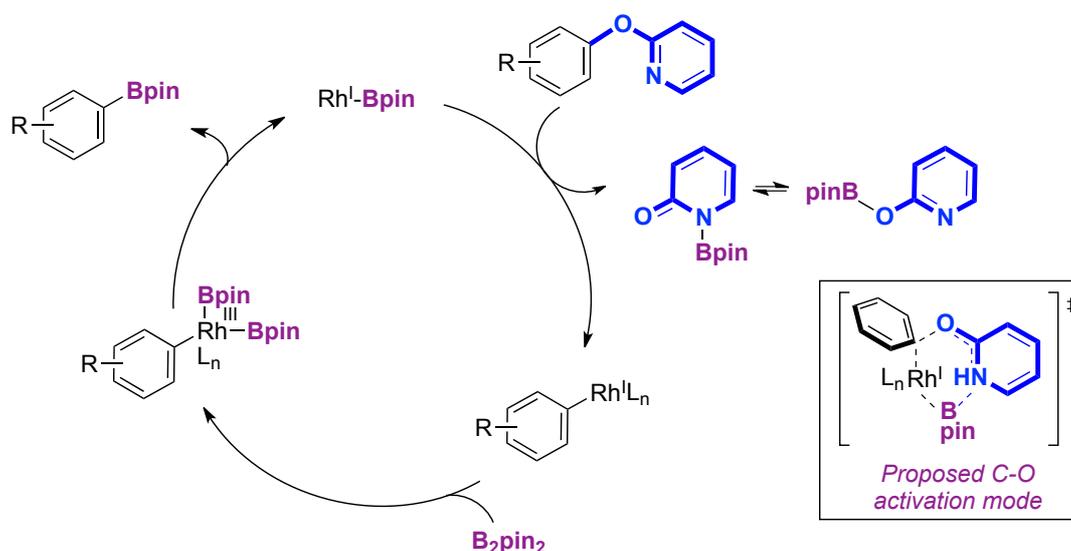
**Scheme 68.** Ni-catalyzed amination of aryl carbamates reported by the group of Shi.

Inspired by their previous catalytic borylation and silylation of nitriles,<sup>138</sup> Tobisu and Chatani developed a base-free Rh-catalyzed borylation of aryl 2-pyridyl ethers via the selective cleavage of C(sp<sup>2</sup>)– and C(sp<sup>3</sup>)–OPy bonds, a useful directing group in C–H bond functionalization reactions (Scheme 69).<sup>139,140</sup> The combination of [RhCl(COD)]<sub>2</sub>, electron-rich ligands such as PCy<sub>3</sub> or IMes<sup>Me</sup>, and B<sub>2</sub>(pin)<sub>2</sub> as the borylating reagent was crucial for obtaining high yields. The reaction proceeded with an excellent selectivity profile, even for precursors possessing other C–O bonds on the pyridyl ring. In all cases, functionalization took place exclusively at the C–O bond possessing an *ortho*-pyridyloxy unit.



**Scheme 69.** Rh-catalyzed borylation of aryl 2-pyridyl ethers

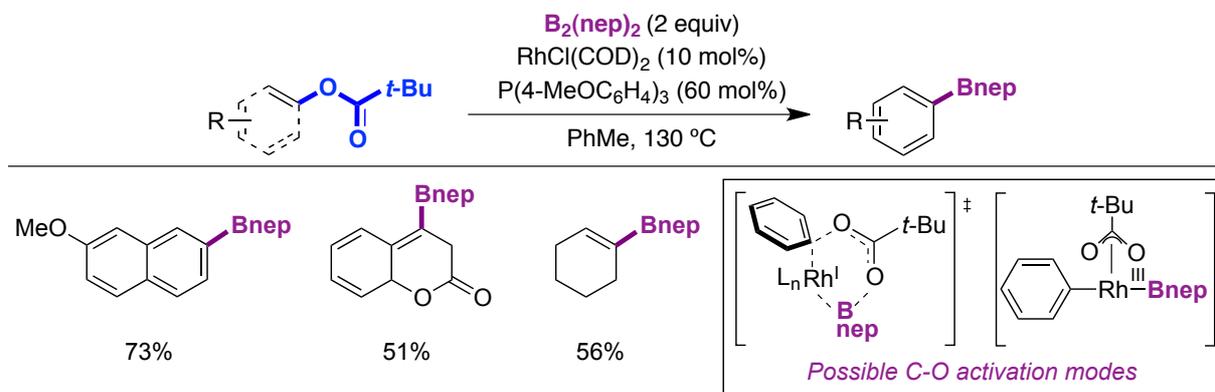
The authors proposed a mechanism consisting of the initial formation of a Rh(I)Bpin species, allowing for a C(sp<sup>2</sup>)-O bond cleavage via a concerted pathway in which the Lewis acidic boryl moiety coordinates to the nitrogen atom of the pyridyl unit (Scheme 70). Deuterium labeling experiments showed that *ortho* C-H functionalization was relatively slow compared with the activation of the C(aryl)-O bond and the scrambling of the C(pyridyl)-H, thus explaining why C-H borylation at the *ortho* position of the pyridyloxy group was not observed.



**Scheme 70.** Mechanistic proposal of the Rh-catalyzed C-OPy cleavage/C-B formation

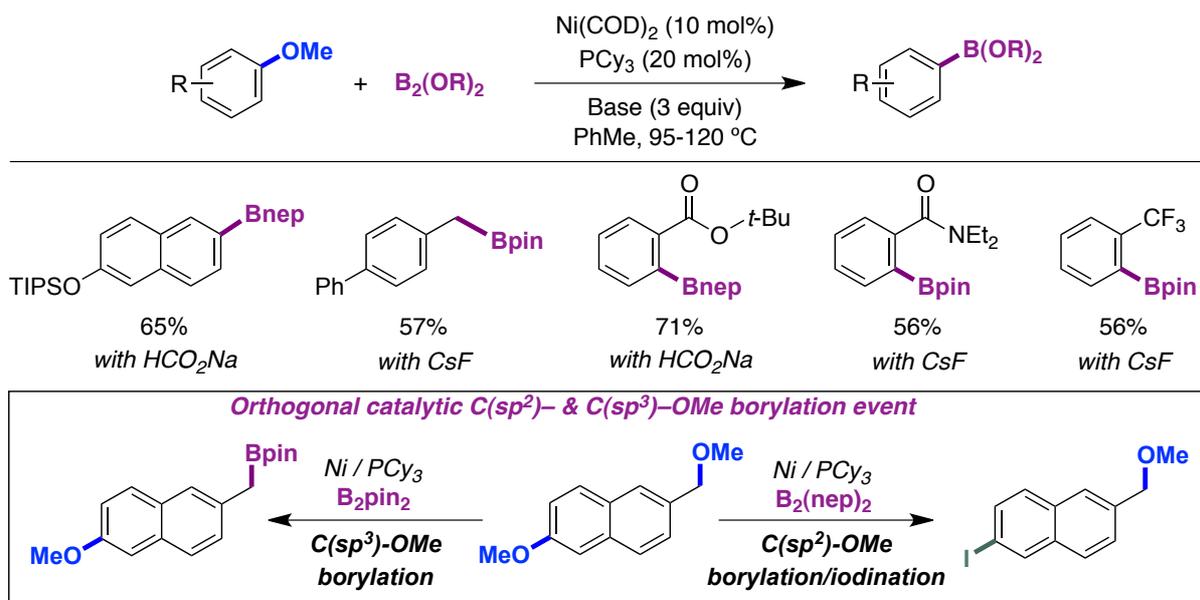
Tobisu and Chatani later demonstrated the generality of Rh-based catalysts for this type of reaction by designing a related borylation of aryl and alkenyl pivalates. This finding demonstrated, for the first time, that Rh catalysts are capable of activating the C-O bond of aryl ester derivatives (Scheme 71).<sup>141</sup> Unfortunately, high temperatures, high catalyst loadings and poly(hetero)aromatic substrates were required to achieve high yields. A catalytic cycle similar to that shown in Scheme 70 was proposed,<sup>139</sup> but it was not confirmed whether C-OPiv bond cleavage occurred via a concerted mechanism and a six-membered rhodacycle transition state, or whether it occurred via oxidative addition to form a

