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Grignard Reagents and Nickel

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1 Introduction

Grignard reagents, discovered more than one century ago, are still widely used to promote carbon–carbon bond formation. Over the time, their reactivity has been modulated by the presence of various additives, especially transition metals salts. In this area, nickel had played a major role in the development of new and selective cross-coupling reactions between organomagnesium derivatives and C(sp²)-halides. It is generally admitted that the respective contributions of Kumada and Tamao in Japan [1] and Corriu in France [2] constitute a major breakthrough in the field of organometallic chemistry. Forty years after these two seminal contributions, the Kumada Tamao-Corriu reaction and related processes are still investigated but also applied in industrial processes and used in the synthesis of complex molecules. Thanks to the design of more and more sophisticated ligands, including pincer and NHC ligands, this coupling reaction initially performed with halogen derivatives has been successfully applied to a large number of starting materials. Nowadays, the cleavage of carbon–oxygen and carbon–sulfur bonds has considerably enhanced the potential of this reaction in term of regioselectivity. Furthermore, the challenging sp³–sp³ cross-coupling has been addressed. Finally, the control of the stereochemistry has been considered, which also allows new perspectives for the future.

The mechanism generally admitted is depicted in Figure 1. A nickel(0) species is generated *in situ* by reduction of a nickel(II) complex mainly by action of the Grignard species present in excess. Then, the oxidative addition results in the formation of a nickel(II) complex **A** which can undergo a transmetalation with the Grignard reagent leading to species **B**. An isomerization step *via* intermediate **C**, followed by a subsequent reductive elimination, release the coupled product **D** and regenerate the effective catalyst.

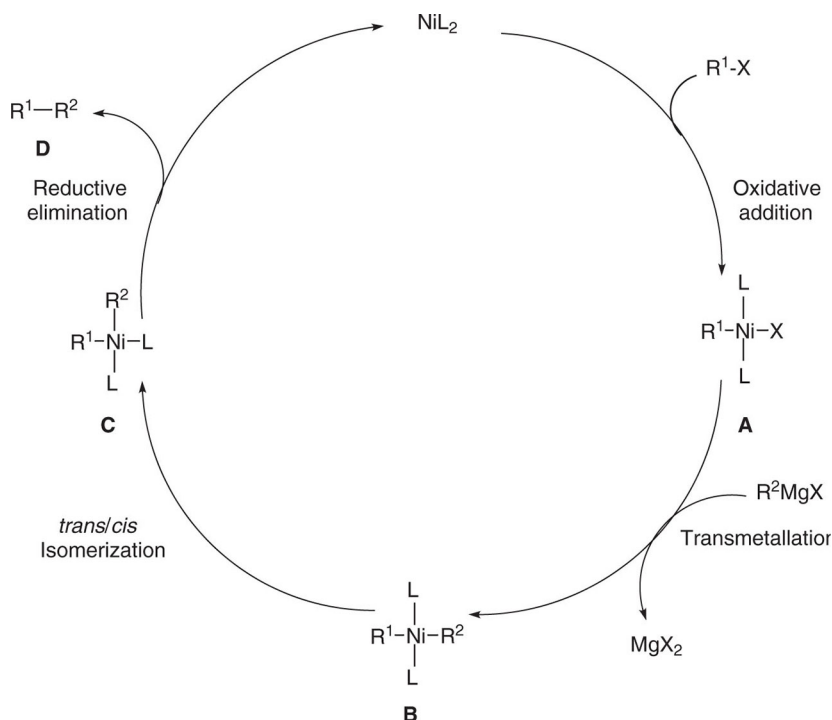


Figure 1: Generally admitted mechanism for the Kumada-Corriu reaction.

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In the context of enantioselective processes, the coupling between an optically active Grignard reagent **1** and vinyl bromide was investigated and led to adduct **2** with almost complete retention of the configuration when conducted in the presence of NiCl_2dppf at low temperature (Figure 2). This demonstrated that the key transmetallation step occurred surely according to a concerted polar mechanism [3]. In contrast, the same reaction promoted by iron or cobalt resulted in partial racemization of the final product which supports a radical based mechanism.

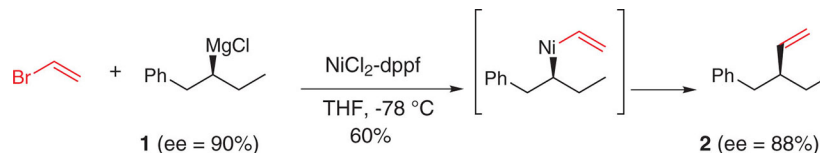


Figure 2: Enantioselective transformation as a proof for a concerted polar mechanism.

The success of the different Ni-catalyzed cross-couplings [4] resulted from a large number of items such as:

- The ligands, especially mono- and diphosphines, which stabilize the organometallic intermediate to avoid a homodimerization process (Kharasch reaction).
- The elimination which usually occurred with alkyl Grignard reagents can be strongly reduced.
- In $\text{Csp}_2\text{--Csp}_2$ cross-couplings, the initial geometry of the vinyl derivatives is maintained.

2 Coupling reactions of aryl Grignard reagents

2.1 With aryl derivatives

2.1.1 With aryl bromides and chlorides

The formation of diaryl compounds has been extensively studied. The success of the couplings depends both on the structure of the substrates (nature of the leaving group, steric hindrance, etc.) but also on the nature of the nickel catalyst and principally the type of ligands directly linked to the metal.

Use of phosphine ligands

At the very beginning of the development of the Kumada-Corriu reaction [5, 6], phosphine ligands were used to stabilize the nickel catalyst, the catalytic activity being significantly dependent on the nature of the phosphine ($\text{NiCl}_2(\text{dppp}) > \text{NiCl}_2(\text{dppe}) > \text{NiCl}_2(\text{PR}_3)_2 = \text{NiCl}_2(\text{dppb})$). The Kumada-Tamao-Corriu reaction has attracted chemical companies to access fine intermediates such as substituted styrenes and biphenyls but also, at a later stage, for the final functionalization of the target molecules [7, 8]. The reactions usually are highly yielding and selective. They are also highly attractive because of the large availability of chloro-derivatives as precursors of both Grignard reagents and cheap coupling partners. Of interest, industrial applications required low charge of catalyst of common and cheap diphosphine ligands. Moreover, these reactions are usually performed under suitable conditions of temperature. However, some drawbacks should be pointed out, for example Grignard reagents require anhydrous conditions, and they are not compatible with a large variety of (reductive) functionalities. Finally, the work-up of the reaction generates a large amount of magnesium salts and thus, requires a process for waste treatment.

PDE472 **4**, a selective inhibitor of the phosphodiesterase PDE4D isoenzyme has been prepared on pilot-plant scale taking advantage of the Kumada-Corriu coupling (Figure 3). The coupling reaction of 4-chloropyridine in toluene, with the *p*-methoxyphenyl Grignard was performed to produce **3** in 74 % yield. The success of the reaction depends on the dryness of the chloropyridine [9].

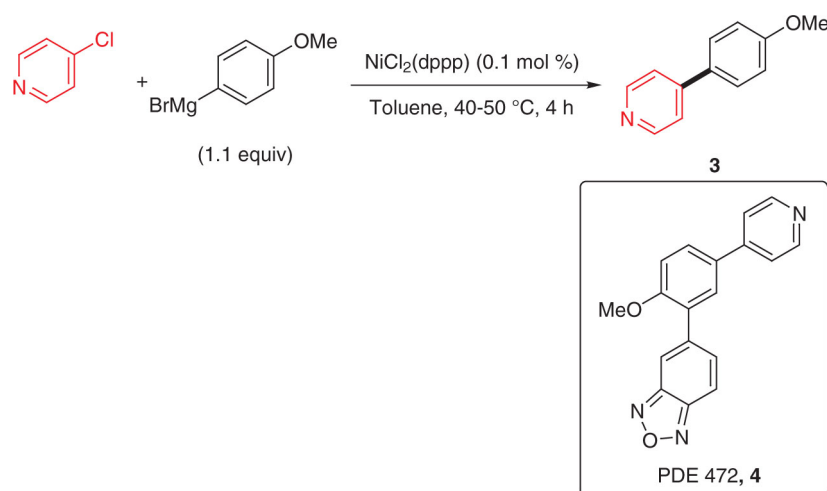


Figure 3: Access to 4-arylpyridine **3**, a key intermediate for the synthesis of PDE 472.

To produce the HIV protease inhibitor atazanavir, chemists at Novartis have reported a multi-kg synthesis of substituted *p*-aryl benzaldehydes based on a Ni-catalyzed coupling between 2-bromopyridine and aryl Grignard derivatives (Figure 4). The Ni(0) which is required for the oxidative addition was generated *in situ* by reduction of the catalyst by DiBAL-H. After removal of the protective group, aldehyde **5** was isolated in 90 % yield. When performed in the absence of DiBAL-H, the yield dropped dramatically to 68 % [10, 11].

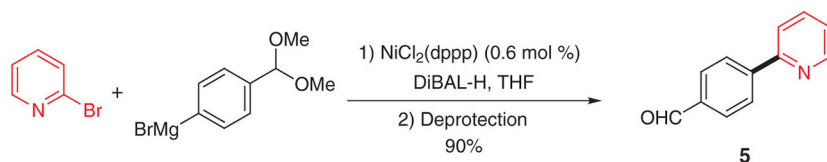


Figure 4: Access to aldehyde **5**, precursor of atazanavir.

Catalyst $\text{NiCl}_2(\text{dppp})$, in combination with lithium triarylmagnesiates, instead of the classical organomagnesium reagents, allowed the Kumada-Corriu cross-coupling of a variety of aryl bromides and chlorides in good yields, and less than 10 % of the homo-coupling products were formed (Figure 5) [12].

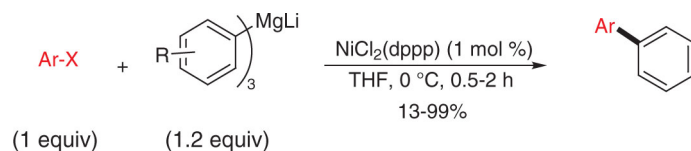


Figure 5: Coupling of aryl halides with lithium triarylmagnesiates catalyzed by NiCl_2 and diphosphine.

Indole-derived air stable diphosphine ligands such as **L1** were also used successfully for the cross-coupling of a variety of aryl and heteroaryl chlorides with aryl Grignard reagents (Figure 6) [13].

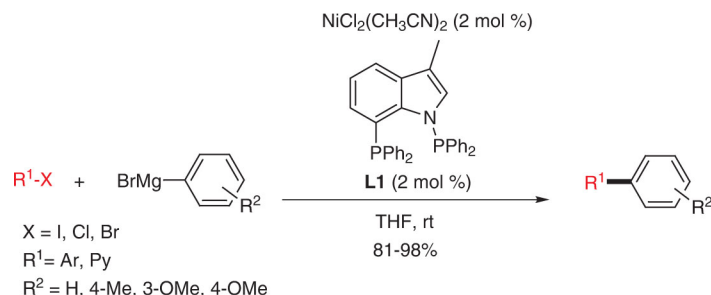


Figure 6: Indole-derived air-stable diphosphine ligand **L1** in Kumada-Corriu reaction.

Calix[4]-diphosphine ligands were synthesized and proved to be efficient ligands, providing that the reactions were performed at 100 °C in dioxane with a PhMgBr/ArX ratio of 2/1. Compared to results obtained with dppp, which is considered in the field of diphosphines as one of the most efficient ligand [1], nickel complexes prepared from **L2** gave better results. The coupling was presumably facilitated by a temporary increase of the P-Ni-P angle and thus an increase of the steric pressure of the P-substituents on the two organic frameworks (Figure 7) [14].

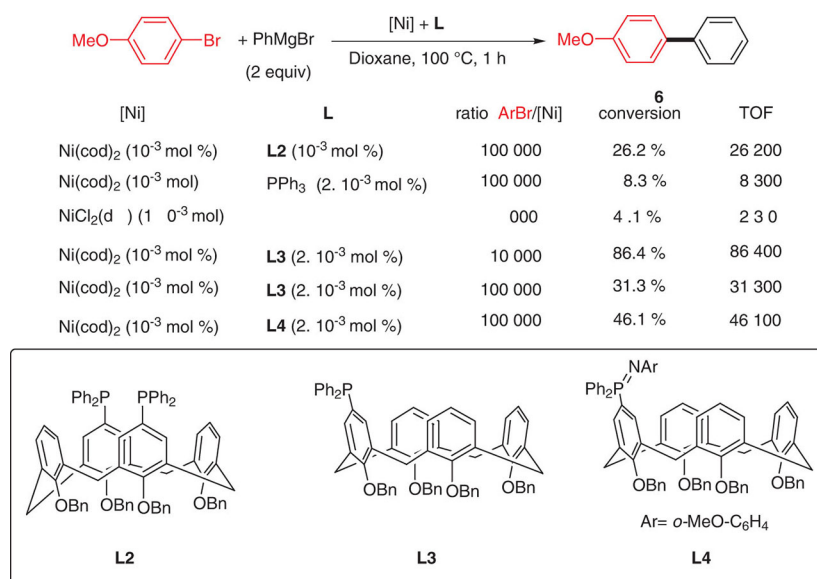


Figure 7: Formation of bis-aryls using calixarene phosphine ligands.

Nevertheless, ligand **L3**, the monophosphine analog of **L2**, turned out to be more suitable and efficient at room temperature with aryl chlorides and four times more active than triphenylphosphine [15]. The orientation of the P–Ni bond towards the calixarene axis (and not outwards) seems to increase the ligand bulk and thus favored the formation of a mono-ligand Ni complex [16]. The mono-iminophosphorane analog **L4** (R = *o*-anisyl) allowed cross-coupling of aryl bromides in dioxane at 100 °C with a very low catalyst loading of 0.001 mol %. Thus, in 1 h, bromoanisole reacted with PhMgBr to give 46 % of the expected coupling product. In comparison with the cavityfree iminophosphorane Ph₃P=N(*o*-anisyl), the activity was ten fold higher, due to a more highly crowded metal environment in favor of a mono-ligated intermediate, more reactive than bis-ligated complexes and *endo*-located metal centers.

Among monophosphine ligands, *tris*(*t*-butyl)phosphane **L5** was also particularly efficient for the cross-coupling of aryl chlorides with aryl Grignard at ambient temperature [17]. The sulfur analog (*t*-Bu)₂P(S)H **L6** [18] and its oxygen analog (*t*-Bu)₂P(O)H **L8**, which revealed to be the best ligand [19], were also used successfully at room temperature in THF, with the advantage of being air stable and particularly low cost and accessible (Figure 8).

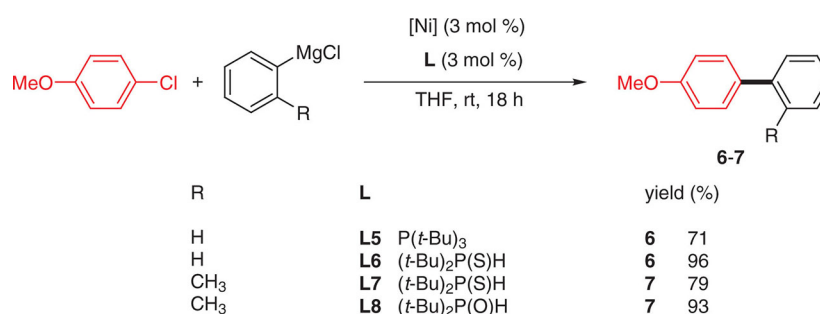


Figure 8: Monophosphine ligands and Kumada-Corriu coupling reaction.

Unactivated, deactivated and functionalized aryl chlorides reacted also with aryl Grignard reagents when monophosphine based catalysts **C1a-b**, in connection with additives such as LiCl or ZnCl₂ were used (Figure 9). This significantly expanded the scope of Kumada cross-coupling reaction [20].

