Nickel N-Heterocyclic Carbene-Catalyzed C−C Bond Formation: Reactions and Mechanistic Aspects

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ABSTRACT: The chemistry of nickel N-heterocyclic carbene complexes is a research area that has blossomed over the last 10 years, and a large number of new complexes with a variety of architectural motifs are now known. The evolution of this chemistry has led to increasing applications of these complexes in catalytic bond formation. The rapid expansion of this field now calls for a review of the kinds of reactions that are catalyzed and a summary of the state of the art at this time. As the breadth of reactions catalyzed by such complexes is vast, this review specifically targets catalytic C−C bond formation, in particular C−C cross-couplings and C−C couplings via C−H bond activation, mediated by nickel−N-heterocyclic carbene complexes. A special emphasis is placed on mechanistic data, because this allows possible new insights into catalyst improvement.

KEYWORDS: nickel, N-heterocyclic carbene, catalysis, C−C bond formation, reaction mechanism
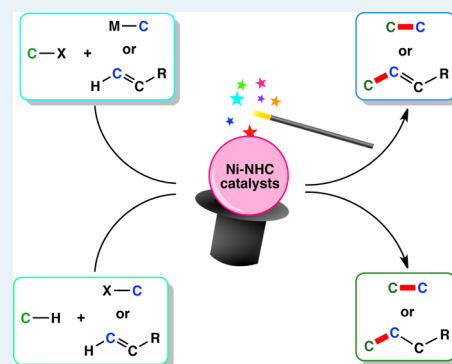
1. INTRODUCTION

The discovery of the "nickel effect" by Ziegler and Holzkamp in the mid 1950s,[1] led to an explosion of research into the chemistry, and subsequently the catalysis, of nickel complexes. Most early research, pioneered by Wilke and his group, was carried out on Ni(0) complexes, especially, $[Ni(cod)_2]$ and related alkene complexes such as $[Ni(C_2H_4)_3]$ (the so-called "naked nickel" complexes) and their phosphine derivatives, and much of this work has been elegantly summarized in a classic pair of volumes by Wilke and Jolly.[2] Nevertheless, although some important catalytic industrial processes, notably the hydro-cyanation process[3] to produce adiponitrile, and the Shell Higher Olefin Process (SHOP) for alkene oligomerization,[4] are based on nickel catalysts, in general, this metal's applications have been eclipsed by those of the noble metals, in particular palladium.

During the past decade, the development of catalytic reactions based on inexpensive earth-abundant materials has become an important research area, driven by declining natural reserves of precious metals and their consequent tremendous price increases. This problem is being tackled globally by two complementary methods: one is based on the development of organic (metal-free) catalysts, while the second method targets catalysts based on cheap, earth-abundant metals, usually first row transition metals. The latter method is buttressed by a recent report (May 2014) from the European Commission,[5] which clearly suggests that homogeneous catalysts will increasingly have to be based on more abundant, cheaper first row elements. Compelling economical and environmental demands are thus driving researchers to use more earth-abundant metals such as iron, copper, or nickel.

Nickel's time in catalysis has arrived. As stated in a recent review that highlights advances in homogeneous catalysis driven by nickel, the metal is cheap (on a molar basis, nickel costs 0.05% of the price of palladium and 0.01% of the price of platinum).[6] Moreover, as is noted in the cited review, nickel has a "*number of readily available oxidation states commonly invoked in catalysis... and catalytic cycles can include Ni(0)/Ni(II) but also Ni(I)/Ni(III) cycles...*". This contrasts with palladium chemistry where Pd(I)/Pd(III) cycles are not commonly proposed.