[Rh(III)OPiv] intermediate (Scheme 71). Recently, Tobisu and Chatani have reported a related methodology for the borylation of C(sp<sup>2</sup>)- and C(sp<sup>3</sup>)-OPy bonds using NiCl<sub>2</sub>(DME) as catalyst and PCy<sub>3</sub>·HBF<sub>4</sub> as ligand. These findings constitute a significant step-forward towards the development of cost-efficient borylation protocols. Additionally, this borylation reaction allowed for the coupling of more challenging substrates, including a stereoretentive borylation of secondary benzylic ethers.<sup>142</sup>



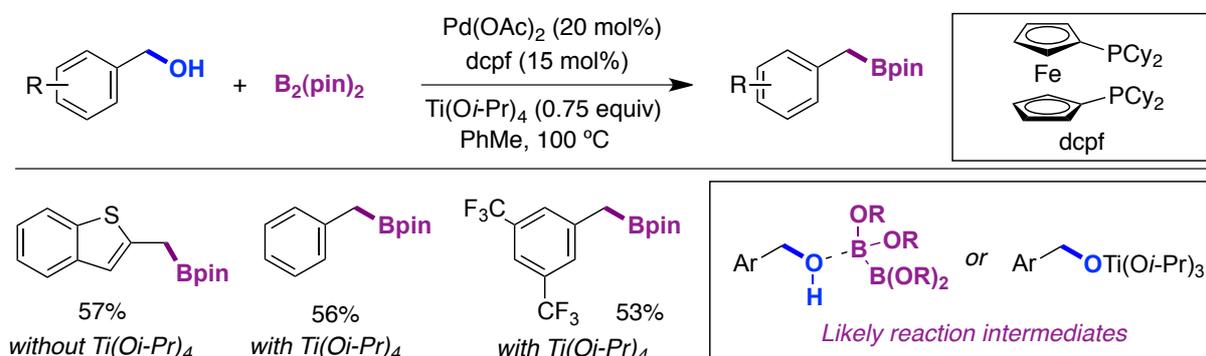
**Scheme 71.** Rh-catalyzed borylation of aryl and alkenyl pivalates

In contrast to previously-developed C–O bond borylation methodologies in which C-OMe bonds remained unreactive, Martin reported in 2015 the first *ipso*-borylation of aryl methyl ethers via C–OMe bond cleavage using a Ni/PCy<sub>3</sub> regime in combination with weak bases (Scheme 72).<sup>143</sup> Importantly, such a transformation represents an alternative to the previously reported *ortho*-, *meta*- and *para*-borylative protocols of anisole derivatives, in which the methoxy group has been used as a mere regiocontrol element.<sup>135c,144</sup> Interestingly, no homocoupling via Suzuki-Miyaura coupling of the *in situ* generated aryl boronate was detected in the crude mixtures, an observation that differs from the one later reported by Tobisu and Chatani.<sup>81</sup> Although  $\pi$ -extended backbones were generally more reactive, regular anisole derivatives possessing electron-withdrawing groups could also be utilized. Strikingly, an orthogonal site-selectivity was observed depending on the boron reagent utilized; while the combination of B<sub>2</sub>(pin)<sub>2</sub> with CsF promoted a C(sp<sup>3</sup>)-O borylation, a protocol based on B<sub>2</sub>nep<sub>2</sub>/HCO<sub>2</sub>Na resulted in an exclusive C(sp<sup>2</sup>)-B bond-formation. This selectivity profile was rationalized by the different electronic and steric properties of the *in-situ* generated nucleophilic boron reagents.



**Scheme 72.** Ni-catalyzed borylation of aryl and benzyl methyl ethers via C-OMe cleavage

Following up on their interest in designing cross-coupling reactions via C(sp<sup>2</sup>)- or C(sp<sup>3</sup>)-OH cleavage, the Shi group described a catalytic borylation of benzyl alcohols, which represent a rare example of a C-heteroatom bond-formation via C-OH cleavage (Scheme 73).<sup>145</sup> As expected, substrates with  $\pi$ -extended backbones were considerably more reactive than regular phenylmethanol compounds. Interestingly, the addition of Ti(Oi-Pr)<sub>4</sub> as a Lewis acid was required to activate the latter. The authors proposed a mechanism based on oxidative addition of the benzylic C(sp<sup>3</sup>)-OH to Pd(0) assisted by the Lewis acid, followed by transmetalation and reductive elimination. Unfortunately, no alcohols possessing  $\beta$ -hydrogens were included, an observation that is likely correlated with the ability of the in situ generated benzyl palladium complexes to trigger competitive  $\beta$ -hydride elimination. Notably, the authors' preliminary experiments showed that phenols could be used as coupling partners, no doubt a step-forward in future C-O bond-functionalization techniques.

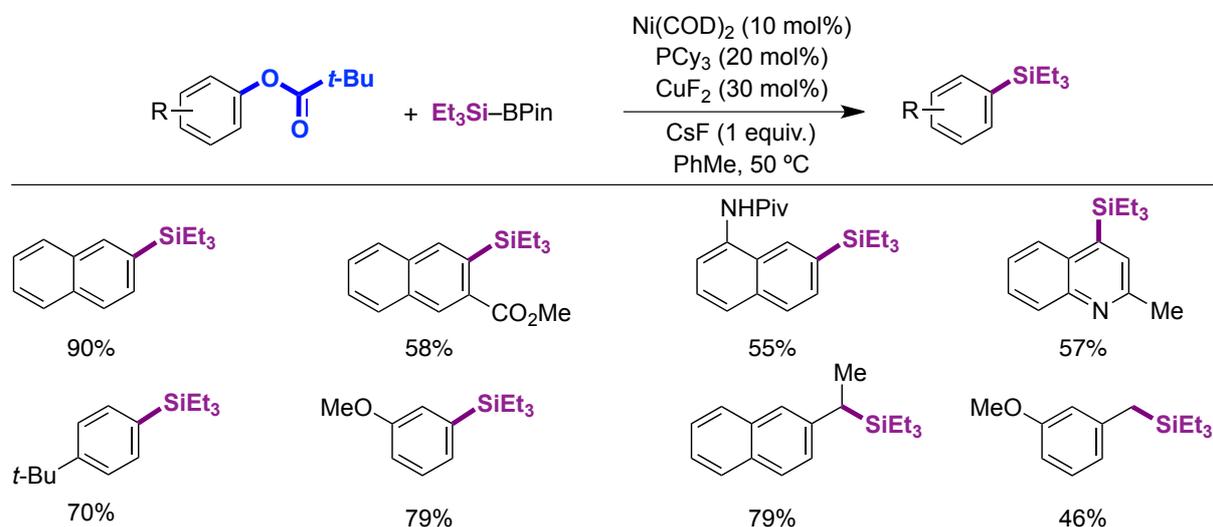


**Scheme 73.** Pd-catalyzed borylation of arylmethanols with B<sub>2</sub>pin<sub>2</sub>

### 3.3. C-Si bond formation

Organosilanes are invaluable intermediates in organic synthesis and important building blocks in pharmaceuticals, material sciences, and medicinal chemistry.<sup>146</sup> The wide variety of