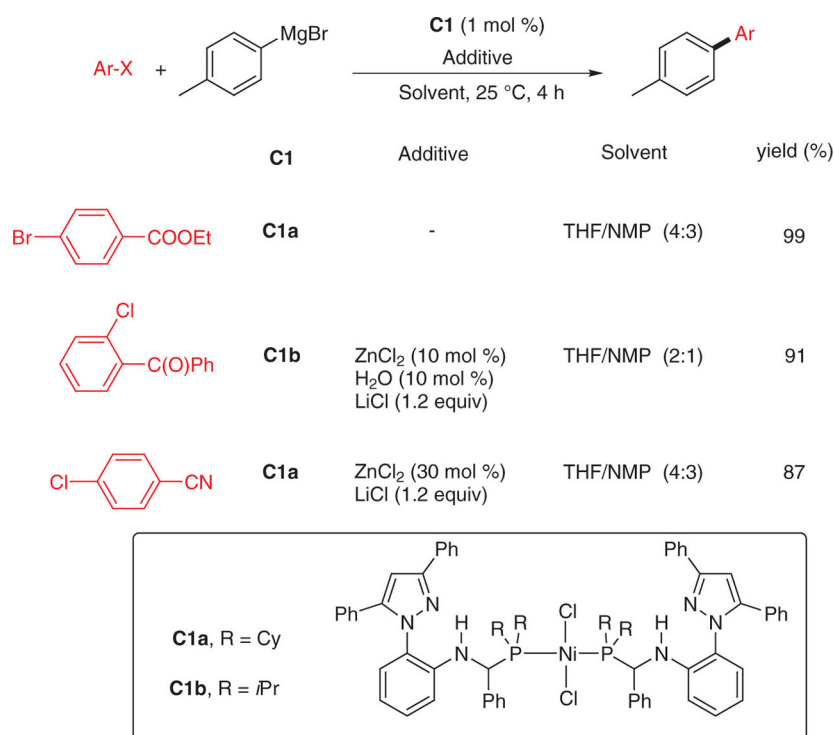


Figure 9: Influence of additives on the coupling of aryl halides with tolyl Grignard reagent.

Phosphine oxides turned out to be excellent ligands for the activation of C–Cl bonds. Thus, the particularly congested structure **L9** showed one of the highest activity among the already described ligands [21]. Its sulfur analog, the diamminophosphine sulfide ligand **L10**, turned out to be less active and selective (Figure 10) [22].

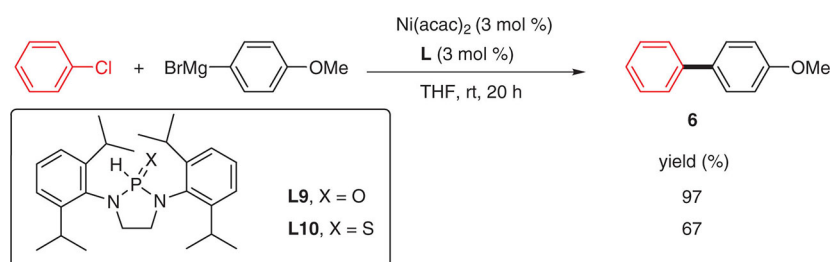


Figure 10: Application of phosphine oxide **L9** in the Kumada-Corriu reaction.

Binaphthyls play a major role as ligands or auxiliaries in numerous asymmetric reactions. To access to related derivatives, the asymmetric cross-coupling of two naphthyl derivatives has been successfully investigated by the group of Hayashi and Ito, in Japan. To significantly favor the formation of one of the two atropoisomers, chiral ferrocenylphosphine ligand **L11** was used and gave excellent stereoselectivities (Figure 11) [23].

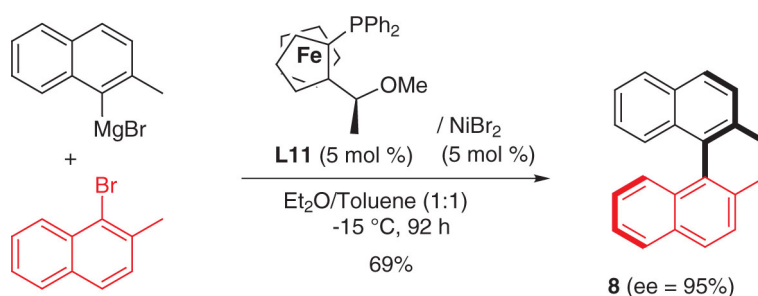


Figure 11: Stereoselective synthesis of binaphthyl derivatives *via* an asymmetric Kumada-Corriu cross-coupling.

Use of bidentate P,N Ligands

Bidentate diarylamido phosphine nickel chelates as **C2** turned out to be involved in very active catalytic systems (Figure 12) [24].

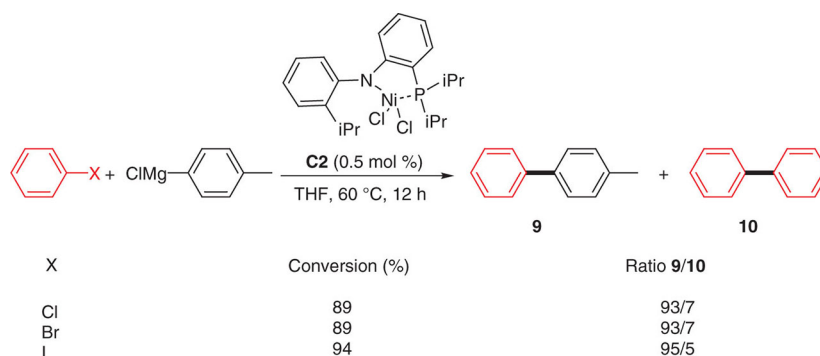


Figure 12: Bidentate diarylamido phosphine **C2** as ligand for the Kumada-Corriu reaction of aryl halides.

Very recently, the Sommer's group [25] used the hybrid P,N ligand **C3** for Kumada-nickel catalyst transfer polycondensation of sterically hindered thiophenes (Figure 13). They showed that such a system is highly suitable to control the polymerization of thiophene-based monomers with sterically very demanding side chain, much more efficient than the commercially available $\text{NiCl}_2(\text{dppe})$ and $\text{NiCl}_2(\text{dppp})$ catalysts.

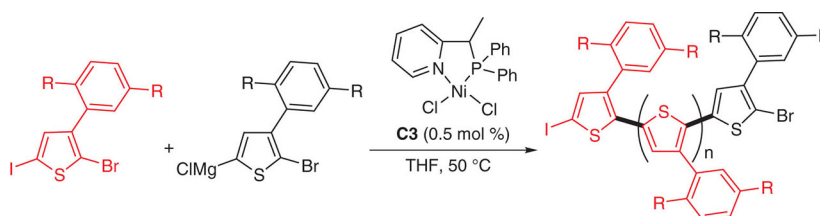


Figure 13: Polycondensation of sterically hindered thiophenes.

Use of tridentate pincer ligands

Tridentate pincer ligands containing phosphorus were also considered (Figure 14). Thus, P,N,P ligands as **C4**, [26] **C5**, [27] or **C6**, P,C,N ligands as **C7**, **C8** [28] and P,C,P ligand such as **C9** [29] have been tested successfully in the aryl-aryl coupling, even with aryl chlorides.

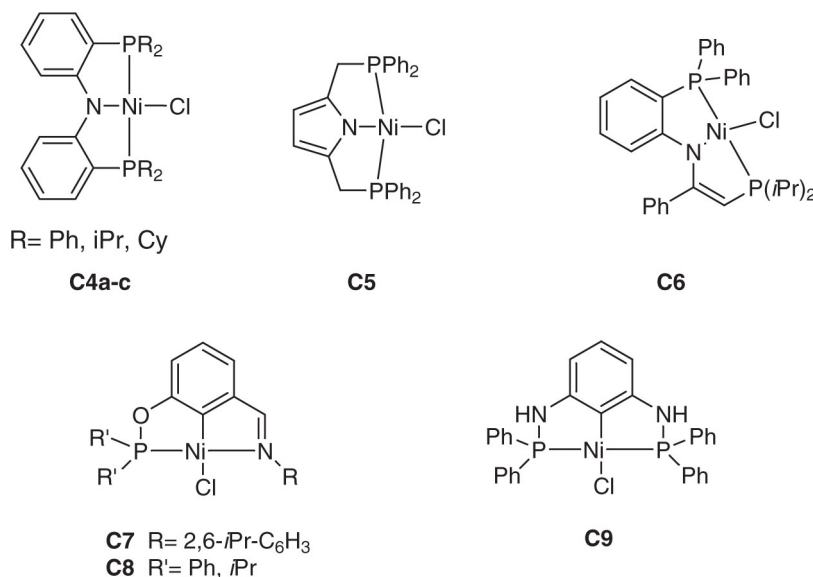


Figure 14: Various P,N,P ligands, P,C,N and P,C,P ligands used for the aryl-aryl coupling.

As depicted in Figure 15, **C6** and other catalysts such as **C10**, **C11** or **C12** are particularly relevant for the formation of biphenyl derivatives [30–32]. It has been assumed that (P,N,P) pincers in **C6** and **C11** are less labile than (P,N,N) ligands as in **C10** and **C12**. This difference directly impacts the oxidative addition step and favors the C–C bond formation [33].

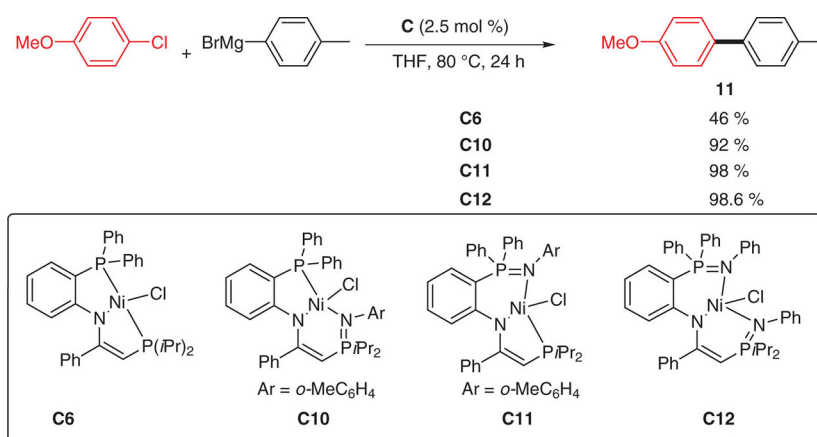


Figure 15: Comparison of (P,N,P) and (P,N,N) pincer ligands for the formation of biphenyl derivatives.

Other pincer ligands of the less widespread P,N,S and P,N,O types were examined in the Kumada-Corriu reaction [34]. If the P,N,O chelate nickel complexes showed high catalytic activity for the coupling of unactivated, or deactivated aryl-, heteroaryl- and vinyl chlorides with aryl Grignard reagents, the P,N,S analogs were far less active (Figure 16).

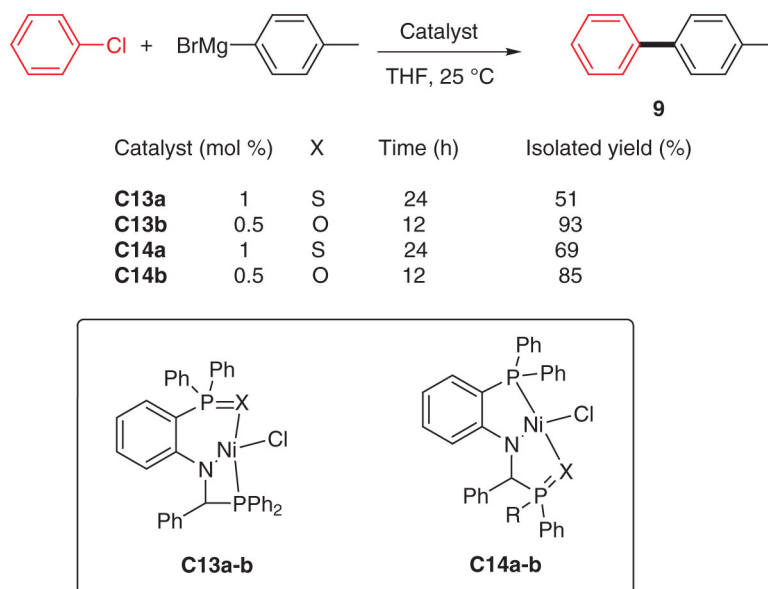


Figure 16: Comparison of (P,N,S) and (P,N,O) pincer ligands for the formation of biphenyl derivatives.

Use of NHC carbenes as ligands

N-Heterocyclic carbenes are strong σ -donor ligands especially effective when the oxidative addition of an aryl halide to the catalyst is the rate-determining step. The main interest of N-heterocyclic carbene ligands resides in the robustness of the associated catalysts in comparison to the phosphorus ones, avoiding decomposition or deactivation. The first described air-stable efficient carbene ligand **L12** (Figure 17) [17] combined with Ni(acac)₂, allowed the cross-coupling of aryl chlorides with aryl Grignard at room temperature, in THF with a catalyst loading of 3 mol %.

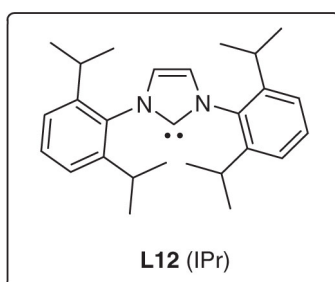


Figure 17: First efficient air-stable NHC ligand for the Kumada-Corriu reaction.

Nakamura *et al.* successfully used NHC carbenes such as **L12** for the coupling of aryl halides with aryl Grignard reagents [35]. The formation of homocoupling byproducts was mainly suppressed by using a nickel halide salt (Figure 18).

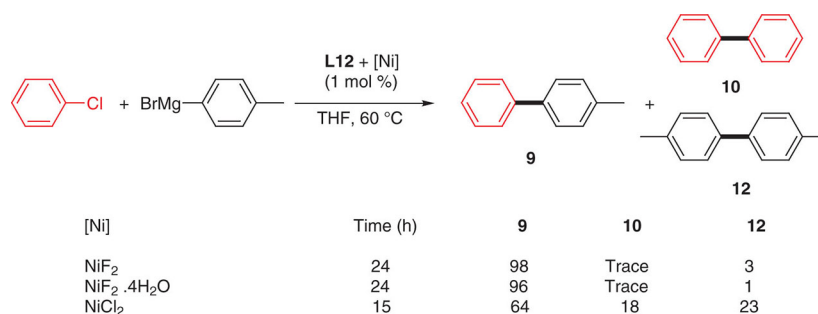


Figure 18: Inhibition of the homocoupling process induced by **L12** and nickel(II) fluoride.

Only one or two NHC ligands could be coordinated to the metal, depending on the steric hindrance on the carbene ring. With ligands **L13** and **L14** (Figure 19), the metal can be coordinated to two NHC subunits leading to a stabilized nickel complex which is efficient for the cross-coupling between an aryl Grignard reagent with an aryl halide [36, 37].

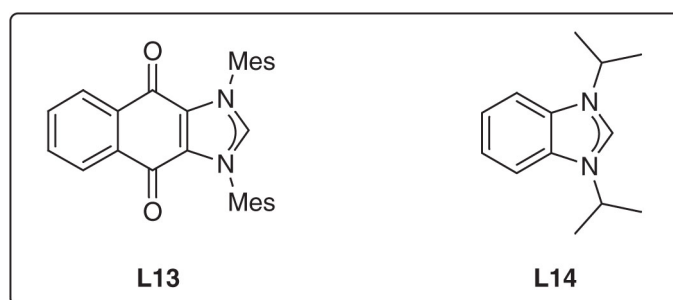


Figure 19: Other NHC ligands used in Kumada-Corriu reaction.

Heterogeneous version of *N*-heterocyclic carbene precursors was proposed using copolymer-embedded nickel nanoparticles **C15** [38]. In this case, no additional coordination site was necessary, the nickel particles being stabilized by the structure of the polymer. After 10 recyclings of the catalyst, no loss of activity and selectivity was observed in the coupling. This catalyst is efficient for the coupling of aryl halides with aryl Grignard reagents (Figure 20).

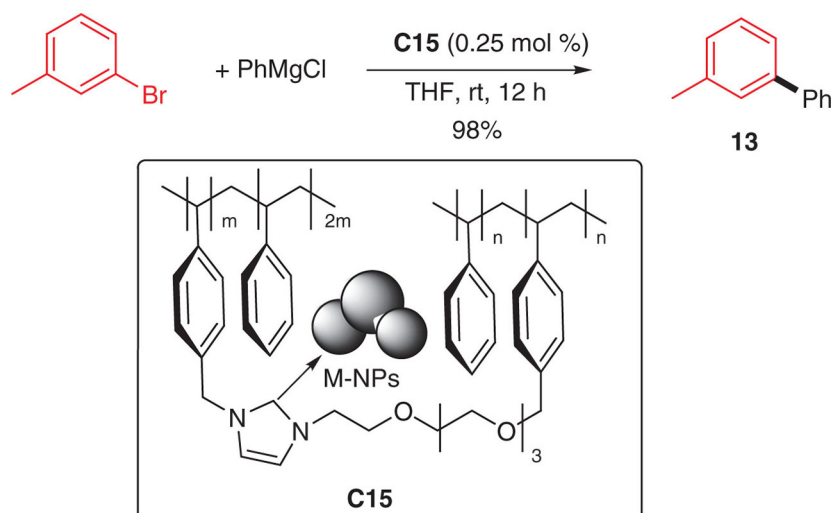


Figure 20: Heterogeneous NHC ligand.