Since the first isolation of a stable imidazole-2-ylidene in 1991,[7] the use of N-heterocyclic carbene (NHC) ligands in organometallic chemistry has exploded (more than 10 000 citations are listed by SciFinder for the word "NHC" at the time of writing). These ligands are indeed generally derived from inexpensive and nonair-sensitive imidazolium salt precursors and are easy to access.[8] Owing to their strong σ-donor properties, they form stronger bonds with metal centers than most classical ligands, including trialkylphosphines.[9] Moreover, they offer significant steric protection to a metal in a metal-NHC complex while retaining the tunability of electronic and steric properties (as is seen in the trialkyl- or triaryl phosphine ligands they are often compared to), principally via permutations of the N-bound hydrocarbyl substituents. Thus, as observed for other metal catalysts,[10] the use of NHC ligands in place of phosphine or amine ligands in nickel chemistry has led to an important enrichment of the observed catalytic activity, and consequently to the significant diversification of nickel-based systems. Catalytic

applications of Ni(NHC) complexes that include reactions as varied as C−C cross-couplings, the amination and dehalogenation of aryl halides, C−S couplings, C−H bond functionalizations, C−F bond activations, the oxidation of secondary alcohols, hydrosilylation reactions, three-component couplings of unsaturated hydrocarbons, aldehydes, silyl derivatives, and [2+2+2] cycloadditions, have already been reviewed in several articles and book chapters,[11] but the field is evolving extremely rapidly, and these reviews are already out-dated and/or did not sufficiently focus on mechanistic aspects. Herein, we attempt to encompass all examples involving these species, as either in situ generated or well-defined catalysts, in C−C cross-couplings and C−C couplings via C−H bond activation with a special emphasis on catalytic systems. In addition, we have attempted to give as much mechanistic detail as possible. Cycloadditions, multicomponent reductive couplings, oligo-, and polymerization reactions also result in C−C bond formation, but these reactions are excluded from the present review in the interest of space. Coverage is as complete as possible to the end of August 2014.

2. KUMADA−TAMAO−CORRIU COUPLING

Kumada−Tamao−Corriu[12,13] (KTC) coupling involves the selective formation of C−C bonds by cross-coupling of Grignard reagents with organic halides or pseudohalides and is historically the first cross-coupling reaction that involved nickel compounds as catalysts. Moreover, despite their sensitivity toward air and moisture, Grignard reagents are often precursors of boronic acids, stannanes, and the organozinc reagents employed for other cross-coupling methodologies, and their use thus avoids extra synthetic steps involving stoichiometric amounts of organometallic reagents.

The classical mechanism of the KTC reaction involves a M(0)/M(II) catalytic cycle (Scheme 1). The M(0) species is

### Scheme 1. Classical M(0)/M(II) Catalytic Cycle for KTC Coupling
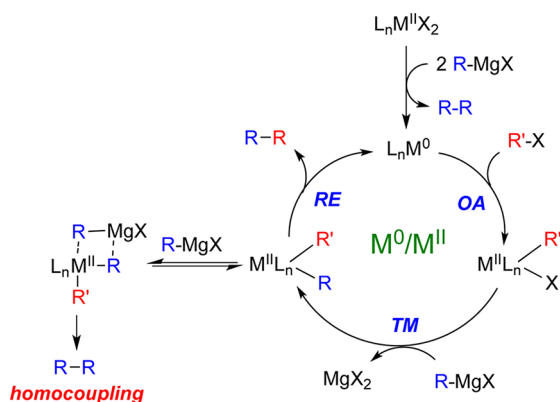
generally generated by two subsequent transmetalation steps on a dihalogenated metal precursor, followed by a reductive elimination step to form the active M(0) species, along with the homocoupling product. Oxidative addition of the aryl halide on M(0) followed by transmetalation with the Grignard reagent and subsequent reductive elimination affords the coupling product. However, the dialkyl intermediate obtained after the transmetalation step can undergo further reaction with a Grignard reagent, and this may give rise to significant amounts of the homocoupling product. Suppression of this step is

therefore of major importance to selectively obtain the cross-coupling product.

2.1. In Situ Generated Ni(NHC) Complexes. From a practical and economical point of view, in situ generation of a Ni(NHC) complex from a commercial source of nickel and an imidazolium salt is the method of choice. Such a system was first reported by Herrmann et al. for KTC coupling of aryl chlorides at room temperature.[14] Remarkably, with only 3 mol % of $Ni(acac)_2/IPr·HX$ (1:1) or $Ni(acac)_2/IMes·HX$ (1:1) (X = Cl^-; BF_4^-), moderate to excellent yields (67−99%) were obtained with a large array of (hetero)aryl chlorides and Grignard reagents (17 examples). Even steric congestion was partially tolerated, as demonstrated by good conversion of 2-substituted chloroaryls; nevertheless, two *ortho*-substituents hamper useful conversions.[14] The $Ni(acac)_2/IPr·HBF_4$ (1:1−5 mol %) catalytic system was also successful for KTC coupling of aryl fluorides (13 examples)[15] and neopentyl arenesulfonates (36 examples)[16] at room temperature (Scheme 2). Regarding the