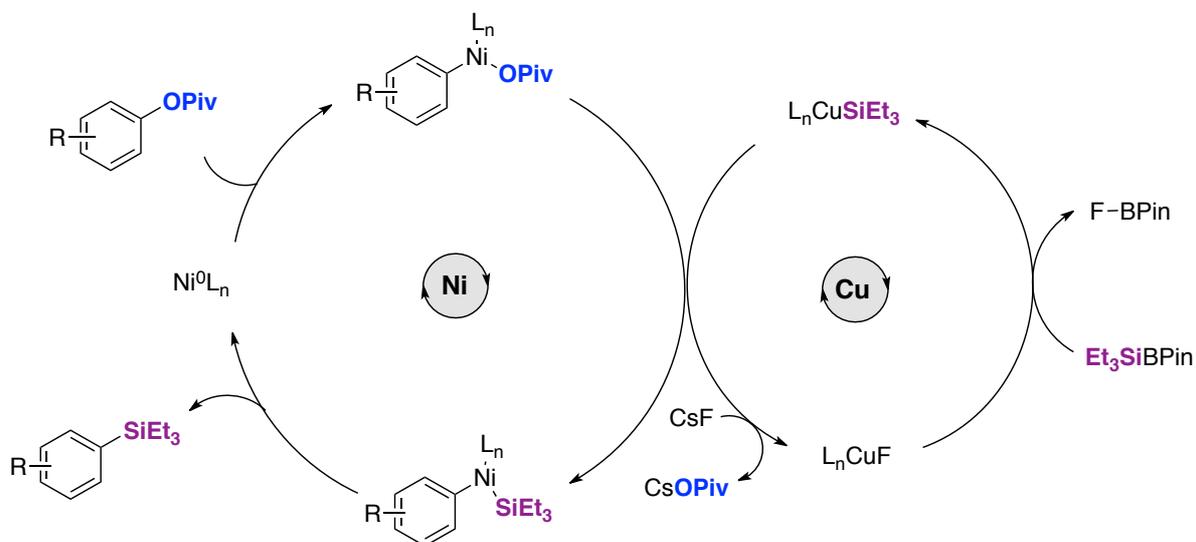
transformations that are within reach using organosilanes as precursors, including C–heteroatom bond-formation, oxidations or C–C bond-formations, renders organosilanes powerful intermediates in organic synthesis, even in the context of total synthesis.<sup>146,147</sup> Classical protocols for their synthesis include the use of stoichiometric organolithium or Grignard reagents via metalation techniques from the corresponding organic halide.<sup>146</sup> However, in recent years, alternatives catalytic methods involving the silylation of nitriles,<sup>138a</sup> organic halides<sup>148</sup> or C–H functionalization techniques<sup>135b,149</sup> have shown to be viable synthetic alternatives. Despite the remarkable advances realized, the need for organic halides, high temperatures, precious metal catalysts (Pd, Rh or Ir) or the presence of proximal directing groups represents drawbacks for the implementation of these techniques by the synthetic Community. In order to address these limitations, in 2014 the Martin group reported the first catalytic C–O functionalization/C–Si bond-formation using aryl esters as coupling partners and silylboronates reagents (Scheme 74).<sup>150</sup> It was found that Ni and Cu catalysts act in a synergistic fashion, a rather intriguing observation as the Ni/Cu couple has rarely been utilized in cross-coupling methodologies.<sup>151</sup> The transformation was distinguished by its generality, accommodating both  $\pi$ -extended systems and regular arenes with similar ease, as well as by its chemoselectivity profile in the presence of a wide variety of functional groups. Unlike other C–O bond activation methodologies, this C–Si bond-forming protocol was not sensitive to the presence of *ortho*-substituents. Additionally, the reaction could be applied to benzylic C(sp<sup>3</sup>)–O bonds, holding promise for the design of future stereospecific or even enantioselective transformations.



**Figure 74.** Ni-catalyzed silylation of aryl and benzyl pivalates

Although tentative, the observation that Cu and Ni catalysts act in concert in a silylation event was somewhat indicative that silylcuprate intermediates might be involved that subsequently promotes transmetalation with the corresponding  $\text{ArNi(II)OPiv}$  en route to  $\text{ArNi(II)SiEt}_3$  (Figure 75). A final reductive elimination would regenerate the propagating  $\text{Ni(0)L}_n$  while delivering the targeted aryl silane. This proposal remains rather speculative and

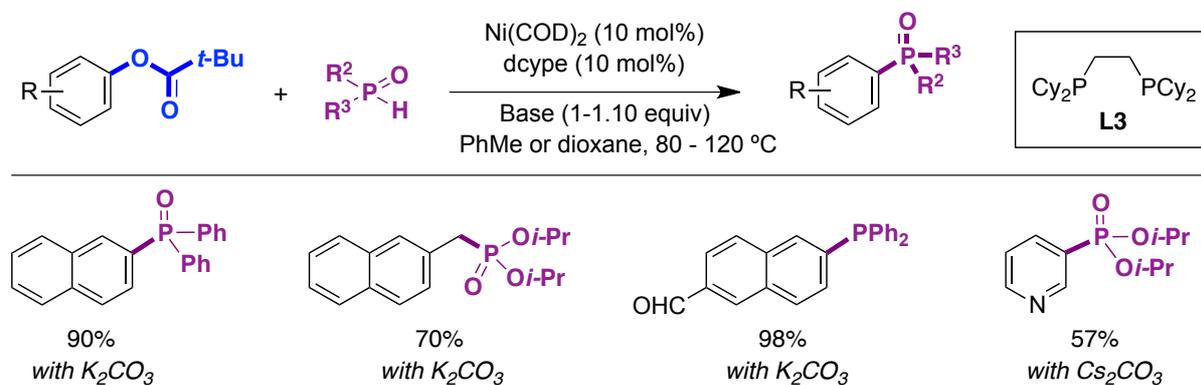
other mechanistic pathways, including single-electron transfer processes, could not be ruled out.



**Figure 75.** Mechanistic proposal for the Ni/Cu-catalyzed silylation of C–O bonds

### 3.4. C-P bond formation

Organophosphorus compounds have not only been utilized extensively as ligands in catalysis and coordination chemistry, but have also found widespread application in medicinal chemistry, agrochemicals, and material sciences.<sup>152</sup> Classical approaches for forging C–P bonds include the utilization of either organolithium species, Grignard reagents, or phosphorous halides. Unfortunately, these methods are rather problematic due to their air-sensitivity, toxicity and poor chemoselectivity profiles. In 2015, Chen and Han reported the first phosphorylation of phenol derivatives, specifically aryl and benzyl pivalates, by using dcype as the ligand and  $K_2CO_3$  as a base (Scheme 76).<sup>153</sup> It is noteworthy that this phosphorylation worked with equal efficiency regardless of whether (hetero)polyaromatics or non- $\pi$ -extended systems were utilized or not. The mechanism of the transformation was proposed to proceed via a classical Ni(0)/Ni(II) mechanism via an oxidative addition into the  $C(sp^2)$ –OPiv bond, a transmetalation and a final  $C(sp^2)$ –P bond-reductive elimination.



**Figure 76.** Ni-catalyzed phosphorylation of aryl and benzyl pivalates

There is a general consensus that the recent years have witnessed significant progress in the area of C–O bond cleavage for forging C–heteroatom bonds. However, the recently reported methodologies cannot compete in efficiency and applicability with the numerous Pd-catalyzed cross-coupling protocols using aryl halides. Undoubtedly, future efforts such as a systematic study of the mechanisms with which these reactions operate, no doubt an achilles heel in the area of C–O functionalization, will contribute to the improvement of these methodologies and enable a more widespread exploitation of C–O electrophiles.