Other NHC-ligands containing additional coordinating functions which should provide a good catalyst efficiency have been successfully developed for the Kumada-Tamao-Corriu reaction involving aryl chlorides and aryl Grignard reagents. Thus, at room temperature in THF with 3 mol % catalyst loading, the ligand **L15** with the phosphane-NHC bidentate ligand [39, 40] turned out to be far more active than **L12**, and remained the best nickel-NHC catalyst to date for the coupling of 4-chloroanisole with phenyl magnesium chloride (Figure 21).

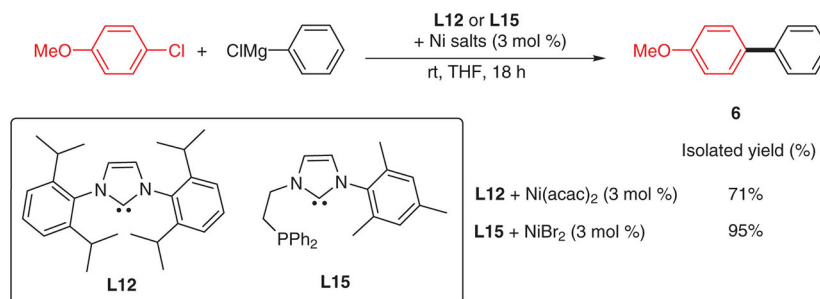


Figure 21: Cross-coupling catalyzed by a NHC-ligand containing an additional phosphane group.

Nickel catalyst possessing six-, seven- or eight-membered ring *N*-heterocyclic carbenes **C16–18** (Figure 22) have also been tested [41]. At room temperature in THF, the best results were obtained in the coupling of aryl chlorides in the presence of **C16** as catalyst.

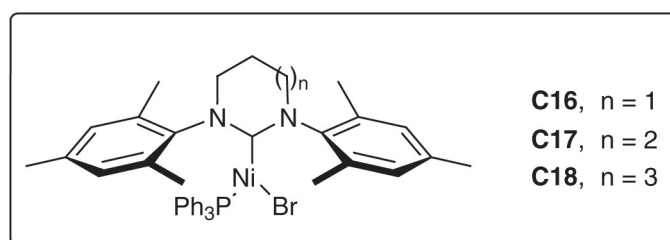


Figure 22: Six-, seven- and eight-membered ring NHC ligands.

NHC-carbene ligand **L16** combined with Ni(acac)₂ [42] or a diaza function [CNN]-pincer nickel complexes such as **C19** [43], **C20** [44], and **C21** [45], were synthesized and successfully involved in Kumada-Corriu coupling between phenyl chloride and tolyl Grignard reagent (Figure 23).

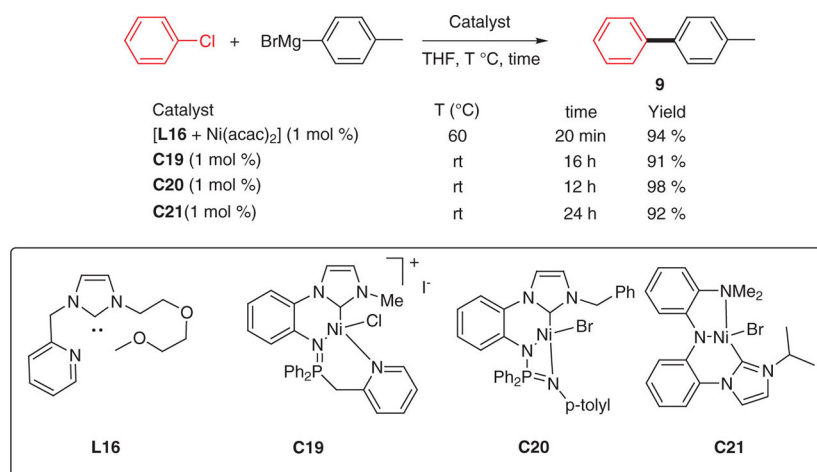


Figure 23: NHC ligands with additional coordinating sites used in the Kumada-Corriu reaction.

Bridged di-NHC complexes, **C22a–c** and **C23**, were also developed and tested for the synthesis of **6** as a model reaction [46–48]. The bridge length influences the formation of monochelate complex *versus* less reactive dichelate species. The 1,3-propanediyl-bridged dicarbene ligand **C22c** turned out to be the most active of the series for the coupling of aryl Grignard reagents with aryl halides (Figure 24).

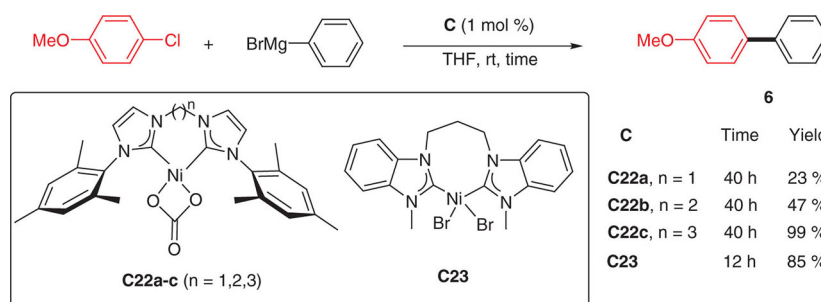


Figure 24: Bridged di-NHC complexes.

Tridentate bis(carbene)-derived nickel(II)-pincer complexes were also developed. Thus, Inamoto *et al.* tested successfully catalyst **C24** on a wide range of aryl halides as electrophiles [49]. The reaction was performed in THF, at room temperature, with a catalyst loading of 5 mol % (Figure 25).

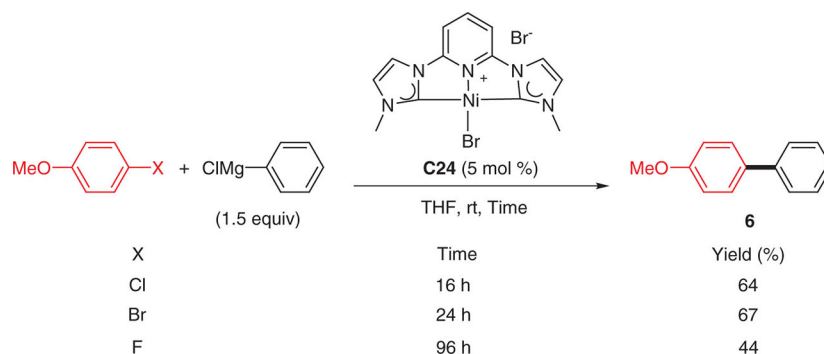


Figure 25: Tridentate bis(carbene)-derived nickel (II)-pincer complexes.

Heterogeneous catalysis

Several heterogeneous systems have been developed for the Kumada-Corriu reaction using Salen ligands bound either on a Merrifield resin, such as **C25** [50, 51] or aminomethylpyrrolidine framework attached on silica, such as **C26** [52] for the aryl-aryl coupling (Figure 26). Isolated yields of cross-coupling reaction were quiet good (around 70 % e.g. for the reaction of 4-bromoanisole and phenyl magnesium bromide). In addition, in both cases, the catalytic systems remained active even after 5 runs with almost no leaching (<1 %), which could be interesting for the development of green industrial processes.

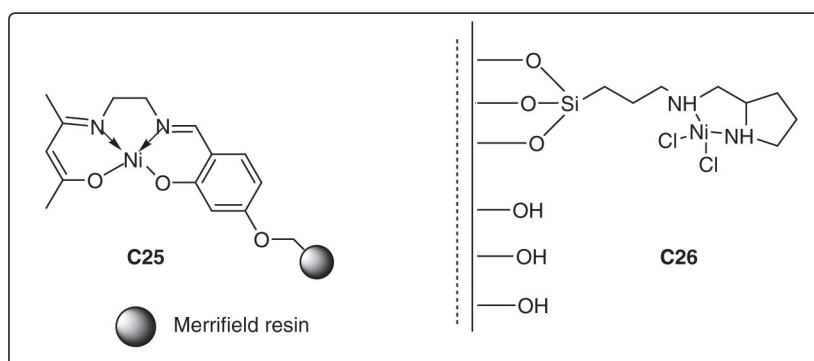


Figure 26: Heterogeneous systems using N containing ligands for the Kumada-Corriu reaction.

As a source of nickel, Ni/C can be used for the Kumada-Corriu reaction of aryl chlorides and aryl Grignard reagents (Figure 27). The best conditions required refluxing THF, the presence of a phosphine (generally PPh_3) to minimize the homocoupling side reaction. While this catalytic system allowed the scale-up, no recycling of the catalyst was reported [53–55].

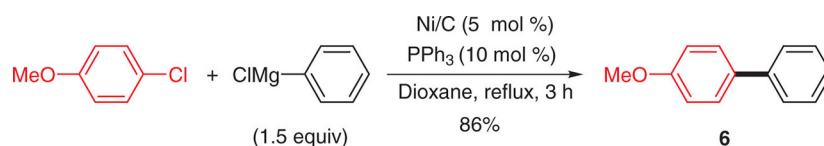


Figure 27: Kumada-Corriu reaction of aryl chlorides and aryl Grignard reagents catalyzed by Ni/C.

2.1.2 With aryl fluorides

For a long time, fluorinated compounds have been considered as inert materials in cross-coupling reactions. Due to the design of new catalysts NHC-Ni(0) **C27**, the Kumada-Corriu reaction has been successfully achieved between fluoroarenes and aryl magnesium bromides. The reaction was efficient in a large number of cases even with electron-deficient substrates. Steric hindrance induced by substitution on the *ortho* position considerably reduced the yields of the couplings. Mechanistic studies revealed that the process occurred probably *via* a polar process, while reaction promoted by NiCl₂ took place *via* a radical process [17]. Air stable phosphine oxide ligands such as **L17** [56] and P,N,N-pincer nickel complexes such as **C28** [57] have also been tested to be efficient even for the coupling of electron-enriched substrates which are usually more reluctant to cross-couplings (Figure 28 and Figure 29).

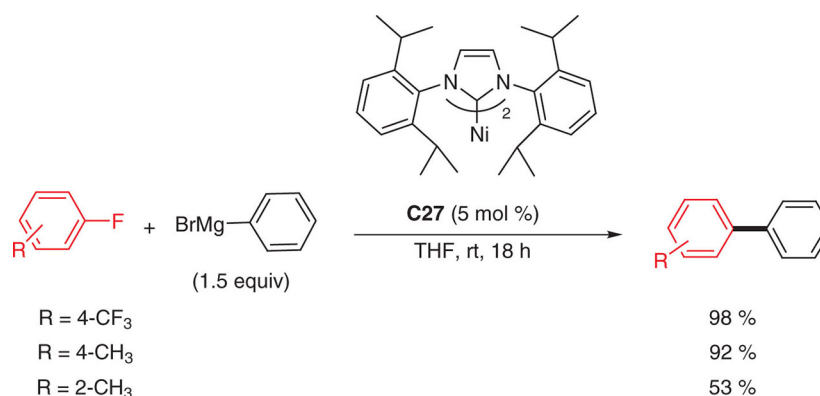


Figure 28: Kumada-Corriu reaction between fluoroarenes and aryl magnesium bromides.

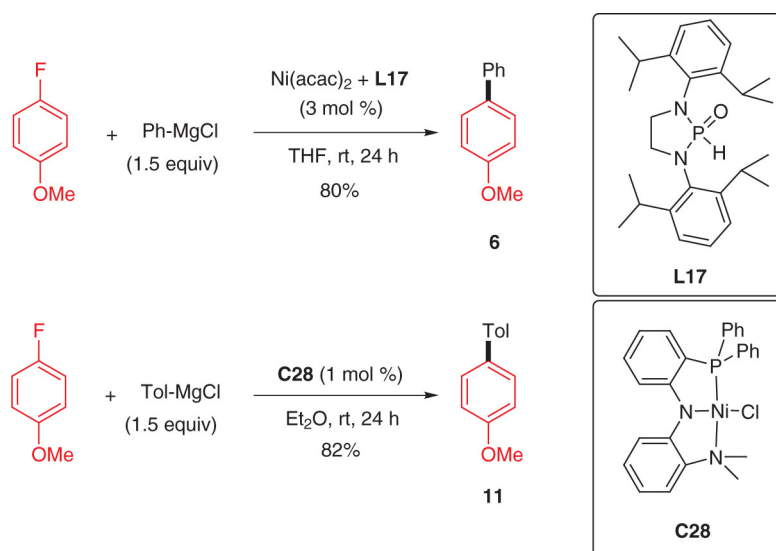


Figure 29: Coupling between fluoroanisole and aryl magnesium bromides.

In order to reach mono- or difluorinated compounds, the activation of di- and trifluoroarenes has been deeply investigated [58–60]. However, no significant selectivities were observed when reactions were realized in the presence of nickel salts. In contrast, palladium catalysis employing PdCl₂(dppf) gave only the monoarylated adduct **14** in 91 % yield (Figure 30).

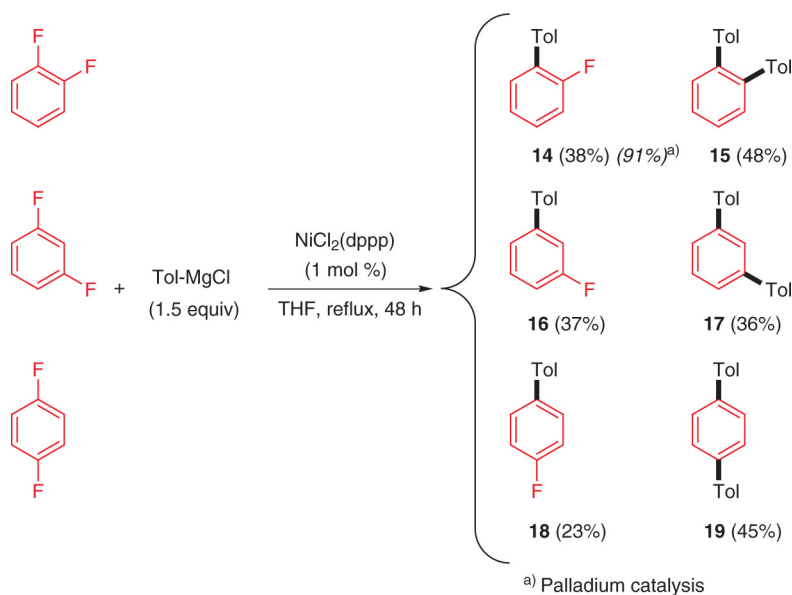


Figure 30: Selectivities of nickel-catalyzed Kumada-Corriu reactions starting from difluoroarenes.

2.1.3 With aryl thioethers

In 1979, Wenkert *et al.* demonstrated that arylthiols, sulfides underwent coupling with phenyl- or *p*-tolyl-magnesium bromides in the presence of 10 mol % of $\text{NiCl}_2(\text{PPh}_3)_2$ catalyst (Figure 31) [61]. The process required higher temperatures and longer reaction times than with halides as the carbon-sulfide bond is stronger and therefore more reluctant to oxidative addition [62].

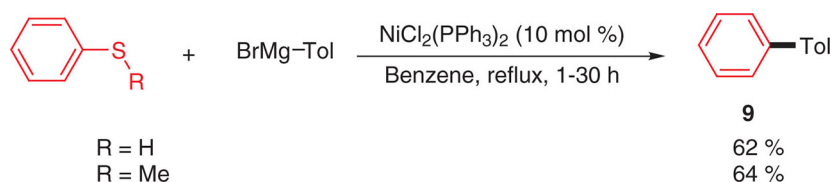


Figure 31: Nickel-catalyzed Kumada-Corriu reaction with arylthiol derivatives.

The scope was expanded to a great variety of heterocyclic aryl sulfides (Figure 32) [63].

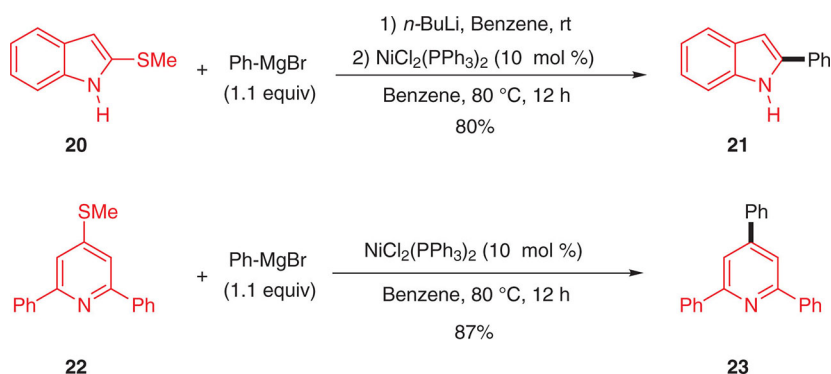


Figure 32: Nickel-catalyzed Kumada-Corriu reaction with heterocyclic aryl sulfides.