### Scheme 2. KTC Coupling with Herrmann's Seminal Catalytic System[14−16]
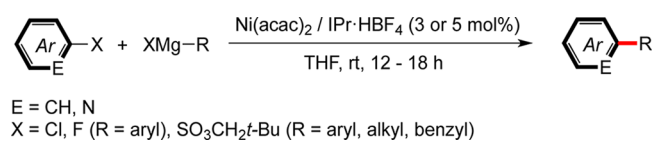
mechanism, initial observations of the crude reaction mixtures by ^{13}C NMR spectroscopy were consistent with a catalytically active imidazol-2-ylidene complex of nickel(0).[14] Latter observations that the $Ni(acac)_2/IPr·HBF_4$ (1:1) mixture worked better than a 1:2 mixture or than the isolated zerovalent complex Ni-$(IPr)_2$[15,16a] allowed Herrmann to propose that a highly reactive 12e $Ni^0(IPr)$ species could act as the real catalyst.[15]

The use of the imidazolium salt **1** bearing a 2-pyridyl group and an ethylenedioxy moiety, as, respectively, strong and weak coordinating groups, with $Ni(acac)_2·H_2O$ in a 1:1 ratio resulted in improved activities compared to $Ni(acac)_2/IPr·HBF_4$ and allowed a catalyst loading of 1 mol % and much shorter reaction times but at 60 °C (Scheme 3).[17]

In 2006, Labande and Poli developed the zwitterionic complexes **2** that contain a phosphine-imidazolium ligand, which catalyze the KTC coupling of aryl chlorides with aryl magnesium chloride or bromide, under conditions similar to those used by Herrmann et al.[18] The imidazolium salt is presumably deprotonated in situ by the Grignard reagent to afford a mixture of monomeric and dimeric nickel phosphine−carbene complexes, which are likely to be the real precatalysts (Scheme 4). The authors claimed that the activity of complexes **2a,b**, bearing the shorter tether, was similar to that of Herrmann's $Ni(acac)_2/IPr·HX$ (1:1) seminal system with a slightly improved selectivity for the cross-coupling product. Interestingly, a more recent study on a related system showed that the nickelate complexes $[NiX_3(PPh_3)][IPr−H]$ (X = Br, Cl) (**3**) displayed similar activities, demonstrating thereof that the tether between the imidazolium salt and the phosphine is not necessarily required to observe a good activity, thus providing simpler precatalysts.[19]

In 2009, Nakamura et al. reported that combinations of IPr·HCl or SIPr·HCl and metal difluorides of the iron-group metals (Fe, Co, and Ni) constitute a very efficient catalytic triad for the coupling of aryl and heteroaryl halides with arylmagnesium bromides. The system exhibited an excellent selectivity for the

Scheme 3. KTC Coupling with Ni(acac)$_2$·H$_2$O/1[17]

E = CH, N Ar = Ph, p-Tol
X = Br, Cl
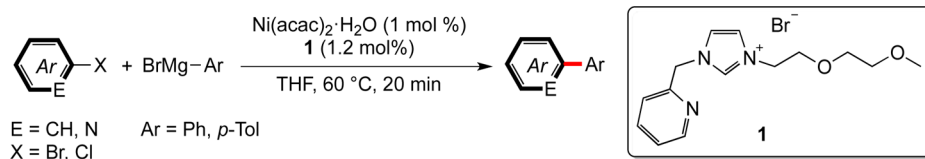
Scheme 4. Plausible Intermediates Formed during KTC Catalysis with Complexes 2[18]