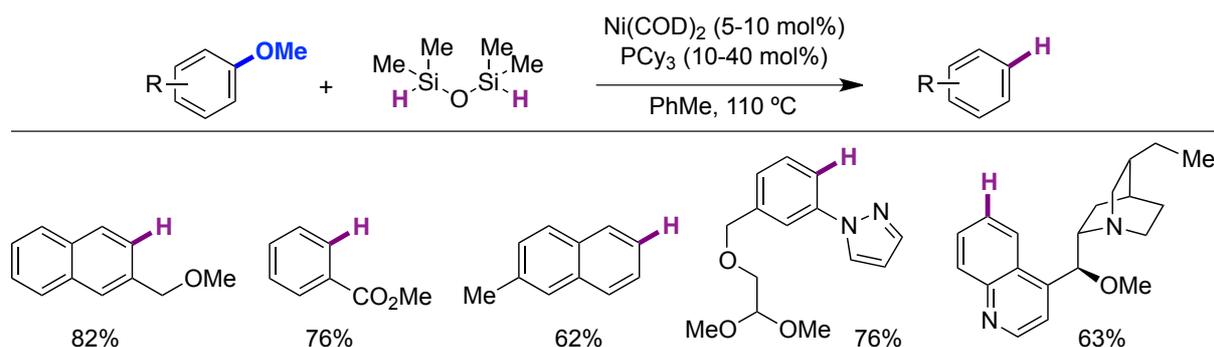
#### 4. Hydrogenolysis of C–O Bonds

The development of homogeneous catalytic techniques for the defunctionalization of robust C–O bonds to C–H bonds has provided chemists with an alternative functionalization strategy based on the unique reactivities of ethers, esters and carbamates. Furthermore, significant advances have been made towards practical methods for the deoxygenation of phenols and benzyl alcohols, a particularly attractive scenario within the context of lignin degradation and functionalization.<sup>154</sup>

##### 4.1. Ethers

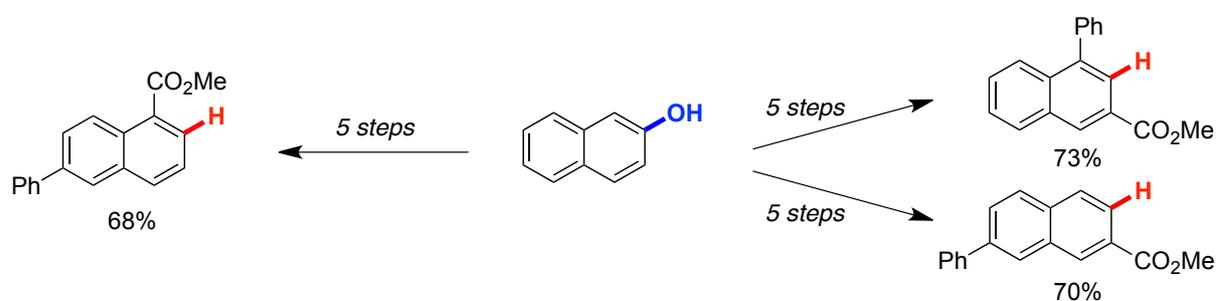
The deoxygenative reduction of aryl ethers has traditionally been conducted with stoichiometric bases,<sup>155</sup> organoalkali-metal compounds,<sup>156</sup> heterogeneous Raney nickel under high hydrogen pressures<sup>154b,157</sup> or within the area of electrocatalysis.<sup>158</sup> However, these methods suffer from low functional group tolerance and may cause the over-reduction of other unsaturated functional groups, including the corresponding aromatic backbones. Overcoming these challenges has obviously been a driving force for the development of reductive cleavage protocols. Additional impetus has also been provided by the desire to control the deoxygenation of lignin, a renewable biopolymer made of aromatic units joined by ether linkages, in order to exploit it as a source of aromatic building blocks.<sup>154</sup>

The Martin group reported the first catalytic reductive cleavage of C–OMe bonds in 2010 (Scheme 77) and took the first step towards liberating chemists from the cumbersome methods described above.<sup>159</sup> The catalytic system required a mixture of [Ni(COD)<sub>2</sub>]/PCy<sub>3</sub> and commercially available tetramethyldisiloxane as the reducing agent. Isotope-labelling studies with DSiEt<sub>3</sub> confirmed that the silane is the hydride source. As for other C–O cleavage reactions,  $\pi$ -extended systems were considerably more reactive than anisole derivatives. However, regular aromatic rings with groups *ortho* to the methoxy group, such as pyridines, esters, oxazolines, and pyrazoles, all underwent C–O cleavage in an efficient manner. Although electronic effects might come into play, the lack of reactivity of compounds possessing such groups in either *meta* or *para* position suggests that chelation-assisted cleavage is the most plausible scenario.



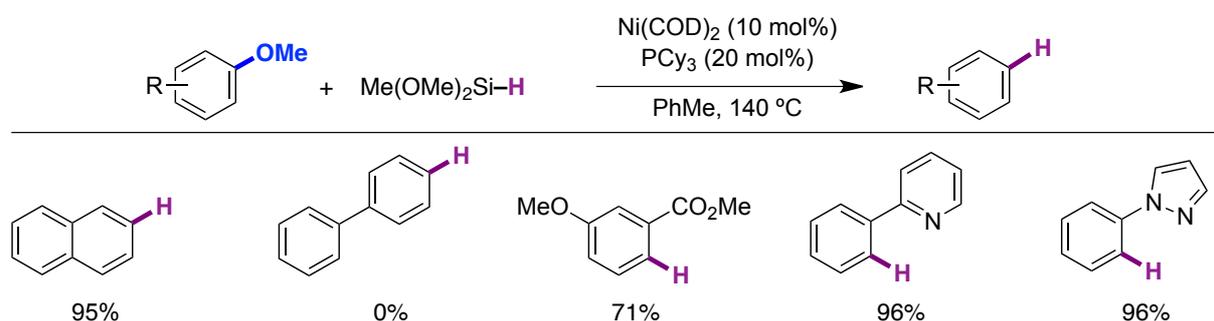
**Scheme 77.** Ni-catalyzed hydrogenolysis of aryl methyl ethers

In addition to the inherent interest generated by the new hydrogenolysis event, this study is also important in that it demonstrated a strategy for using aryl methyl ethers as temporary directing groups by preparing three different regioisomeric products from 2-naphthol (Scheme 78).