The electron-rich $\text{NiCl}_2(\text{PPh}_3)(\text{IPr})$ catalyst **C29** was successfully employed in the cross-coupling of bulky 2-methylthio-substituted benzofurans with aryl Grignard reagents, yielding highly fluorescent benzofurans such as **25** (Figure 33) [64].

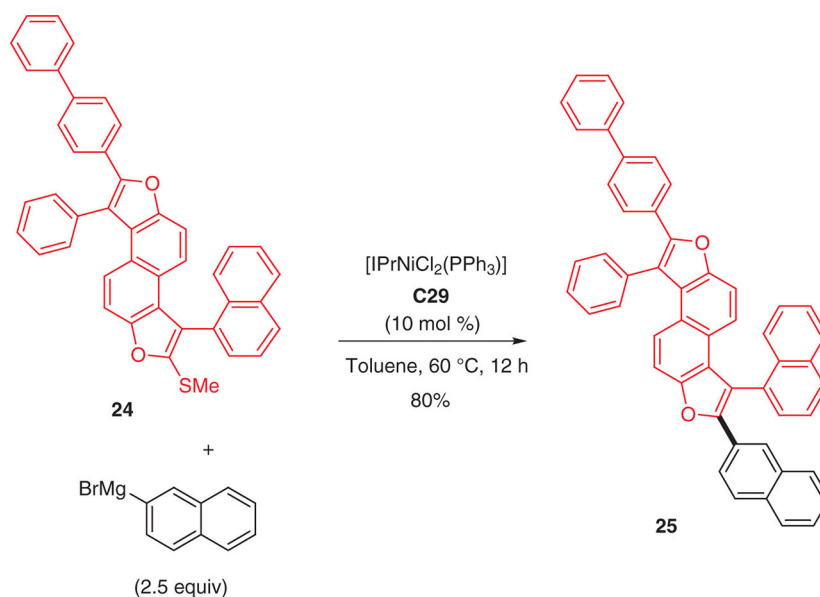


Figure 33: Access to highly fluorescent benzofurans *via* the nickel-catalyzed Kumada-Corriu reaction.

Taking advantage of this coupling, a flexible access to eupomatenoids, a class of natural products has been designed [64]. A Kumada-Corriu coupling between 2-methylthiobenzofuran **26** and the Grignard reagent **27**, prepared from 5-bromo-1,3-benzodioxole, led the expected compound **28** in high yield (Figure 34).

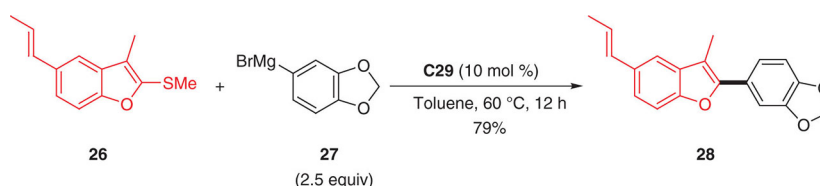


Figure 34: Access to eupomatenoids using the Kumada-Corriu reaction.

2.1.4 With aryl sulfones, sulfonates, sulfonamides

The use of aryl *tert*-butyl sulfones as electrophilic coupling partners was described by the group of Julia. The ability of the *tert*-butyl sulfonyl group to direct *ortho*-lithiation was later applied to the synthesis of *ortho*-substituted unsymmetrical biaryls (Figure 35) [65].

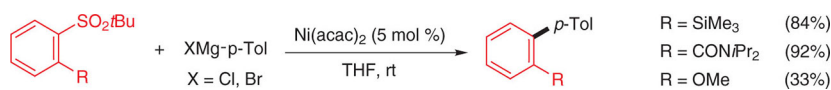


Figure 35: Aryl *tert*-butyl sulfones as electrophilic coupling partners.

Arenesulfonates can undergo nickel-catalyzed cross-coupling with aryl Grignard nucleophiles to give unsymmetrical biaryls. Park *et al.* studied the C–C bond formation from neopentyl arylsulfonates with arylmagnesium halides and showed that the $\text{NiCl}_2(\text{dppf})$ catalyst inserts in the $\text{C}(\text{sp}^2)\text{--S}$ rather than in the $\text{C}(\text{sp}^3)\text{--O}$ bond (Figure 36) [66].

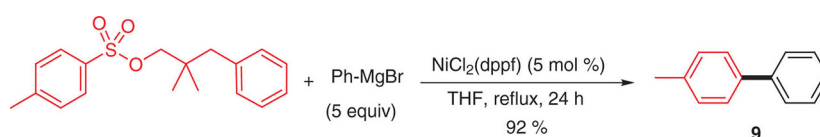


Figure 36: Arenesulfonate used for the synthesis of unsymmetrical biaryls.

Similarly, Snieckus *et al.* reported the coupling of a variety of arenesulfonamides with phenylmagnesium halides in refluxing toluene under classical nickel catalysis (Figure 37) [67].

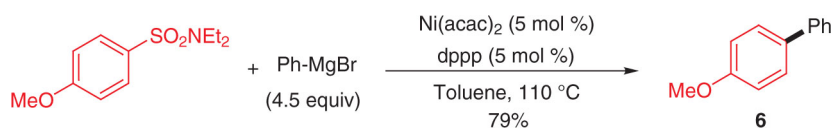


Figure 37: Arenesulfonamides as partners for the synthesis of unsymmetrical biaryls.

2.1.5 With aryl ethers

Cross-couplings with oxygenated derivatives represent new perspectives in Kumada-Corriu reactions. Due to their large availability from natural biosources, they represent an interesting pool of starting materials. Their use has been recently reviewed [68] and will probably increase in the near future.

2.1.5.1 Aryl alkylethers and aryl silylethers

Aryl ethers constitute more attractive electrophiles than sulfonates as they are more readily available and more environmentally benign as they generate less waste. However, the C-OMe bond is more reluctant towards oxidative addition and, thus, less reactive in cross-coupling reactions due to the higher activation energy for its cleavage. In a pioneering work, Wenkert and co-workers described the cross-coupling of aryl methyl ethers with phenyl magnesium bromide in the presence of 10 mol % of $\text{NiCl}_2(\text{PPh}_3)_2$ in refluxing benzene [69]. Two decades later, Dankwardt found that nickel complexes with electron-rich phosphine ligands possessing a larger cone angle (e.g., PCy_3 or PhPCy_2) were efficient at 60 °C for the arylation of diversely substituted methoxyarenes (Figure 38) [70].

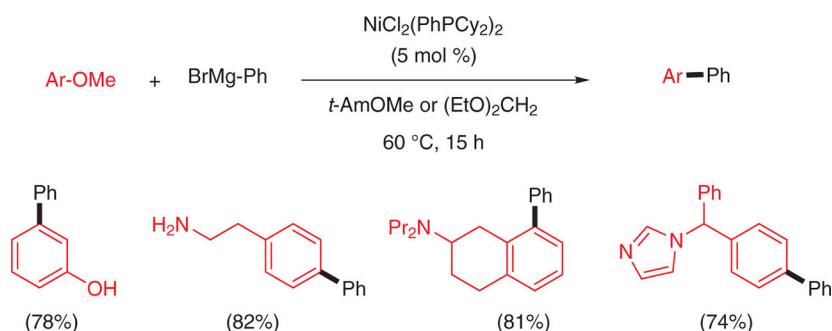


Figure 38: Functionalized ary ethers as efficient electrophiles for the Kumada-Corriu reaction.

More recently, several contributions reported the design of new ligands to improve the efficiency and the selectivity of nickel-catalyzed Kumada-Corriu coupling reactions of aryl ethers. In 2011, Wang and Xie reported that electron-rich and sterically hindered pyrazolyl amino phosphines **C1b** (cf. Figure 9) allowed for the coupling of π -extended aromatic and alkenyl ethers under mild conditions (THF, room temperature or 50 °C) [71]. The more challenging aryl methyl ethers still required high temperatures to react (toluene, 120 °C). In 2012, and for the first time, Nicasio *et al.* reported the use of *N*-heterocyclic carbene ligands as an alternative to phosphine ligands in the nickel-catalyzed Kumada-Tamao-Corriu coupling of π -extended and regular aryl methyl ethers under relatively mild conditions (THF, 60 °C) [72]. The scope was again limited to non-functionalized coupling partners due to the high reactivity of Grignard reagents (Figure 39).

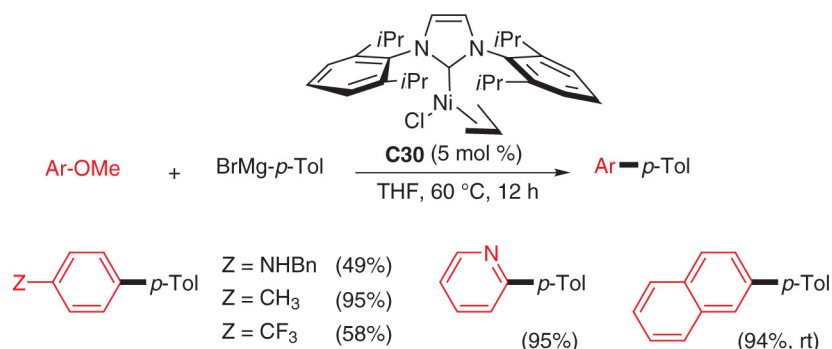


Figure 39: NHC ligand for the coupling of ary ethers.

An initial study on the nickel-catalyzed alkenyl C-OSi bond activation for C-C bond formation with aryl and alkyl Grignard reagents was reported in 1980 by Kumada *et al.* [73]. Although a few aromatic silyl ethers were mentioned to react under the conditions optimized for the Kumada-Corriu coupling of aromatic alkyl ethers, no systematic study had been carried out on these substrates until 2011. Different silyloxy groups were tested and led to the cross-coupling products in similar yields compared to the OTMS derivatives whatever the steric hindrance of the silyl protecting group. It is worth to note that the C-OSi bond can be activated in the presence of a methoxy group (Figure 40) [74].

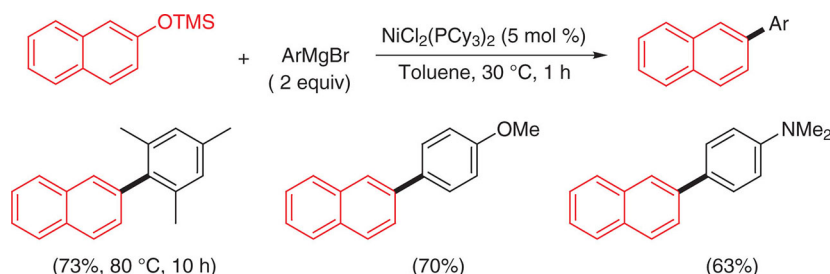


Figure 40: C-C bond formation using silyloxyaryl derivatives.

2.1.5.2 Aryl and alkenyl carbamates and phosphates

In 1992, the group of Snieckus showed that aryl carbamates and triflates could be coupled to aryl Grignard in similar conditions [75].

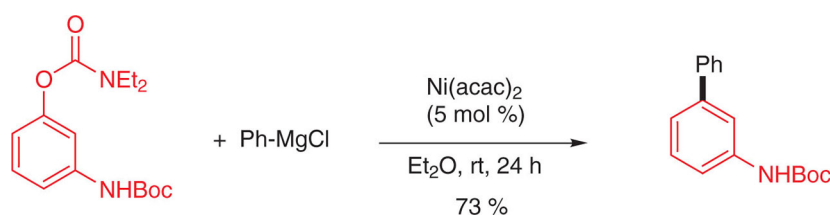


Figure 41: Carbamates as electrophiles in nickel-catalyzed Kumada-Corriu reaction.

Compared to other O-based electrophiles, the carbamate moiety offers the ability to effect directed *ortho*-metallation, thus providing a potential entry to complex poly-substituted aromatics. The use of hydroxyphosphine ligand **L18** proved efficient in the rate acceleration of the nickel-catalyzed coupling of aryl carbamates (Figure 42) [76].

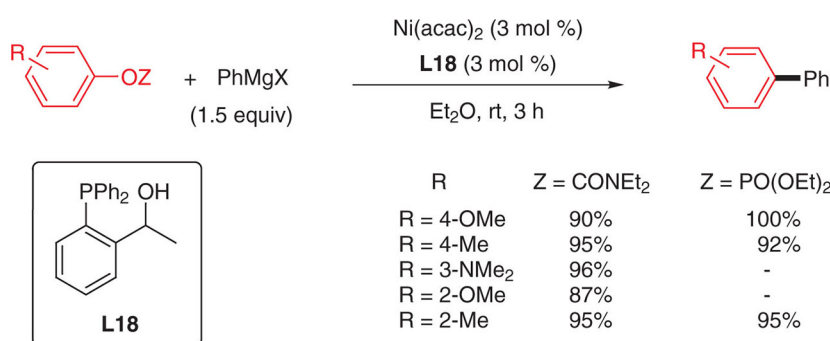


Figure 42: Hydroxyphosphine **L18** as an efficient ligand for the nickel-catalyzed coupling of aryl carbamates.

The intermediate nickel phosphine/magnesium alkoxide bimetallic catalytic species induces the C-O bond cleavage by a synergetic push-pull action. These conditions were also effective with aryl phosphates, which were initially considered in 1981 by Kumada *et al.* using Ni(acac)₂ as the catalyst [77, 78].

2.1.5.3 Diaryl sulfates and aryl sulfamates

In the search of environmentally benign cross-coupling transformations, diaryl sulfates were found by Shi *et al.* to be efficient green organic electrophiles [79]. Both of the aryl groups can be inserted into the product, while the process generates harmless inorganic salts (e.g. MgSO₄ and MgX₂) as by-products. Interestingly, the reaction conditions are mild enough to leave C-F and C-OMe bonds unreactive. The proposed mechanism involves a

monosulfate magnesium salt which proved to be a reactive intermediate in the catalytic cycle (Figure 43). In 2005, Snieckus *et al.* described the use of more electron-rich IMesNHC ligands for the nickel-catalyzed cross-coupling of *O*-sulfamates electrophiles in moderate to good yields [80].

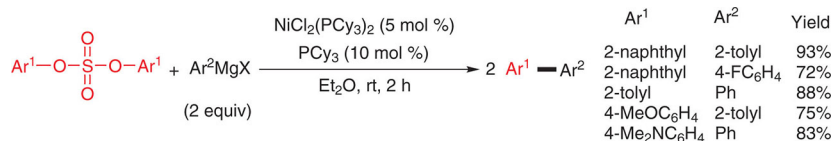


Figure 43: Diaryl sulfates as efficient green organic electrophiles for the Kumada-Corriu reaction.

2.1.5.4 Magnesium aryloates

The direct transformation of readily available phenol derivatives would represent a major breakthrough in nickel-catalyzed cross-coupling reactions as the use of free alcohols would be step- and atom-economic as well as environmentally benign. The process would indeed generate less organic waste and would avoid additional transformations of the alcohol to good leaving groups (e.g., phosphonates or sulfonates) or the use of toxic organic halides as electrophiles. The first achievement towards this goal was reported by Shi *et al.* using magnesium naphtholates [81]. The NiF₂/PCy₃-catalyzed cross-coupling of aryl Grignard reagents with different naphthols was performed in non-polar solvents after *in situ*-preformation of the corresponding magnesium salts with methylmagnesium bromide. The process was believed to proceed through the Ni(0)/Ni(II) catalytic cycle and the C-O naphthoxide bond cleavage was supposedly activated by Mg²⁺ in the oxidative addition step to the Ni(0) species. Unfortunately, the parent phenols could not be converted to biphenyls under these conditions (Figure 44).

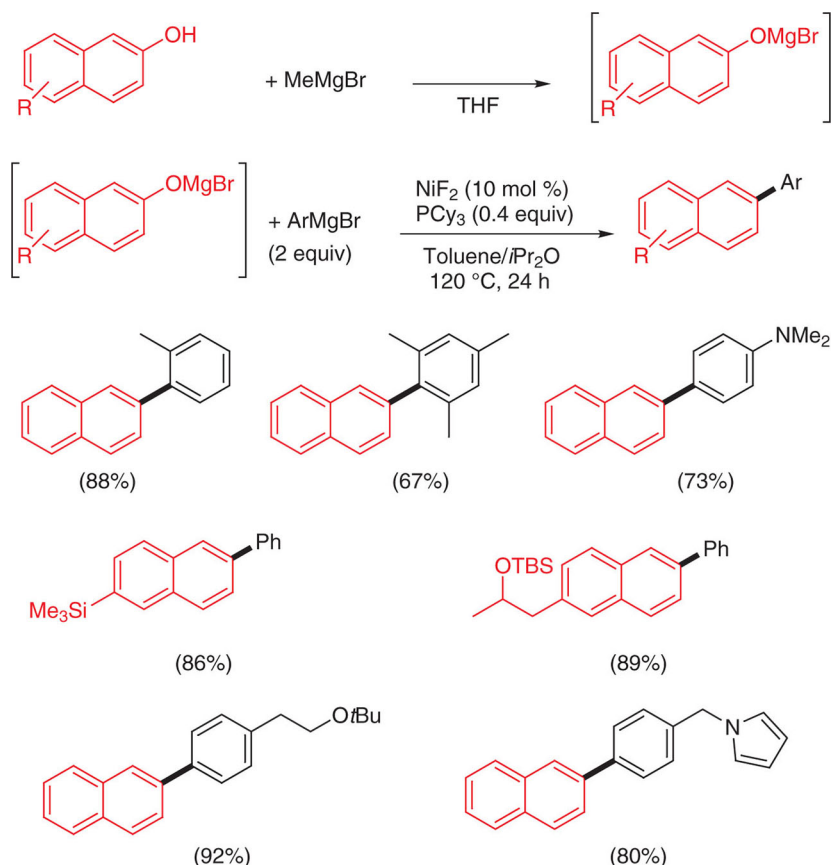


Figure 44: Cross-coupling of aryl Grignard reagents with functionalized 2-naphthols.

2.2 With vinyl derivatives

2.2.1 Vinyl halides

Vinyl chloride is one of the most reactive C(sp²)-halides and has been widely used in the industry for the synthesis of styrene derivatives in multi-tons scale. Chemists at Hokko Chemical industry in Japan have used inexpensive NiCl₂(dppp) as catalyst. For security reasons, they have replaced highly flammable ether by a mixture of benzene/ THF or toluene/THF (Figure 45) [82].

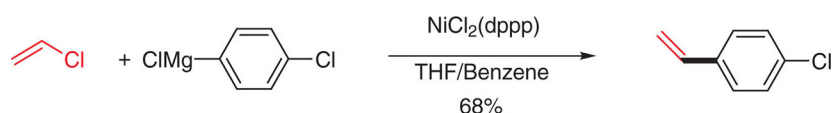


Figure 45: Cross-coupling of vinyl chloride with aryl Grignard reagents.

Dppp can be replaced by 4,6-bis(3-diisopropylphosphinophenyl) dibenzofuran **L19**, a related diphosphine ligand, which coordinate to Ni(I) to produce the [(iPr)₂DPDB-Fphos]NiCl complex and allowed the synthesis of styrene from vinyl chloride and phenyl Grignard reagent in nearly 85 % isolated yield (Figure 46) [83].

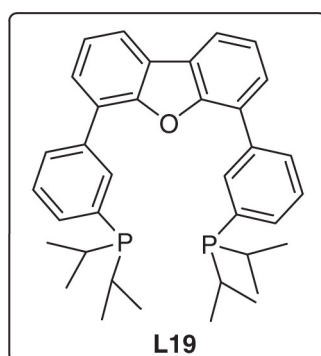


Figure 46: Diphosphine ligand **L19** designed for the synthesis of styrenes from vinyl chloride.

Tetradentate nickel catalyst **C31** was also particularly efficient for the coupling of unactivated vinyl chlorides (Figure 47) [84].

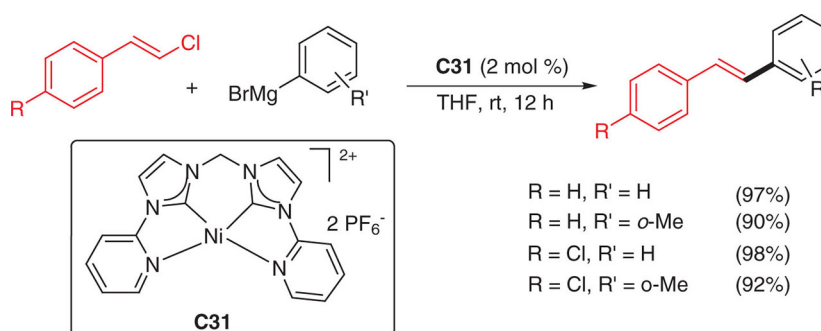


Figure 47: Tetradentate nickel complex **C31** for the coupling of unactivated vinyl chlorides.

In 2014, Pugh *et al.* used the same NiCl₂(dppp) system for the synthesis of a polymerizable 1-ethoxyvinylbenzocyclobutenes. These latter could undergo radical polymerization at 100–150 °C leading to cross-linked polymers (Figure 48) [85].

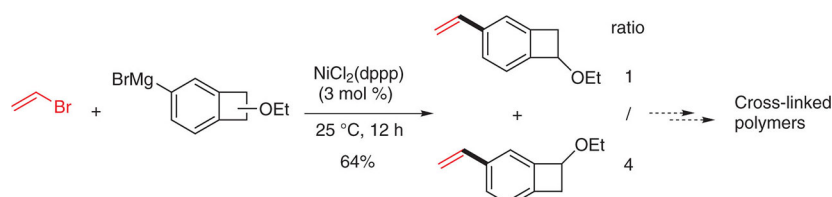


Figure 48: Access to polymerizable cyclobutene from vinylbromide.

2.2.2 With vinyl thioethers

Following the early results obtained by Wenkert *et al.*, Takei *et al.* reported the reaction between alkenyl and aryl sulfides in nickel-catalyzed cross-coupling reactions with phenyl Grignard reagents [86]. The olefinic products were obtained with retention of configuration suggesting a high stereospecificity for each step of the process (Figure 49).

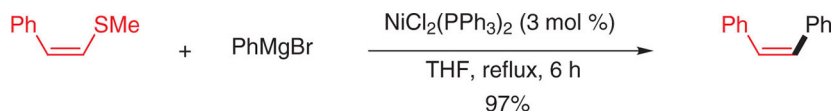


Figure 49: Stereoselective cross-coupling of alkenyl sulfides.

2.2.3 With cyclic enol ethers

The group of Martin found that a combination of $\text{Ni}(\text{cod})_2$ with **L20**.HCl, a NHC precursor, and LiCl as the additive allowed the cross-coupling of cyclic vinyl ethers when performed at low temperatures [87]. Under these conditions, the use of functionalized Grignard reagents furnished the corresponding homoallylic alcohols with complete Z-stereoselectivity (Figure 50).

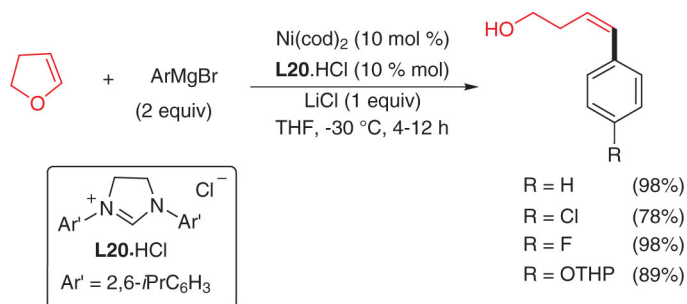


Figure 50: Stereoselective access to homoallylic alcohols from dihydrofuran.

2.3 With alkynyl halides

1-Bromoalkynes have also been used as electrophiles to achieve Ni-catalyzed cross-coupling reactions with aryl magnesium bromides [88]. Among the different catalysts tested, the combination of NiCl_2 with a triarylphosphine appeared as the most promising system to obtain high yields in the coupling product (Figure 51).

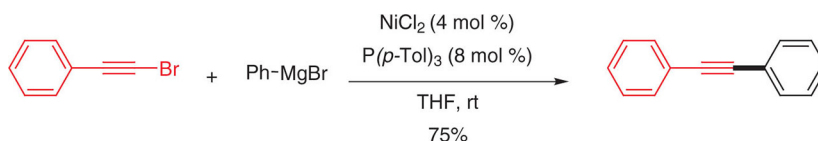


Figure 51: 1,2-Disubstituted acetylenes from bromo(ethynyl)benzene.

2.4 Miscellaneous

2.4.1 With propargyl bromide

The coupling of aryl Grignard with propargyl bromide led to an arylallene derivative **29** contaminated by small amounts of the corresponding propargyl arene **30** (Figure 52) [89].

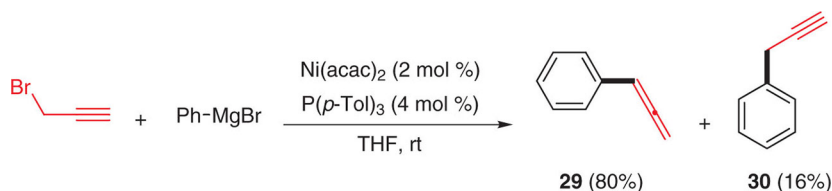
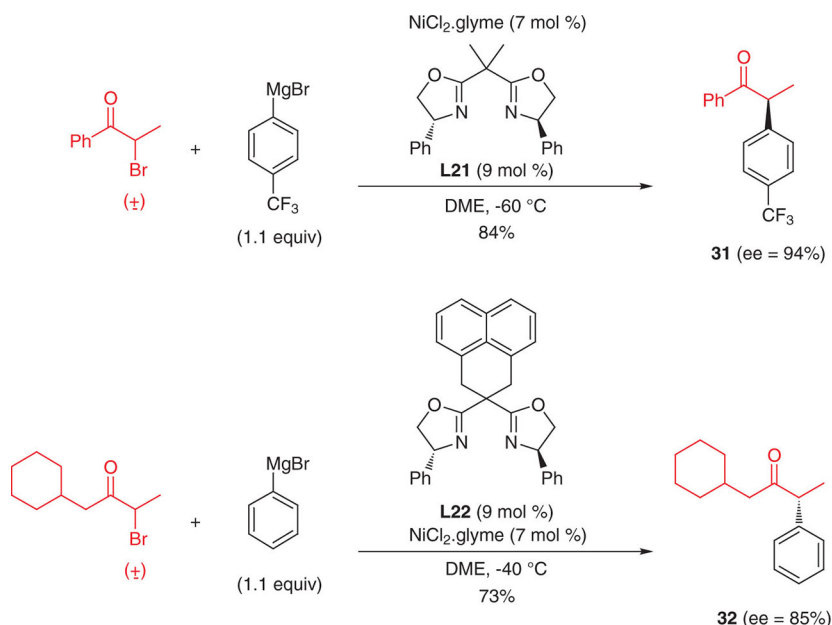


Figure 52: Allene derivatives from propargyl bromide.

2.4.2 With α -bromoketones

α -Bromopropiophenones can be easily substituted by an aryl group when treated with an aryl Grignard and a small amount of a nickel catalyst. This reaction has been extensively studied in the presence of chiral ligands. Of interest, the reaction is stereoconvergent: both enantiomers of the starting material led to the final chiral product with the same configuration and a similar level of induction. The best results were obtained when dimethyl bis-oxazoline ligand **L21**, derived from arylglycine, was used. To reach similar ee with dialkylketones, the process needed however to be conducted in the presence of the less common and more hindered ligand **L22** and with this ligand, the ee values culminate to the range of 85–90 % (Figure 53) [90].

Figure 53: Enantioselective formation of α -arylketones.

We have to point out that, recently, the group of Walsh has shown that the Kumada-Corriu reaction gave even better results when performed in the presence of cobalt salts associated to the same bis-oxazolidine ligands [91].

2.4.3 Three component reaction

To extend the scope of the Kumada-Corriu coupling reaction, nickel-catalyzed three component process has been designed [92]. The reaction was carried out in the presence of the two classical partners, an alkyl halide and a phenyl Grignard reagent, and also in the presence of 2,3-dialkyl-1,3-butadienes. Interestingly, functionalizations occurred selectively on the two opposite terminal positions of the diene and delivered polysubstituted alkenes in reasonable yields but with a poor *E/Z* ratio (Figure 54). It was assumed that alkyl radical species were generated by a Single Electron Transfer (SET) process from a nickelate complex intermediate.

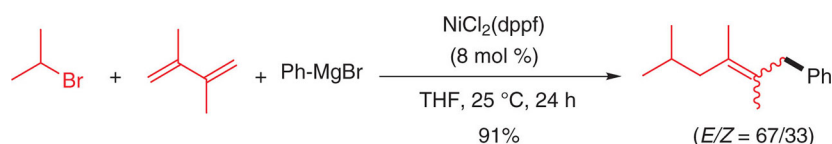


Figure 54: Cross-coupling of alkyl halides, 1,3-butadienes and aryl Grignard reagents.

A three-component reaction leading to tetrasubstituted alkenes has been devised by Zhao, Hayashi *et al.* [93]. By adding a very small amount of a nickel salt to a mixture of an internal alkyl(phenyl)acetylene, an aryl Grignard reagent and an aryl iodide, an arylmagnesiumation occurred rapidly, followed by an efficient Kumada-Corriu coupling. The *Z*-selectivity observed for the first step was essential for the stereoselective synthesis of pharmaceutical compounds such as tamoxifen **33** (Figure 55).

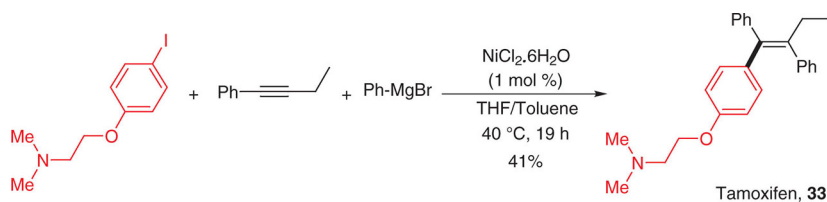


Figure 55: Tetrasubstituted alkenes by a three-component reaction.

3 Coupling reactions of alkenyl Grignard reagents

3.1 With aryl derivatives

3.1.1 With aryl halides

In contrast to the Kumada-Tamao-Corriu reaction with aryl Grignard reagents, the nickel-catalyzed coupling of alkenyl magnesium reagents received much less attention since a first report in 1975 by the group of Kumada [94]. The cross-coupling of alkenyl Grignard reagents with aryl or vinyl halides was found to occur with *cis/trans* isomerization of the olefinic bond depending on the reactivity of the halide, the bulkyness of the Grignard reagent and the $\text{ArX}/\text{R}'\text{MgX}$ ratio (Figure 56). The vinyl Grignard reagents appeared far less reactive than their aryl counterparts [95].

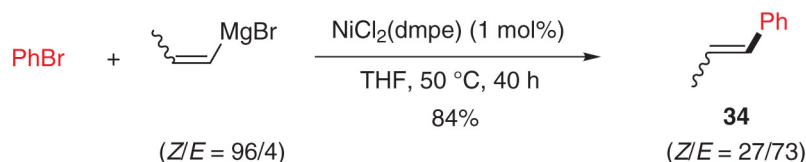


Figure 56: Unselective access to styrene derivatives from vinyl Grignard reagents.

The group of Bach studied the functionalization of dibromobenzofurans **35** and observed a selective alkenylation at the C-5 position in high yields under Kumada-Corriu conditions. A further Negishi coupling reaction led to different eupomatenoids **37** in high yields (Figure 57) [96].

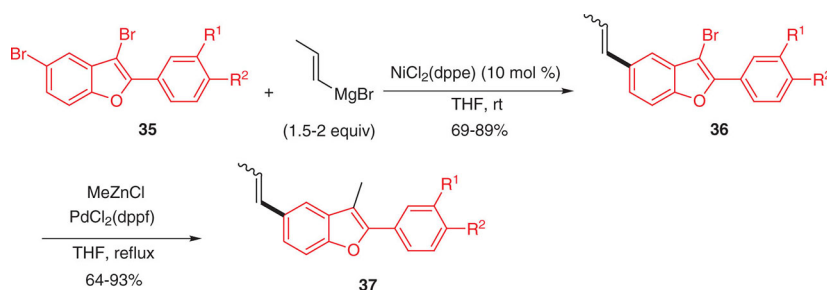


Figure 57: Selective alkenylation of dibromobenzofurans with vinyl Grignard reagents.

3.1.2 With aryl sulfides

The group of Wenkert reported the selective cross-coupling of methyl aryl sulfides over *iso*-propyl aryl sulfides with alkenyl Grignard reagents, albeit in moderate yields [97]. The coupling conditions using $\text{NiCl}_2(\text{PPh}_3)_2$ as catalyst also led to the reduction product of the thiomethyl substituent (Figure 58).

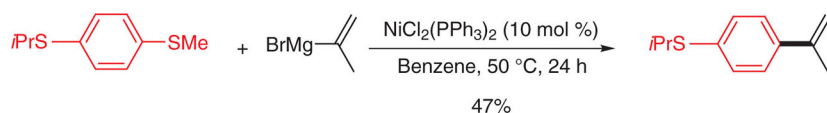


Figure 58: Regioselective coupling of aryl sulfides with vinyl Grignard reagents.