**Scheme 78.** Traceless directing group strategy for arene functionalization

Several months later Tobisu and Chatani independently reported a closely-related hydrogenolysis protocol (Scheme 79).<sup>160</sup> As for the protocol described by Martin,<sup>159</sup> the C(sp<sup>2</sup>)-O bond was cleaved preferentially over the weaker benzylic C(sp<sup>3</sup>)-O bond.<sup>159</sup>

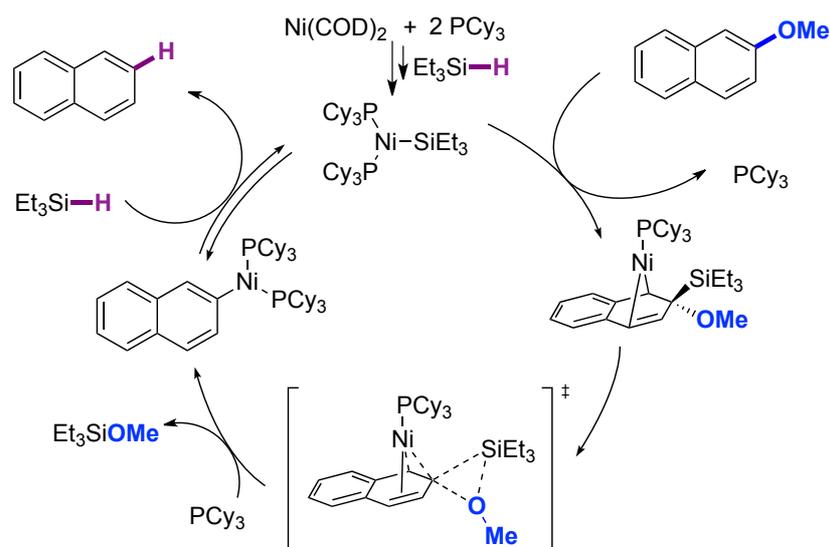


**Scheme 79.** Ni-catalyzed reductive cleavage of aryl methyl ethers

Neither Chatani nor Martin addressed the mechanism of the transformation in their first reports. Taking as an initial working hypothesis a simple catalytic cycle involving the rate-determining oxidative addition of the C-OMe bond followed by  $\sigma$  bond metathesis and reductive elimination, the Martin group strove to identify the mechanism of C-OMe reductive cleavage in these systems (Scheme 80).<sup>29</sup> They discovered subtleties underlying

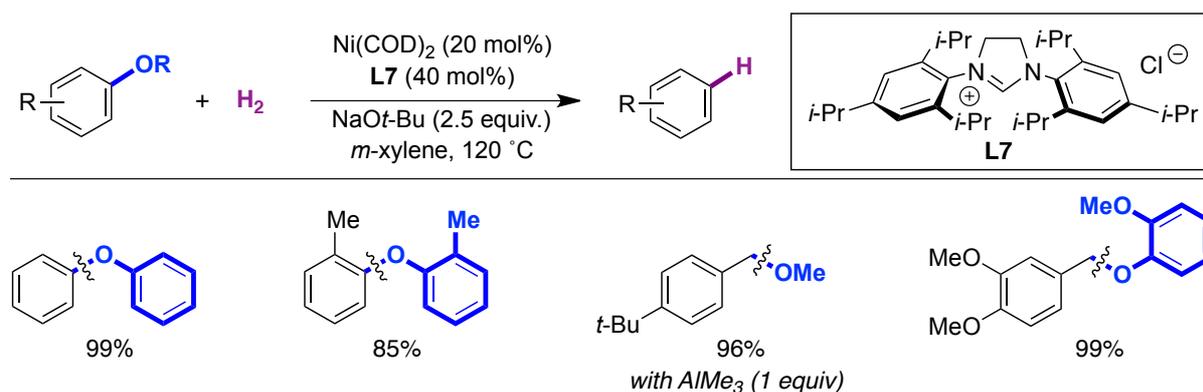
this methodology that have had repercussions for the development of other C–O cleavage reactions.<sup>159</sup> First, oxidative addition of the C–OMe bond was explored. Significantly, the oxidative addition complex could not be isolated, neither directly by reacting 2-methoxynaphthalene with  $[\text{Ni}(\text{COD})_2]/2\text{PCy}_3$  nor indirectly from  $[\text{Ni}(\text{PCy}_3)_2\text{Cl}(2\text{-naphthyl})]$  via anion metathesis. Instead, in the absence of cyclooctadiene, catalytically inactive  $[\text{Ni}(\text{CO})(\text{PCy}_3)_2]$  and naphthalene were produced. These products were explained by rapid  $\beta$ -hydride elimination from the initial methoxy complex to form a Ni-hydride complex, which releases naphthalene through reductive elimination. The formation of catalytically inactive  $[\text{Ni}(\text{CO})(\text{PCy}_3)_2]$  in the absence of cyclooctadiene suggested that this ancillary ligand has “non-innocent” character that might stabilize the active species within the catalytic cycle<sup>113,143,150,159</sup> and prevent  $\beta$ -hydride elimination.

An enlightening clue to the identity of the active species was discovered when a stoichiometric reaction of  $[\text{Ni}(\text{COD})_2]$ ,  $\text{PCy}_3$  and  $\text{Et}_3\text{SiH}$  was monitored by  $^1\text{H}$  and  $^{29}\text{Si}$  NMR spectroscopy. Rapid consumption of  $\text{Et}_3\text{SiH}$  was observed by  $^1\text{H}$  NMR but was not followed the appearance of any additional  $^{29}\text{Si}$  signals. This lack of  $^{29}\text{Si}$ -NMR signals was rationalized by the formation of paramagnetic Ni(I)-silyl species, and their persistence throughout the reaction was confirmed by EPR spectroscopy. Interestingly, a characteristic multiplet was observed by  $^1\text{H}$ -NMR spectroscopy at -15 ppm, suggesting the formation of diamagnetic dimeric Ni(I) species with a  $d^9$ - $d^9$  interaction and bridging hydrides. This hypothesis was supported by comparison with the  $^1\text{H}$ -NMR spectrum of dimeric  $[(\text{dcype})\text{Ni}(\mu\text{-H})]_2$ . The authors ruled out Ni(I)-hydrides as reaction intermediates and postulated that the Ni(I)- $\text{SiR}_3$  species was involved in the catalytic cycle, observations that were additionally supported by computational studies. Taking all the data into account, a mechanism was proposed involving  $\eta^2$ -coordination of the key Ni(I)- $\text{SiR}_3$  species to the aryl ether, followed by migratory insertion, a [1,2]-shift to form  $\text{R}_3\text{SiOMe}$  and a Ni(I)-aryl intermediate (Scheme 80). This ultimately undergoes  $\sigma$ -bond metathesis with the silane to provide the desired reduced product and recover the propagating Ni(I)- $\text{SiR}_3$  species. Because the rate-determining step involves arene dearomatization, the proposed mechanism also explains the increased reactivity of  $\pi$ -extended systems compared to regular anisole derivatives.



**Scheme 80.** Proposed mechanism for the hydrogenolysis of aryl ethers by  $R_3SiH$

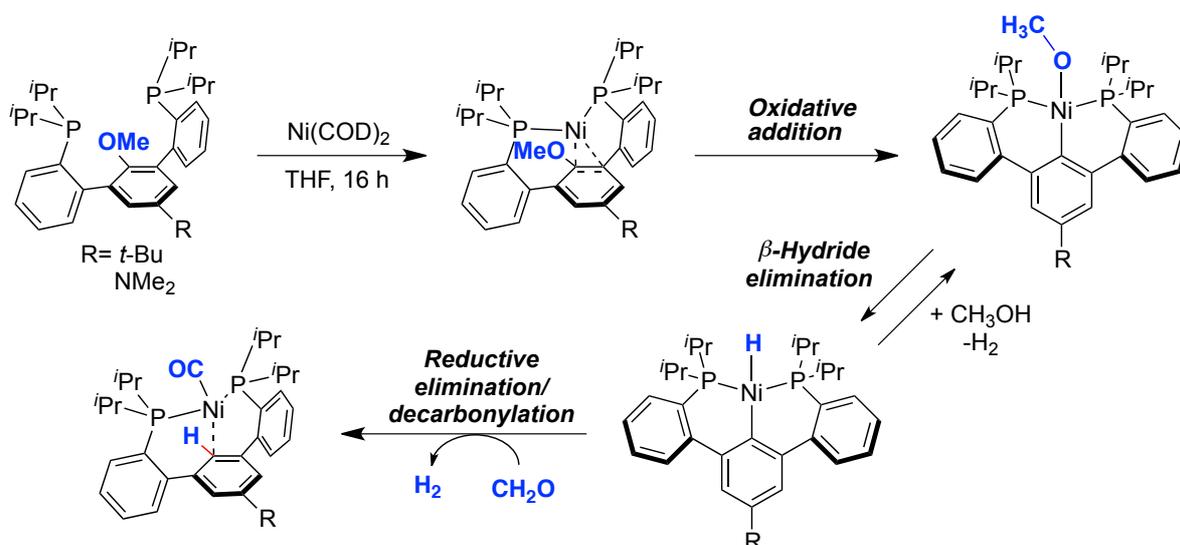
Following the first reports by Martin and Chatani, the field of C–O reductive cleavage underwent significant growth, starting with the nickel-catalyzed selective hydrogenolysis of aryl ethers developed by Hartwig,<sup>161</sup> and extending to heterogeneous and transition metal free systems.<sup>162,163</sup> In 2011, Hartwig reported the Ni-catalyzed homogeneous hydrogenolysis of  $C_{aryl}$ –O bonds in diaryl, alkyl aryl, and benzyl ethers with dihydrogen (Scheme 81).<sup>161</sup> Unlike previous metal-catalyzed hydrogenation methodologies,<sup>157</sup> over-hydrogenation of the aromatic ring could be avoided. An important feature of Hartwig's contribution was the application of the methodology to lignin model compounds, showing the prospective impact of C–O reductive cleavage for biomass degradation and functionalization.