3.1.3 With aryl carbamates

The coupling of a phenanthrenyl (*N,N*-diethyl)carbamate was performed with vinyl magnesium bromide and Ni(acac)₂ as the catalyst to deliver a styrene derivative however, in moderate yield [75].

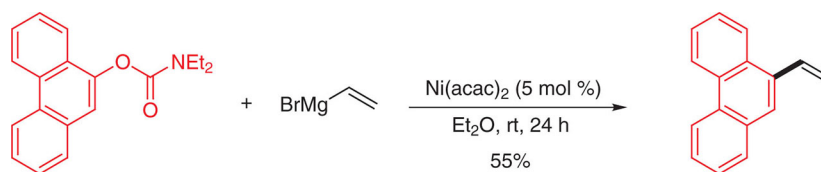


Figure 59: Coupling of arylcarbamates with vinyl magnesium bromide.

3.2 With vinyl derivatives

3.2.1 With vinyl sulfones

Conjugated dienes can be obtained with complete retention of configuration by the Ni-catalyzed coupling of vinyl sulfones with vinylmagnesium bromide (Figure 60) [98]. The outcome of the reaction is highly dependent on the nickel catalyst (40 % yield with Ni(acac)₂ and 23 % yield with NiCl₂/2PPh₃) leading, in all cases, to the formation of the reduction product along with the coupling product.

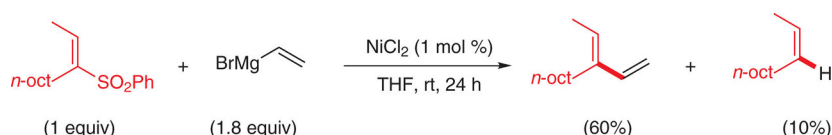


Figure 60: Synthesis of 1,3-dienes from vinylsulfones and vinyl Grignard reagent.

3.2.2 With vinyl carbamates

The coupling of (*Z*)-vinyl (*N,N*-diisopropyl)carbamate **38** with different vinyl magnesium bromides in the presence of 10 mol % of Ni(acac)₂ led to (*Z*)-alkenyl derivatives with high stereoselectivity (Figure 61) [99].

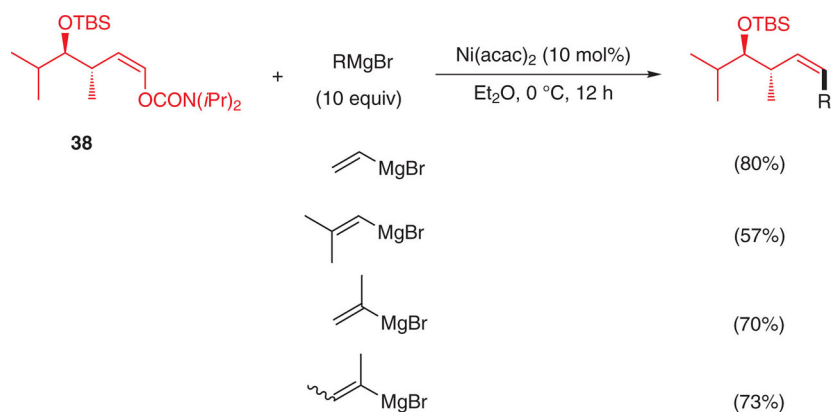


Figure 61: Coupling of (*Z*)-vinyl carbamates with vinyl magnesium bromides.

3.3 With alkyl derivatives

The coupling of vinyl magnesium chloride with alkyl fluorides in the presence of a nickel catalyst gave rise to an alkylative dimerization of the vinyl Grignard reagent to form a 2-alkyl-3-butenyl Grignard intermediate which is hydrolyzed to the corresponding butene (Figure 62) [100]. The nickelate complex **C32** was suggested by Kambe *et al.* to be a reactive intermediate in the different plausible reaction pathways.

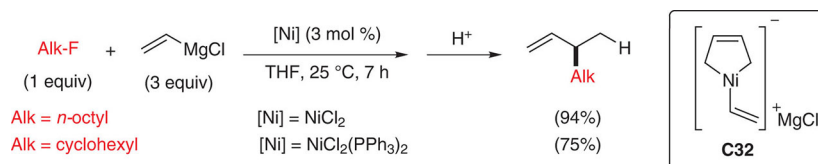


Figure 62: Coupling of alkylfluorides with vinyl Grignard reagent.

3.4 Miscellaneous

3.4.1 Three component reactions

A novel nickel-catalyzed coupling reaction between alkenyl magnesium reagents and methylenecyclopropanes in the presence of a chlorosilane, as the terminal electrophile, was developed by Kambe *et al.* [101]. The corresponding carbomagnesation products were obtained by the selective cleavage of the distal C–C bond of methylenecyclopropanes through nickel oxidative addition (Figure 63).

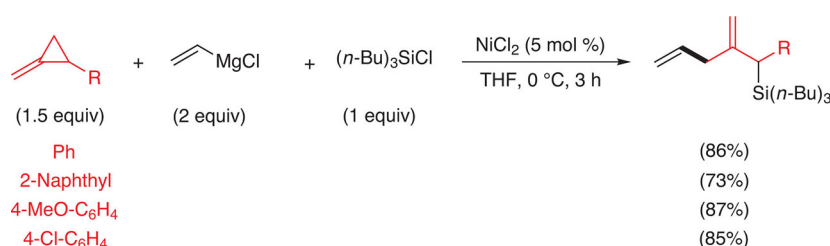


Figure 63: Selective cleavage of methylenecyclopropanes with vinyl Grignard reagents.

3.4.2 Ring-opening of cyclic ethers

Kambe *et al.* have explored the nickel-catalyzed coupling of vinyl magnesium chloride with 3- or 4-membered cyclic ethers [102]. As for alkyl fluorides, the vinyl Grignard reagent underwent a dimerization prior to the coupling with the electrophile giving access to pentenol or hexenol derivatives **40** (Figure 62). The postulated mechanism involves the nickelate complex **C47** which can either react directly with cyclic ethers to form the coupling product **40** or undergo a transmetalation step to yield (2-buten-1,4-diyl)magnesium **39**, followed by electrophilic trapping with a cyclic ether. Interestingly, no reaction took place when using substituted vinyl Grignard reagents (Figure 64). Chlorosilanes as electrophilic partners led to 1,4-disilyl-2-butenes under the same reaction conditions.

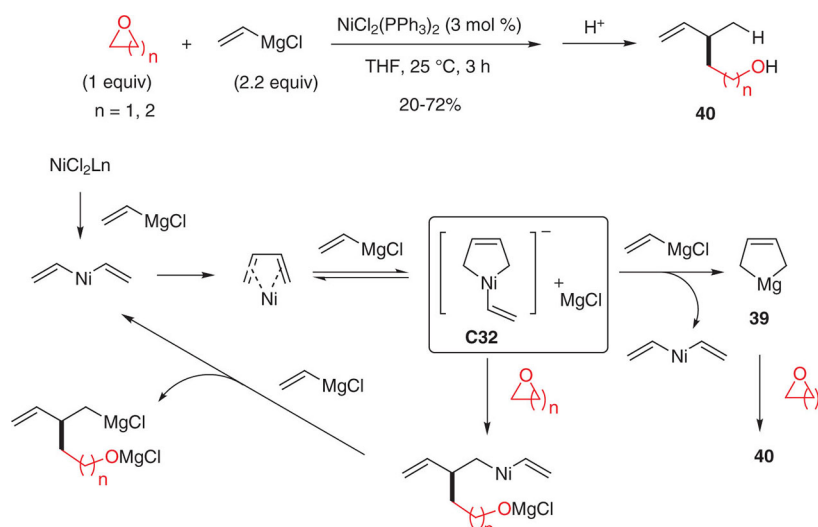


Figure 64: Catalyzed dimerization of vinyl Grignard with 3- or 4-membered cyclic ethers.

4 Coupling reactions of Alkynyl Grignard Reagents

4.1 With alkyl halides

The functionalization of terminal alkynes is usually achieved by well-established and high yielding Sonogashira reaction conditions. In order to avoid the use of expensive palladium salts, the development of reactions between alkynyl Grignard reagents and primary alkyl halides are still challenging, especially due to the lower nucleophilic character of metal alkynylides and their propensity to dimerize. Very recently, successful processes have been published (Figure 65). For example coupling between acetylenic Grignard reagents and primary alkyl iodides or bromides have been reported in the presence of Nickamine **C33** and diamine *O*-TMEDA as the additive [103]. From a mechanistic point a view, this additive plays an important role: it could coordinate to the magnesium salt favouring the transmetalation and the formation of an alkynyl complex with Nickamine, but it could also minimize the homocoupling side-reaction. Moreover, radical intermediates are probably involved as suggested by the ring-opening observed with cyclopropylmethyl bromide used in this reaction as the cross-coupling partner.

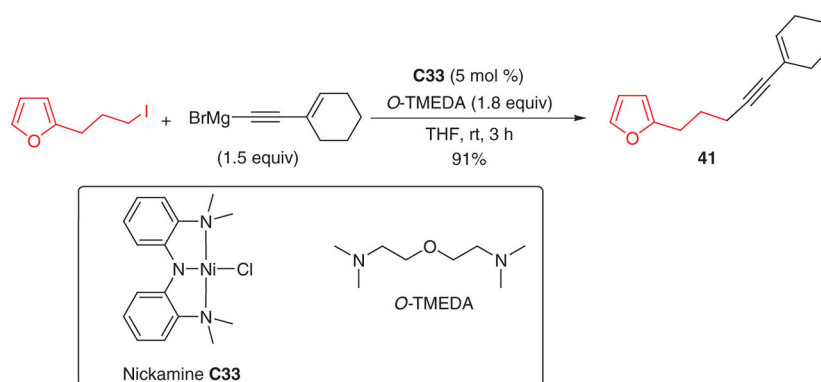


Figure 65: Disubstituted alkynes from alkynyl Grignard reagents using Nickamine complex **C33**.

Interestingly, the reaction is compatible with sulfur-containing groups. Attempts to perform the same process with secondary halides are however unsuccessful.

4.2 With alkynyl sulfones

Diene derivatives have also been prepared at room temperature by condensation of readily available alkynyl Grignard reagents onto alkynyl sulfones (Figure 66). The process is an extension of the Ni-catalyzed cross-coupling of aryl sulfones with Grignard reagents previously discovered by Julia *et al.* [65], in which the catalyst $\text{Ni}(\text{acac})_2$ was reduced *in situ* to $\text{Ni}(0)$ by the acetylide present in excess. The yields are in the range from 42 % to 83 %. The best results were observed for the formation of bisaryldiynes ($\text{R} = \text{Ar}$) [104].

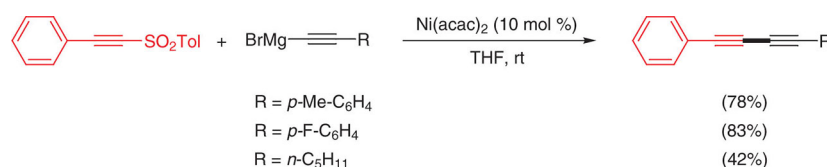


Figure 66: 1,3-Diynyl derivatives from alkynyl sulfones.

4.3 With ethers

4.3.1 Aryl ethers

The functionalization of terminal alkynes has also been extended to anisole derivatives [105]. In the presence of $\text{Ni}(\text{cod})_2$ and a NHC ligand bearing bulky groups, the reaction of triisopropylsilylacetylide with electron-enriched anisoles delivered the cross-coupling adducts in high yields (Figure 67). The presence of sterically hindered substituents on the acetylide has also a major impact on the success of the process (Figure 68). Under

these conditions, a selective cleavage of the C-F bond of fluoroanisole was observed and this difference of reactivity could be promising for multi- and sequential cross-coupling reactions.

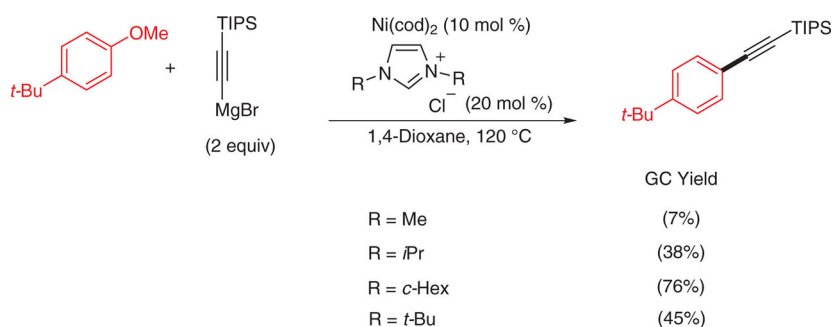


Figure 67: Influence of the NHC ligand on the coupling of TIPS-alkynyl-MgBr with *p*-*tert*-butylanisole.

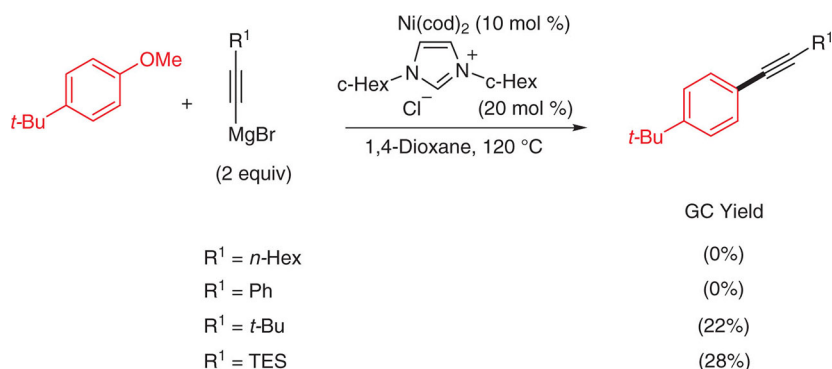


Figure 68: Influence of the alkynyl nucleophile on the NHC-Ni-catalyzed coupling of *p*-*tert*-butylanisole.

This coupling reaction found application for the ethynylation of a large number of methoxyaryl derivatives and tolerate numerous functionalities (alcohol, phenol, amine, etc.) without significant decrease of the yields.

4.3.2 Enol derivatives

Enol ethers

Silyl enol ether **42** underwent a smooth coupling with an alkynyl Grignard reagent leading to enyne **43**, while dihydrofuran **44** underwent a ring-opening leading to compound **45** (Figure 69) [105].

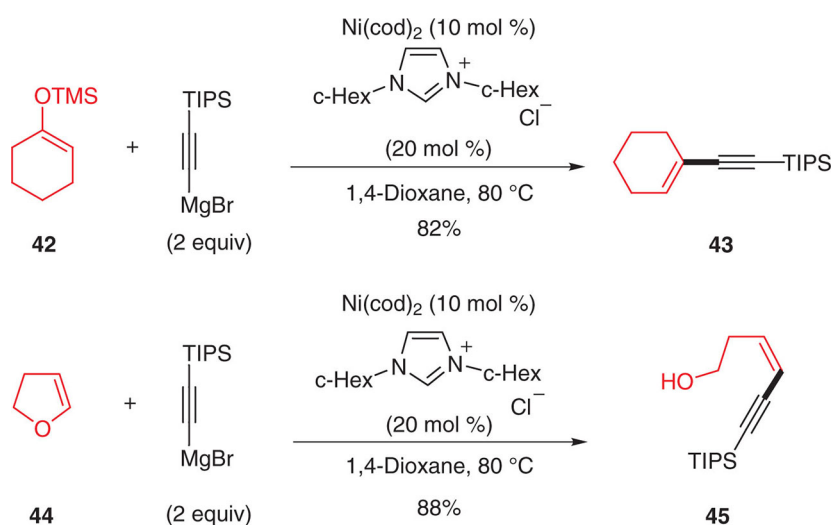


Figure 69: 1,3-Enynes by Ni-catalyzed alkynylation of TMS enol ethers and dihydrofurans.

Vinyl carbamates

We have to point out that (Z)-vinylcarbamates **46** were also implicated in reaction with alkynyl Grignard reagents to deliver enynes **47** which could find application in the total synthesis of complex molecules such as avermectins [106]. The Z/E ratio was affected by both the nature of the catalyst but also by the substitution of the oxygen atom present at the homoallylic position (Figure 70).

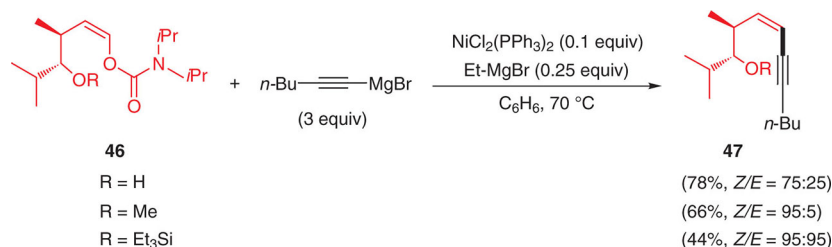


Figure 70: (Z)-Enynes from (Z)-vinyl carbamates and hexynyl magnesium bromide.

5 Coupling reactions of Alkyl Grignard Reagents

5.1 With aryl derivatives

5.1.1 Aryl halides

As an example, the Kumada-Corriu reaction between alkylmagnesium reagents and aryl halides has been advantageously applied to the synthesis of (S)-macrostomine **48** by Comins *et al.* in only five steps (Figure 71). After optimization of the reaction conditions, three equivalents of a benzyl Grignard and a large amount of nickel catalyst were required to achieve the final step in 63 % yield [107].

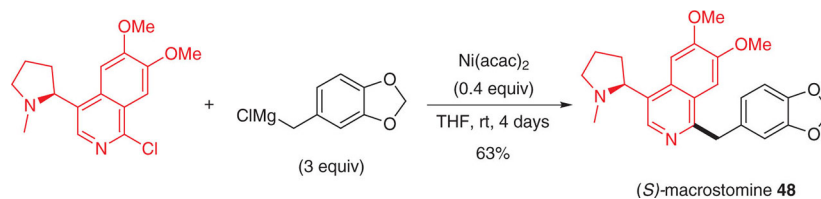


Figure 71: Key Kumada cross-coupling of a benzyl Grignard fragment in the synthesis of (S)-macrostomine.

Similarly, as reported for aryl Grignard reagents in Section 2.2, the coupling between aryl fluorides and alkyl magnesium reagents can be also efficiently achieved. As depicted in Figure 72, the reaction can be performed in the presence of catalyst **C34**, with alkyl Grignard without observation of β -hydride elimination. It is anticipated that magnesium phenolate could be the key element for the success of the reaction. Moreover, cleavage of C-F bond, under these conditions, was observed in the presence of weaker carbon-halogen bonds [108].

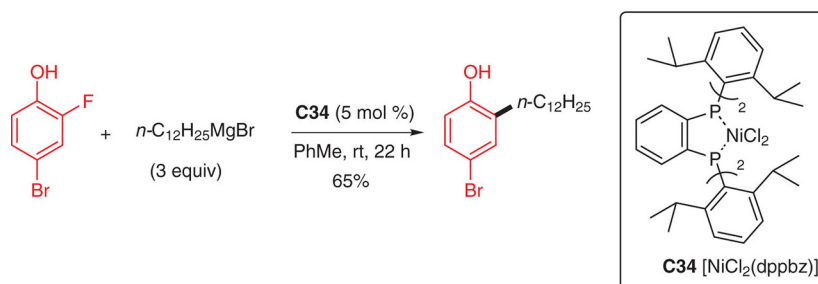


Figure 72: Selective coupling of aryl fluorides with alkyl-MgX using catalyst **C34**.

5.1.2 Aryl sulfides

As already pointed out with aryl Grignard, efficient coupling reactions were noticed between methyl Grignard and aryl thiols, thioethers, sulfoxides or sulfones when performed in the presence of 10 mol % of $\text{NiCl}_2(\text{PPh}_3)_2$ (Figure 73) [61].

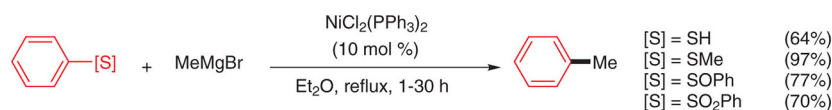


Figure 73: Coupling of methyl magnesium bromide with different thioaryl derivatives.

In the presence of this additive, the reductive cleavage of $\text{C}(\text{sp}^2)$ -sulfide bonds by secondary alkyl Grignard reagents has been reported. Fortunately, the use of bidentate phosphine ligands allowed a higher selectivity for the cross-coupling product [109]. For example, the synthesis of 4-cyclohexyl-2,6-diphenylpyridine *via* the coupling of cyclohexylmagnesium bromide and the corresponding 4-thiomethyl derivative occurred when $\text{NiCl}_2(\text{dppp})$ was present in the reaction media (Figure 74) [63].

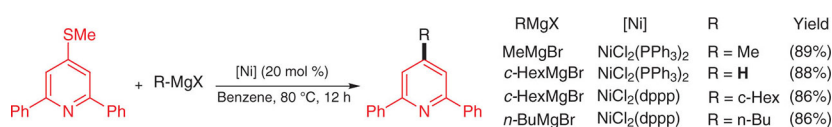


Figure 74: Coupling of aryl thioethers with primary and secondary alkyl magnesium reagents.

A combination of $\text{Ni}(\text{acac})_2$ and (Z)-1,2-diphosphinoalkene **L23** was also described for the cross-coupling of arylsulfides with primary and secondary alkyl Grignard reagents (Figure 75) [110]. Nevertheless, the coupling reactions with *i*PrMgX led to partial isomerization of the alkyl nucleophile.

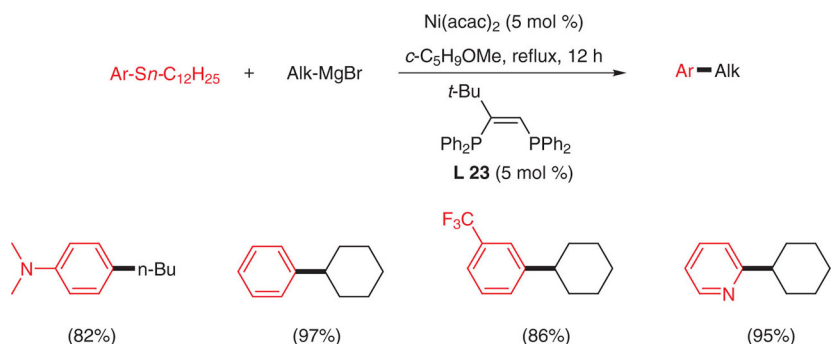


Figure 75: Coupling of aryl thioethers with $\text{Ni}(\text{acac})_2$ and (Z)-1,2-diphosphinoalkene **L23** as an additive.

More recently, the NiCl_2 /butadiene catalytic system developed by Kambe *et al.* proved efficient in the coupling of 2-thiomethyl-substituted 1,3-benzothiazoles with secondary alkyl Grignard reagents [111]. Under these conditions, the formation of isomerized products and the possible reduction of thioethers are minimized. However, non π -extended systems such as thiazoles and thiazolines are not reactive. In the case of arylsulfonates, alkylmagnesium reagents bearing no β -hydrogen reacted efficiently at room temperature, when the more electron-rich NHC ligand $\text{IPr}.\text{HBF}_4$ was used as the ligand (Figure 76) [112].

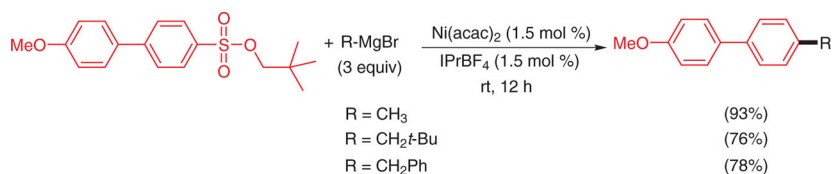


Figure 76: Coupling of aryl sulfonates with alkyl Grignard reagents using the electron-rich NHC ligand.

5.1.3 Aryl methyl ethers

In 2008, Shi *et al.* reported the methylation of different alkoxy naphthalenes including alkyl-, aryl- and silyl ethers by using 5 mol % of $\text{NiCl}_2(\text{PCy}_3)_2$ in toluene [113]. Comparative experiments showed that π -extended aryl methyl ethers reacted faster than phenyl methyl ethers (Figure 77).

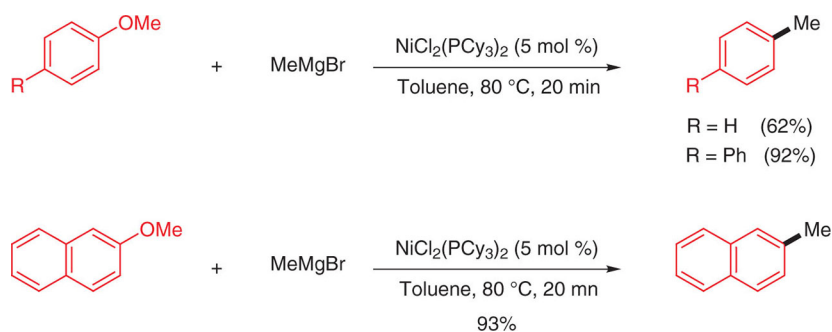


Figure 77: Ni-catalyzed methylation of aryl or naphthyl methyl ethers with MeMgBr.

5.1.4 Aryl phosphonates

Functionalization of **49** by using a similar coupling allowed the introduction of a prenylated chain onto 1,5-naphthalenediol derivatives (Figure 78) [114]. The resulting compound was transformed in few steps into (+)-cryptotanshinone **51**.

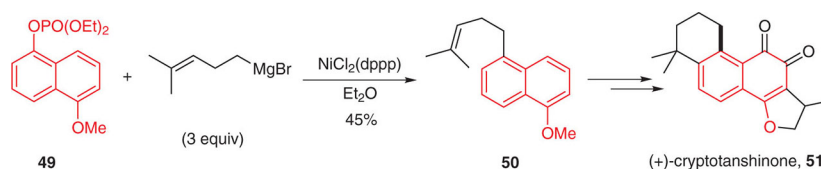


Figure 78: Selective coupling of aryl phosphate with an alkyl Grignard in the synthesis of **51**.

5.2 With alkenyl derivatives

5.2.1 Alkenyl halides

The access to chiral 2-aryl propanoic acids is of great interest due to their pharmaceutical properties. In this context, the synthesis of precursors such as 3-aryl-1-butenes, has been intensively studied. Enantioselective Kumada-Tamao-Corriu reaction between benzyl Grignard reagents and vinyl bromide has been carried out in the presence of various chiral phosphine ligands [115–119]. Enantiomeric excesses up to 88 % were recorded with the readily available ligands **L27** and **L28** (Figure 79) [118, 119]. However, the process cannot actually compete in terms of selectivities with other procedures to access α -aryl propionic acids as hydrogenation or hydroformylation of parent styrenes are extremely efficient.

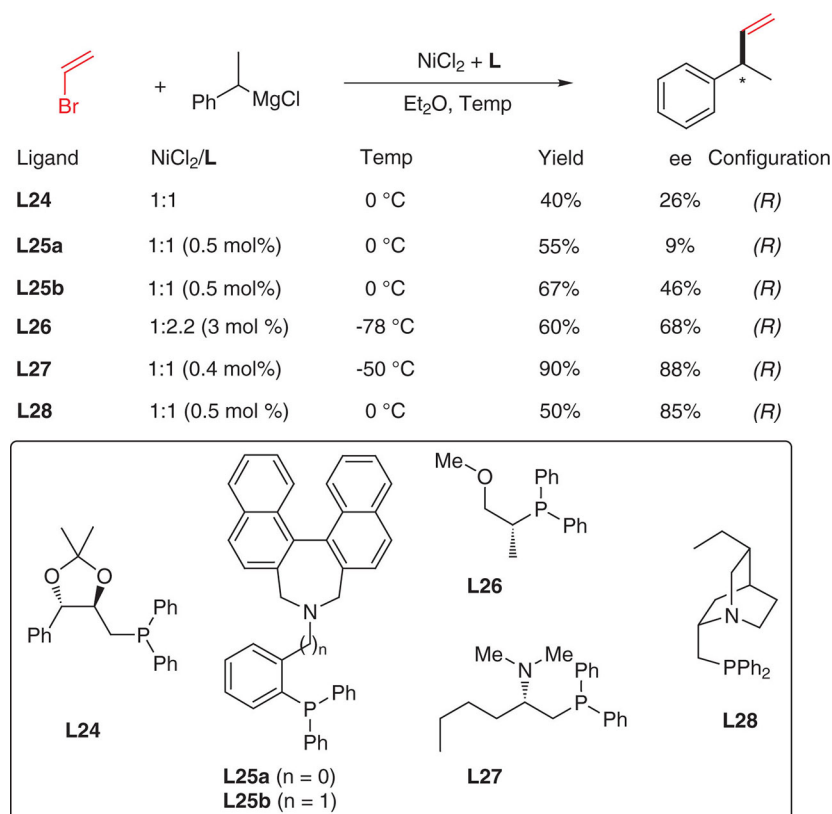


Figure 79: Enantioselective coupling of secondary benzyl Grignard reagents with vinyl bromide.

The coupling of *gem*-difluoroalkenes has also been considered (Figure 80). The Nicatalyzed reaction was attractive with alkyl Grignard reagents compared to the process performed in the presence of palladium salts for which lower yields were recorded, probably due to side processes such as β -elimination [120].

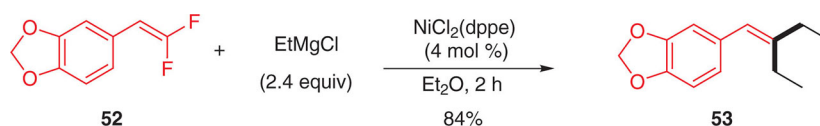


Figure 80: Trisubstituted alkenes from *gem*-difluoroalkenes and ethyl magnesium chloride.

5.2.2 Enol carbamates and phosphates

The reaction of enol carbamates **54** with alkyl Grignard reagents initially reported by Kocienski *et al.* occurred with retention of configuration (Figure 81) [121].



Figure 81: Coupling of (Z)-enol carbamates and alkyl Grignard nucleophiles.

Kumada-Corriu reactions involving the cleavage of a C–O bond has been advantageously achieved to prepare different natural products. For example, phosphate enol ether **56** was easily generated from the corresponding bicyclic ketone. When this phosphate enol ether was involved in a nickel-catalyzed coupling with methyl Grignard reagent, it was transformed to the corresponding alkene in 73 % yield and was further transformed into the marine diterpene fuscol (Figure 82) [122].

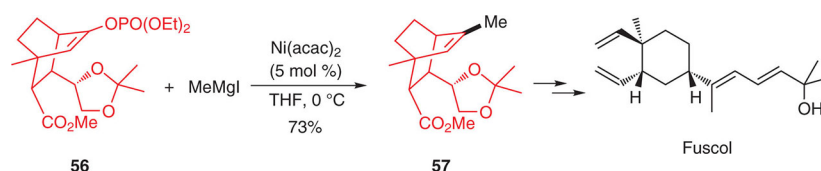


Figure 82: Synthesis of fuscol involving the coupling of intermediate enol phosphate 56.

A key intermediate in the total synthesis of Δ^1 -*trans*-tetrahydrocannabinol 58 was also prepared in excellent yield by a 1,4-addition/regioselective phosphorylation/ Kumada-Corriu coupling sequence (Figure 83) [123].

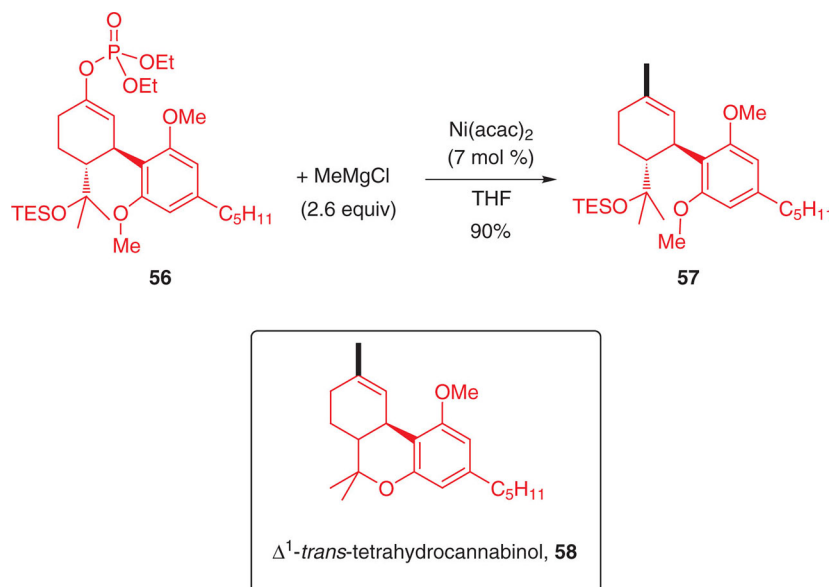


Figure 83: Methylation of enol phosphates 56 in the total synthesis of 58.