**Scheme 81.** Ni-catalyzed hydrogenolysis of aryl and benzyl ethers with hydrogen

Mechanistic investigations by Agapie et al. shed light on the mechanism of the Ni-catalyzed hydrogenolysis of  $C_{aryl}$ –OMe bonds (Scheme 82).<sup>164</sup> Specifically, the authors developed a system containing a (diphosphinearyl)methyl ether ligand that would promote the reaction in an intramolecular fashion and allow isolation of the corresponding reaction intermediates (Scheme 81). It was shown that the hydride source is derived from the ether group via  $\beta$ -hydride elimination, rather than from dihydrogen. These results differ from Martin's studies,

where the silane is the reducing agent, and is in contrast with speculation by Hartwig that the hydride originates from dihydrogen.

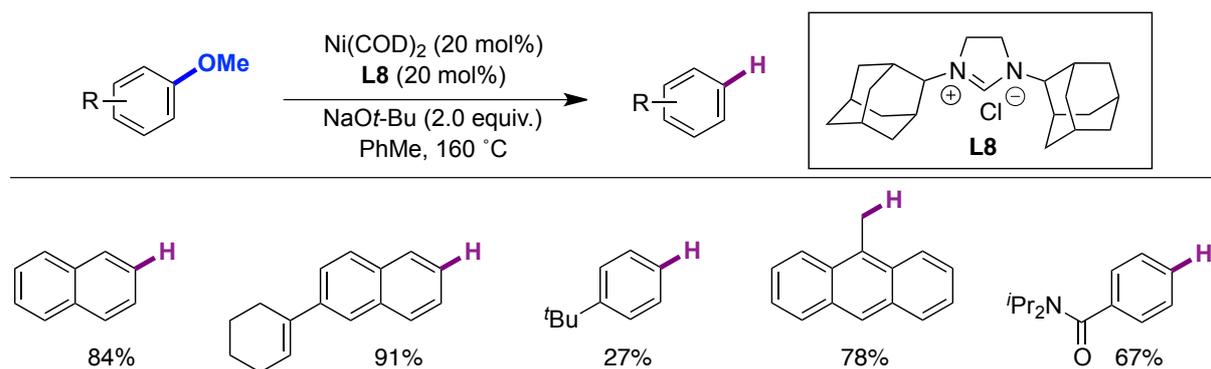


**Scheme 82.** Mechanistic studies of the Ni-catalyzed hydrogenolysis of C(sp<sup>2</sup>)-OMe bonds

Two independent computational studies of this mechanism were recently published in quick succession by the Chung and Surawatanawong groups.<sup>165,166</sup> Chung scrutinised the role of the excess NaOt-Bu in the Ni/NHC-catalyzed hydrogenolysis of aryl alkyl and diaryl ethers reported by the Hartwig group. It has been demonstrated that the presence of the base both improves the yield and reduces the reaction temperature. Chung proposed that in the case of Ph-OPh hydrogenolysis, the *tert*-butoxy anion coordinates to nickel prior to the rate-determining C-O oxidative addition step. Due to the extra electron density, the resulting complex is considerably more stable than the analogous base-free product (Scheme 83, A); however, the authors also mentioned that a S<sub>N</sub>Ar-like pathway could compete with base-assisted oxidative addition for certain substrates. The mechanism for the hydrogenolysis of aryl methyl ethers was found to diverge. Rather than undergoing σ-CAM with H<sub>2</sub> or classical β-hydride elimination from the Ni-OMe complex, a five-centered direct hydrogen transfer might form a nickel formaldehyde complex and the reduced product. After evaluating Martin's finding that the [Ni(COD)<sub>2</sub>]/PCy<sub>3</sub> system involves nickel(I) species, Chung argued that the NHC pathway involves a Ni(0)/Ni(II) cycle because the bulkiness of the NHC ligand disfavors the comproportionation of Ni(SIPr)<sub>2</sub> and [*cis*-(SIPr)<sub>2</sub>NiH<sub>2</sub>] to form the equivalent dimeric Ni(I) species.<sup>29</sup>

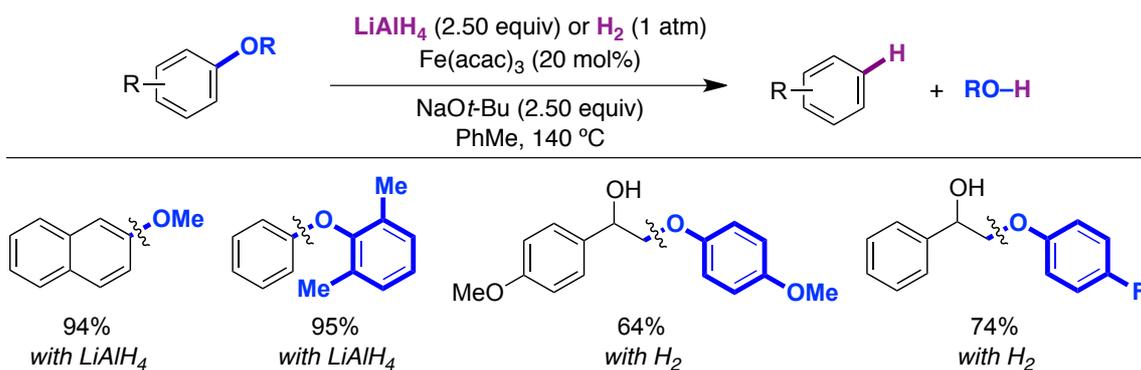


In 2015, the Chatani group published a methodology in which the need for an external reductant was replaced by reaction conditions that exploited the ability of the methoxy group to undergo  $\beta$ -hydride elimination.<sup>167</sup> Although oxidative addition of the C–OMe bond has so far eluded experimental verification, Chatani and co-workers envisaged that the correct ligand choice could favour the desired oxidative addition/ $\beta$ -hydride elimination pathway (Scheme 84). Systematic screening of *N*-heterocyclic carbene ligands showed that employing a newly developed ligand with 2-adamantyl substituents, L8, produced high yields of the reductive C(sp<sup>2</sup>)– and C(sp<sup>3</sup>)–O cleavage product. Interestingly, PCy<sub>3</sub>, which is necessary in many C–O bond cleavage methodologies, could not produce any of the reduced product without the presence of an external reductant. The Martin group also observed a similar effect in the PCy<sub>3</sub> system, with only stoichiometric reduction possible in the absence of silane.<sup>29,159</sup> Notably, this method tolerates pendant alkenes and ketones, substrate classes that are reduced in the presence of stoichiometric amounts of silanes or hydrogen.<sup>168</sup> No mechanistic studies were carried out to provide direct support for the proposed catalytic cycle, but indirect evidence was obtained by changing the leaving group from ethoxy to methoxy and comparing the resulting yields. The decrease in yield supports the conclusion that  $\beta$ -hydride elimination occurs from an *in situ* generated Ni-OR complex.