5.3 With alkyl derivatives

5.3.1 Alkyl halides

The major challenge in the alkyl–alkyl Kumada cross-coupling reactions is to suppress the β -hydride elimination step that may occur from the intermediate alkyl–nickel complex, leading to olefins as the side products. Therefore, the reductive elimination step has to occur rapidly to avoid this competing process. The first Ni-catalyzed alkyl–alkyl cross-coupling between primary alkyl halides (Br, Cl) and tosylates and primary or secondary Grignard reagents was reported by Kambe *et al.* in 2002 using NiCl_2 /1,3-butadiene as a unique catalytic system [4, 124]. Interestingly, the $\text{Csp}_3\text{-Br}$ bond reacted faster than the $\text{Csp}_2\text{-Br}$ bond yielding *p*-bromohexylbenzene in quantitative GC yield even if $\text{Csp}_3\text{-X}$ bonds are more electron-rich than $\text{Csp}_2\text{-X}$ bonds and thus more reluctant to oxidative addition. Moreover, (bromomethyl)cyclopropane led to the corresponding alkylcyclopropane in 87 % yield which seems to preclude the formation of an alkyl radical as intermediate (Figure 84).

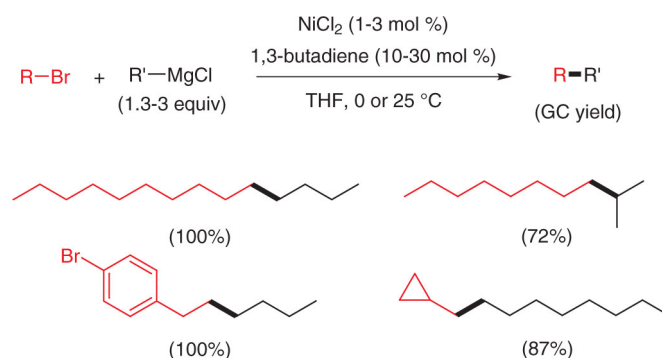


Figure 84: Alkyl–alkyl coupling in the presence of Ni(acac) and 1,3-butadiene.

Based on these results, a non-radical mechanism involving Ni(II)/Ni(IV) species in the catalytic cycle was proposed by Kambe *et al.* (Figure 85). The 1,3-butadiene additive converts Ni(0) to a bis- π -allyl nickel(II) complex **E** which reacts first with $R^1\text{-MgX}$ to form an anionic complex **F** with enhanced nucleophilicity as a key intermediate. The oxidative addition of alkyl halides to complex **F** then yields Ni(IV) complex **G** which undergoes reductive elimination to the coupled product, regenerating the bis- π -allyl nickel complex **E**. The activation of the alkyl halide may also be due to a strong interaction with the magnesium salt.

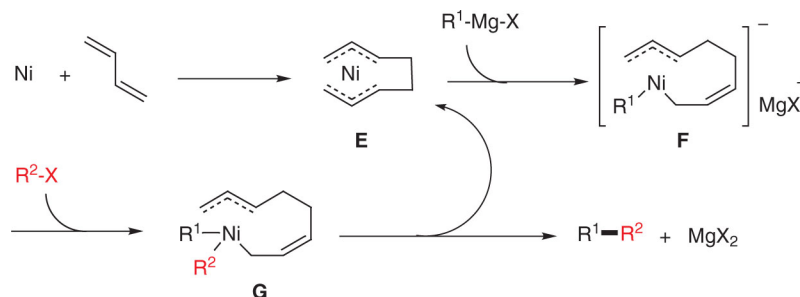


Figure 85: Postulated mechanism for the alkyl-alkyl coupling using Ni/1,3-butadiene system.

This catalytic system also proved to be efficient for the coupling of primary alkyl fluorides albeit in lower yields due to the formation of elimination products [125]. In this case, CuCl_2 was found to be superior to NiCl_2 for the coupling. It was later shown that the combination of $\text{Ni}(\text{acac})_2$ (0.6 mol %) and a 1,3,8,10-tetraene as an additive improved the efficiency of the coupling of alkyl fluorides [126]. Functionalized alkyl halides and tosylates could also be coupled by using these conditions [127].

The use of 3 mol % of a pincer (NN_2)-Ni catalyst **C33** synthesized from an amidobis(amine) tridentate ligand was described by Hu *et al.* for the coupling of functionalized primary and secondary alkyl iodides and bromides with alkylmagnesium nucleophiles [128, 129]. At low temperature (-35°C) and, using dimethylacetamide as solvent, a slow addition of an alkyl Grignard reagent (1 equiv) on a large range of unactivated alkyl halides yielded the coupled product in moderate to high yields (Figure 86). Notably, alkyl triflates and alkyl tosylates were inert. A structure-activity study demonstrated that bidentate nickel catalysts **C35** and **C36** gave better yields for the coupling of secondary alkyl halides, which was attributed to a higher structural flexibility around the nickel center [130].

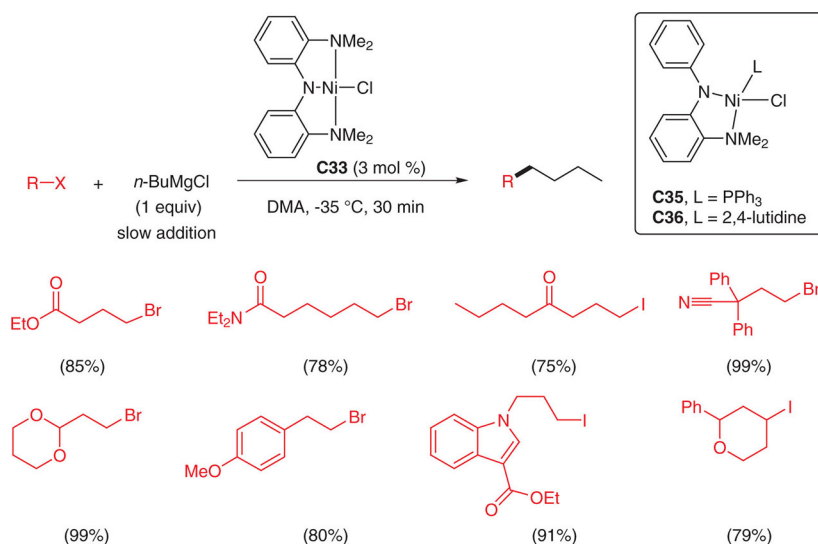


Figure 86: Alkyl-alkyl Kumada-Corriu coupling by using pincer **C33**-nickel complex.

Under these catalytic conditions, a diastereoselective alkyl-alkyl Kumada coupling was also reported by Hu *et al.* for the formation of the conformationally most stable 1,4-*trans*-dialkyl cyclohexanes and 1,3-*cis*-dialkyl cyclohexanes and tetrahydropyrans, whatever the diastereomeric ratio of the corresponding cyclic halide substrates [131]. The alkyl-alkyl cross-coupling was believed to occur *via* the transmetalation of **C33** by RMgX in a first step to form a Ni-alkyl intermediate, followed by oxidative addition of the alkyl halide and reductive elimination step to produce the coupled product. An extensive mechanistic investigation revealed that the key intermediate for the activation of the alkyl halide was a bimetallic $[(\text{N}_2\text{N})\text{Ni-R}](\text{RMgCl})$ complex and that the oxidative addition step involved radical alkyl intermediates [132].

More recently, the group of Cardenas reported the use of tetramethylethylenediamine (TMEDA) as additive in the $\text{Ni}(\text{acac})_2$ -catalyzed coupling of non-activated primary and secondary iodides with alkylmagnesium reagents [133]. On the basis of experimental and computational studies evidencing the intermediacy of an alkyl radical from the alkyl iodide, a cascade cyclization-coupling was applied to a variety of iodoalkene substrates for the sequential formation of two alkyl-alkyl bonds (Figure 87).

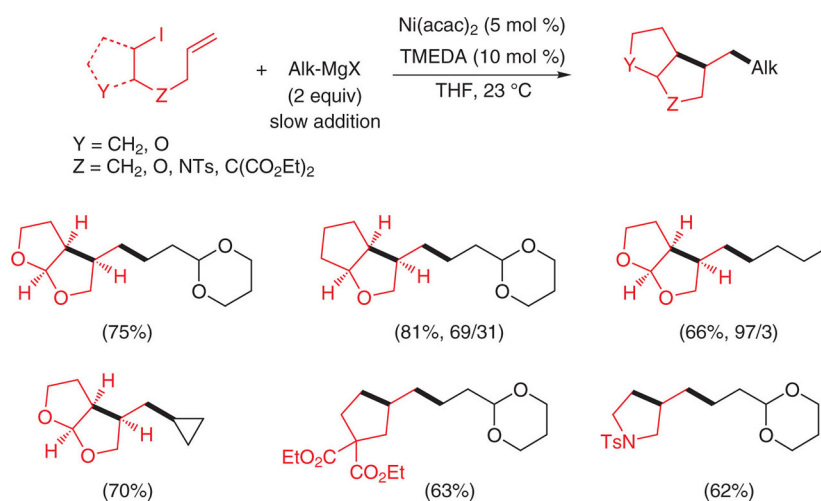


Figure 87: Ni-catalyzed sequential radical cyclization Kumada-Tamao-Corriu coupling of iodoalkenes.

The catalytic system was also efficient in the cross-coupling of functionalized benzyl chlorides with alkyl Grignard reagents [134].

5.3.2 Sulfones

Li and co-workers reported the Kumada coupling of activated alkyl sulfones with Grignard reagents with the $\text{NiI}_2(\text{PPh}_3)_2/\text{PCy}_3$ system (Figure 88) [135]. A range of aryl ketones were synthesized in good yields (61–77 %) from 1-aryl-2-tosylethanones without affecting the carbonyl group. Interestingly, the outcome of the coupling of 1-(1-tosylethyl)arenes was completely reversed by changing the solvent: the coupled product **62** was obtained in toluene or cyclohexane whereas the use of THF yielded the methylstyrene derivatives **64**.

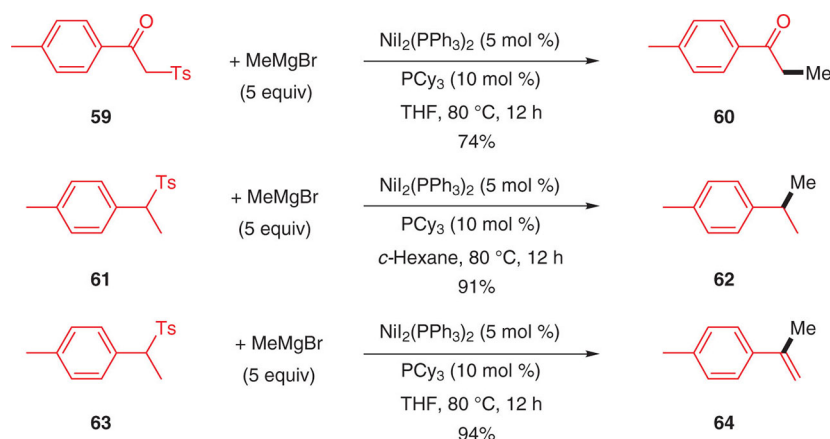


Figure 88: Ni(II)-catalyzed reactions of ketosulfones and sulfones with methyl Grignard reagent.

5.3.3 Alkyl ethers

In 2008, Shi *et al.* reported the first $\text{C}(\text{sp}_3)\text{-O}(\text{ether})$ activation in the coupling of benzyl alkyl ethers with alkyl Grignard reagents [136]. Primary and secondary benzyl ethers reacted in the presence of $\text{NiCl}_2(\text{dppf})_2$ as a catalyst to give similar yields in the cross-coupling products (Figure 89). The use of *i*PrMgX and *n*-BuMgBr led to lower yields in the coupled products, probably due to a competitive α - β -H elimination pathway.

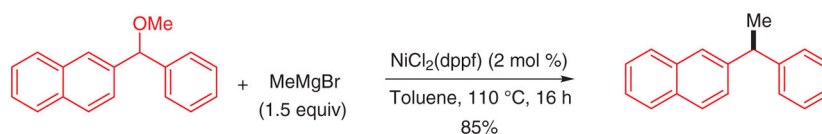


Figure 89: Methylation of benzyl methyl ether using $\text{NiCl}_2(\text{dppf})_2$ as catalyst.

Cross-coupling of non racemic bis-aryl ethers **65** with methyl Grignard reagent has been applied to prepare enantio-enriched diarylethanes **66**, precursors of anti-insomnia drugs (Figure 90) [137, 138] It is worth noting that the transfer of chirality is sizeable.

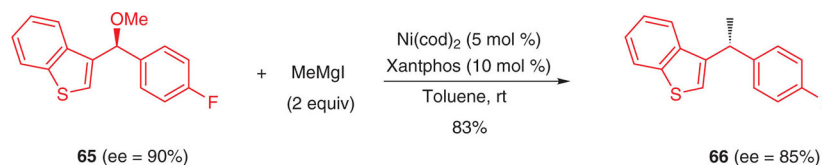


Figure 90: Diastereoselective Ni-catalyzed methylation of chiral bis-aryl ether **65**.

A similar coupling has been also realized starting from both racemic chiral cyclic ethers **67** and **69**. Introduction of a methyl group occurred in a stereospecific manner with a complete inversion of configuration at the electrophilic center (Figure 91). It is noteworthy that the same authors reported the ring-opening of the corresponding lactones with organozinc reagents (Negishi coupling) which also occurred nicely and with very high stereoselectivities [139]. The reactions were conducted in the presence of DPEphos **L29** and of (*R*)- or (*S*)-BINAP, **L30**. No match/mismatch effects were observed in the later case demonstrating that the chirality of the ligand has no influence on the stereoselectivity of the reaction.

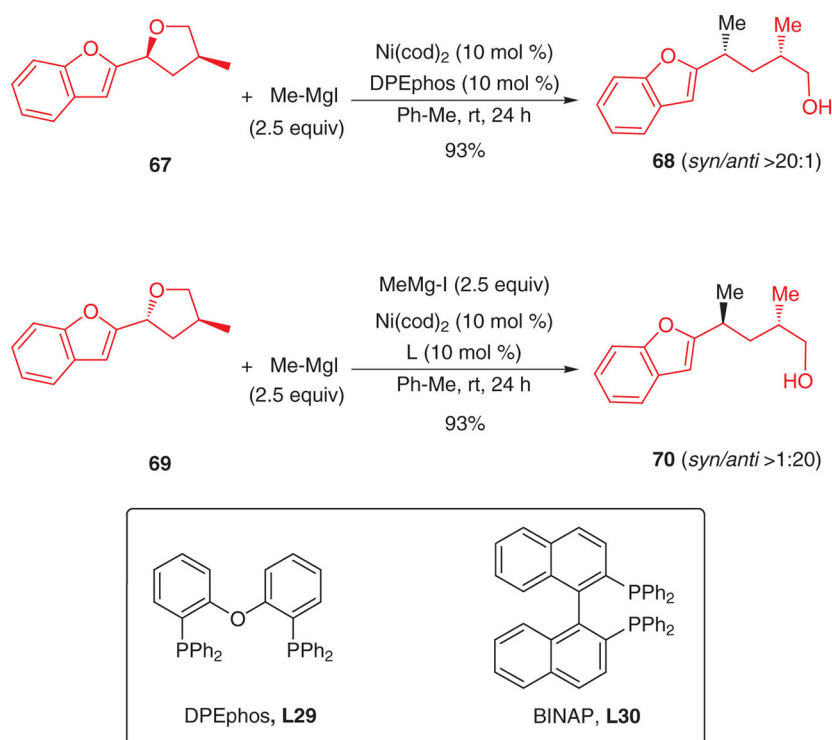


Figure 91: Diastereoselective ring-opening of chiral cyclic benzyl ethers by Kumada-Corriu reaction.

5.3.4 Benzyl alcohols

The cross-coupling of benzylic $\text{C}(\text{sp}^3)\text{-OH}$ bond was also successfully achieved with methyl Grignard reagent (Figure 92) [140]. Starting from naphthylmethanol, 2-ethylnaphthalene was obtained in 68 % yield by using bidentate 1, 2-bis(dicyclohexylphosphino)ethane (DCyPE) **L31** as ligand. Unfortunately, other alkyl Grignard reagents led mainly to reductive products.

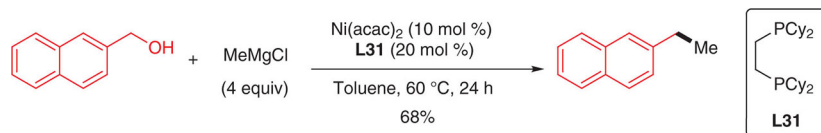


Figure 92: Methylation of benzyl alcohols with Ni(acac)₂ and bidentate phosphine L31.

6 Conclusion

In parallel to the well-established reactivity of Grignard reagents towards electrophiles, a complementary set of reactions has been designed when these organomagnesium derivatives are associated with appropriate nickel catalysts. Due to the lower cost of nickel salts, the coupling reactions depicted in this Chapter seems of particular interest when compared to procedures using palladium salts. The major drawbacks are still the use of substoichiometric amounts of Grignard reagents and the β -hydride elimination frequently observed with alkyl derivatives.

Acknowledgment

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