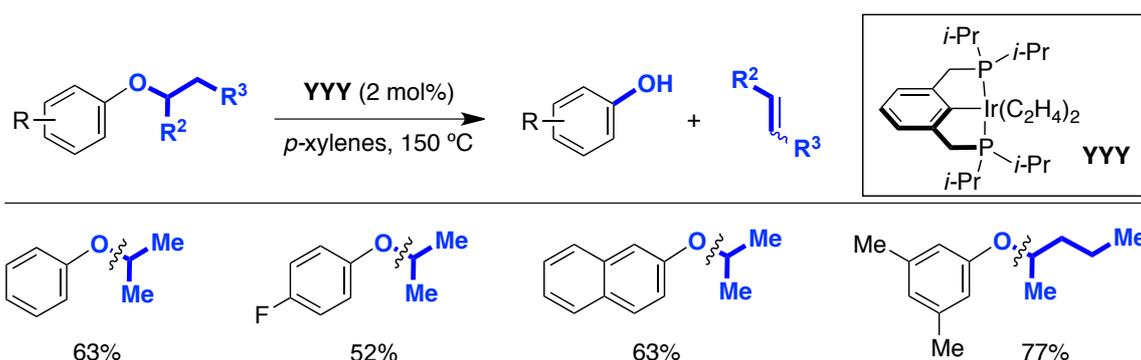
**Scheme 84.** Ni-catalyzed reductive cleavage in the absence of external reductant

Although nickel catalysts are used in the majority of C–O cleavage methodologies, Wang recently reported the ability of simple and commercially available Fe catalysts to catalyze this reaction in combination with LiAlH<sub>4</sub> or H<sub>2</sub> (Scheme 85).<sup>169</sup> Unfortunately, the need for strong reductants dramatically limited the chemoselectivity profile of the method. Still, however, this method could be applied to lignin model compounds under a hydrogen atmosphere. Although the mechanism is unclear, the authors proposed that Fe clusters or nanoparticles formed from the reduction of the [Fe(acac)<sub>3</sub>] could be the catalytically active species. Subsequently, Wang showed that under otherwise identical conditions, Co(II) precatalysts could be utilized with similar efficiency.<sup>170</sup> As for the iron-based process, the presence of both LiAlH<sub>4</sub> and KOt-Bu severely limited the functional group tolerance of the reaction.



**Scheme 85.** Iron-catalyzed reductive cleavage of aryl and benzyl ethers

As discussed throughout this chapter, metal complexes have been used to activate etheric C–O bonds. Pincer complexes have been of particular interest as they are often stable and well-defined, facilitating studies of their reactivity and structure.<sup>171</sup> Despite the numerous stoichiometric examples dealing with the use of pincer-type complexes in C–O bond-functionalization,<sup>172</sup> a limited number of catalytic transformations have been reported. Building on previous stoichiometric studies,<sup>171b,173</sup> Goldman developed an iridium complex that can effectively catalyze the reductive cleavage of aryl alkyl ethers, and in doing so illustrated the potential impact of applying pincer complexes to catalytic C–O bond-functionalization.<sup>174</sup> This report built on the stoichiometric studies reported by the Goldman group. Unlike the reactions discussed in previous sections, this reaction occurs via a distinctive dehydroaryloxylation pathway whereby the alkyl group becomes the source of the hydrogen atom. The mechanism of the transformation is proposed to occur via C–H oxidative addition followed by  $\alpha$ -migration of the OAr group, as proposed to occur for the previously reported stoichiometric reaction.<sup>175</sup> The reaction is distinguished by low catalyst loadings and a different selectivity profile to that reported for Ni-catalyzed C–O bond-functionalization reactions (Scheme 86).

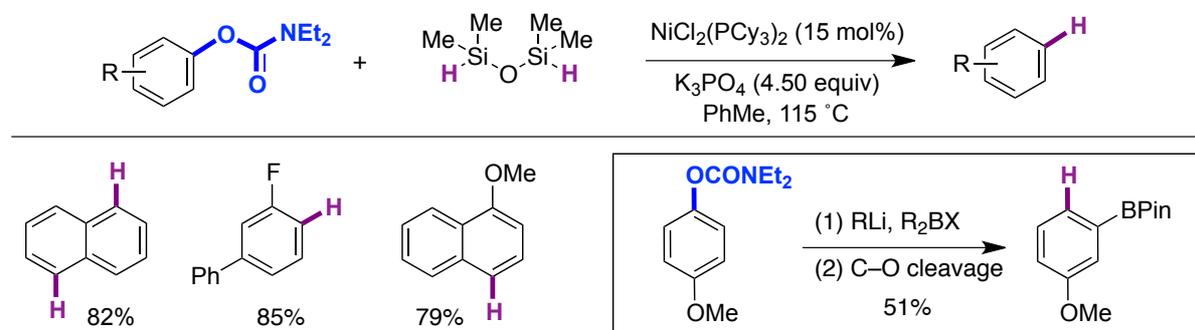


**Scheme 86.** Ir-catalyzed reductive cleavage catalyzed by an Ir pincer complex

## 4.2. Carbamates

Following the seminal report by Martin,<sup>159</sup> Garg identified aryl carbamates as suitable C–O electrophiles to undergo catalytic hydrogenolysis. In line with Martin's results, the best results were accomplished with PCy<sub>3</sub> as the ligand and tetramethyldisiloxane as the reducing

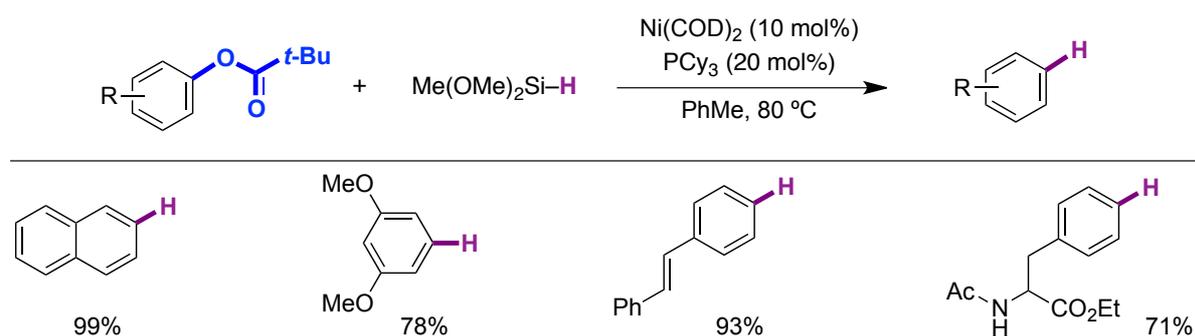
agent (Scheme 87).<sup>176</sup> In order to showcase the synthetic potential of their reaction, the authors focused on heterocycles that are relevant to the pharmaceutical industry and demonstrated the synthesis of C4-substituted indoles from the more readily available C5-indoles via *cine*-substitution.



**Scheme 87.** Ni-catalyzed hydrogenolysis of aryl carbamates

### 4.3. Esters

As part of their studies on the catalytic reductive cleavage of aryl methyl ethers, Chatani and Tobisu reported the nickel-catalyzed hydrogenolysis of aryl esters.<sup>160</sup> In line with Martin's initial studies,<sup>29,159</sup> the combination of  $\text{PCy}_3$  as the ligand and a silane as the reducing agent turned out to be particularly efficient and the desired arenes were obtained in high yields (Scheme 88). The ability of the pivalate group to act as a temporary directing group was highlighted with a four-step synthesis of a terphenyl derivative. Mechanistic aspects of this transformation were briefly addressed by considering the role of the  $\text{R}_3\text{SiH}$  as a Lewis acid in the formation of a Ni(II)-hydride. However, the assumption that oxidative addition of the  $\text{Ar}-\text{OPiv}$  bond occurs before  $\sigma$ -bond metathesis between  $\text{HSiR}_3$  and the Ni(II)- $\text{OPiv}$  species was not supported with experimental evidence.

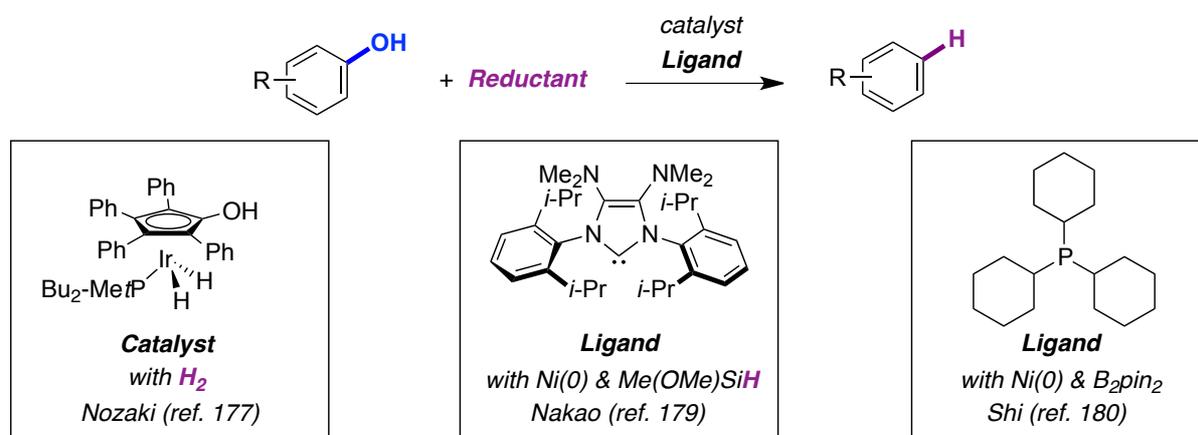


**Scheme 88.** Ni-catalyzed reductive cleavage of aryl pivalates

### 4.4. Alcohols

It is evident from the evidence presented above that the deoxygenation of phenol derivatives allows for the exploitation of esters, carbamates, and ethers as temporary directing groups. However, these reactions are not yet ideal from an atom economy standpoint. Ideally, these strategies should be applicable to the removal of free phenolic

moieties found in biomass-derived feedstocks. In 2015, Nozaki et al. demonstrated that phenols could be reductively cleaved with dihydrogen without reduction of the unsaturated aromatic rings (Scheme 89, left).<sup>177</sup> The transformation was thought to occur via an outer-sphere mechanism involving metal-ligand cooperation on hydroxycyclopentadienyl iridium complexes. Liu also showed that reaction of phenols with a mixture of  $\text{LiAlH}_4/\text{KOt-Bu}$  at 180 °C resulted in the cleavage of aromatic  $\text{C}(\text{sp}^2)\text{-OH}$  bonds.<sup>178</sup> The first inner-sphere reductive cleavage of the  $\text{C}(\text{sp}^2)\text{-OH}$  bond was reported by the Nakao group and employed a nickel catalyst bearing a highly electron-rich *N*-heterocyclic carbene ligand (Scheme 88, middle).<sup>179</sup> In this case, the authors invoked a mechanistic pathway consisting of the *in situ* formation of an aryl silyl ether that undergoes oxidative addition, deoxygenation via  $\text{O-Si}$  bond formation upon reaction with a second equivalent of silane, and reductive elimination to form the  $\text{C-H}$  bond. Concurrently, Shi disclosed the reductive cleavage of phenols with  $\text{B}_2\text{pin}_2$ . In this protocol, the Lewis acidic boron atom reduces the electron density of the  $\text{C-O}$  bond and the Lewis basic phenolic oxygen atom weakens the  $\text{B-B}$  bond, thus decreasing the energy required for the  $\text{C-O}$  bond oxidative addition (Scheme 89, right).<sup>180</sup> Free amines and nitrogen-containing heterocycles could be tolerated, and benzyl hydroxyl groups could be reduced in good yields. However, the reaction could not be extended to simple phenol rings, and only moderate yields were obtained for biaryl systems. Unfortunately, the experimental data provided did not allow the authors to establish the mechanistic rationale behind these results.



**Scheme 89.** Reductive cleavage of aromatic  $\text{C}(\text{sp}^2)\text{-OH}$  bonds

Since the first demonstration of the catalytic reductive cleavage of unactivated  $\text{C-O}$  bonds,<sup>4</sup> the far-reaching consequences of this discovery have made an immediate impact. Indeed, the rapid proliferation of methodologies employing different metals, reducing agents, and substrates is testament to the considerable importance of the reaction. In the future, issues such as the reluctance of anisole derivatives to undergo  $\text{C-O}$  cleavage, the elevated reaction temperatures and catalyst loadings, the low substrate scope of the phenol cleavage reactions, and the lack of consensus regarding the mechanism must be addressed.

## 5. Conclusions and Outlook

The seminal work of Wenkert in 1979 undoubtedly set the basis for modern cross-coupling reactions via catalytic functionalization of C–O bonds in aryl esters, carbamates or aryl ethers. As judged by the meteoric development of these technologies in recent years, it is evident that Wenkert's work was a giant leap forward and opened up new vistas in a relatively unexplored terrain. A common feature of these reactions is the superior ability of low valent Ni catalysts to facilitate C–O functionalization. This is a rather striking outcome considering the general lack of reactivity found with Pd species, which are privileged catalysts in related cross-coupling reactions of otherwise related-aryl sulfonates. Although remarkable levels of sophistication have been achieved when using aryl esters, carbamates or aryl ethers, these methods are unfortunately not as general as classical metal-catalyzed cross-coupling reactions of organic halides. Additionally, a number of these technologies remain essentially confined to  $\pi$ -extended systems, probably due to the intermediacy of Meisenheimer-type complexes, dearomatization pathways, or the involvement of charge-transfer scenarios. Unlike the reactions employing organic halides or organic sulfonates, the means to promote enantioselective catalytic protocols based on the C–O bond cleavage of aryl esters, carbamates or aryl ethers is virtually absent in the literature, and constitutes a formidable opportunity in years to come. Additionally, the underlying mechanisms by which many of these reactions operate remain rather speculative. In view of the available literature data, it is apparent that that a "classical" regime based on oxidative addition of the C–O bond, followed by transmetalation and reductive elimination might not be operative in some cases and that other scenarios might come into play. We certainly anticipate that unraveling the intricacies of these processes will lead to the discovery and development of conceptually new processes. Although significant efforts will need to be conducted, fortune certainly favors the brave, and we predict a bright future for the use of phenol derivatives as modern electrophiles in cross-coupling reactions.

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