n = 1 Ar = Mes **2a**
　　　　 DIPP **2b**
n = 2　 Mes　 **2c**
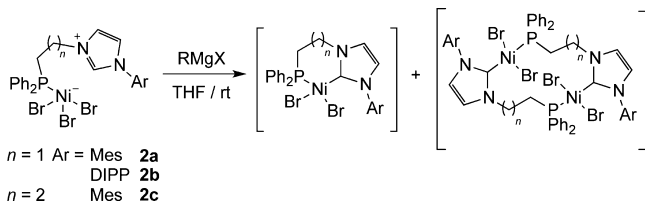
cross-coupling products.[20] Very good to excellent yields (84–99%) of the biaryl products, with generally less than 5% of the homocoupling product, were obtained for a large array of aryl and heteroaryl chlorides and bromides (19 examples) by choosing the appropriate metal difluoride/NHC·HCl (1:1) combination. The Fe(SIPr) system allowed highly selective coupling using various aryl chlorides, whereas the Co(IPr) system proved particularly efficient for the coupling of heteroaromatics. In addition, the Ni(IPr) system showed high catalytic activity when aryl bromides and hindered substrates were employed. Experimental results and theoretical calculations suggest that a "fluoride effect" could be responsible for the observed excellent selectivity for the cross-coupling products. This effect would consist in strong coordination of the fluoride ligands to the magnesium center, which would subsequently inhibit reduction of the metal by a conventional transmetalation/reductive elimination process (see Scheme 2). The reaction would therefore proceed via a Ni(II)/Ni(IV) catalytic cycle, which is less favorable for the formation of the homocoupling product than a Ni(0)/Ni(II) cycle (Scheme 5).

Scheme 5. M(II)/M(IV) Cycle Proposed by Nakamura (M = Ni, Fe, Co)[20]
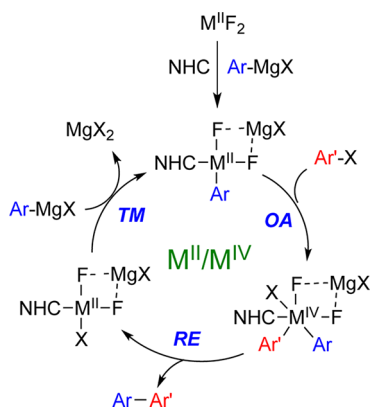
More recently, Sémeril and Matt described the synthesis of three resorcinarene-cavitands bearing a 3-R-1-imidazolium substituent (R = n-propyl, isopropyl, or benzyl) grafted to the wider rim of the cavitand. Their combination with Ni(COD)$_2$ in a 1:1 ratio resulted in highly efficient catalysts for KTC coupling of aryl bromides and chlorides at high temperature.[21] The

catalyst loading could be decreased to levels as low as 0.001 mol % when the reaction was run at 100 °C in dioxane, and a remarkable TOF of 60 400 h^{-1} could be obtained in the coupling of 2-bromo-6-methoxynaphthalene with tolylmagnesium bromide (with R = isopropyl). The high activities were attributed to steric interactions between the metal complex and the flexible substituents attached to the methine carbon atoms that would facilitate the reductive-elimination/product decoordination step (Scheme 6). Nevertheless, decreasing the reaction temperature

Scheme 6. Steric Interactions in a Possible Ni(0) Intermediate Preceding the Reductive Elimination Step[21]
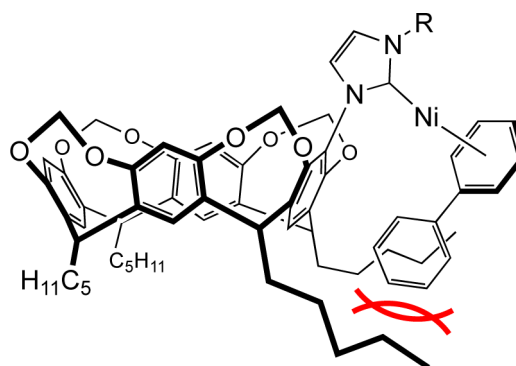
resulted in lower activities, and catalyst loadings of 1 mol % were required at room temperature to observe full conversions in 24 h.

A significant improvement in the Ni(NHC)-catalyzed KTC coupling was the possibility of using sterically demanding tertiary alkyl Grignard reagents, which still represents a challenge because of competitive β-hydride elimination and isomerization reactions.[22]

In this respect, Glorius reported the use of the flexible imidazolium salt **4** with Ni(acac)$_2$ in a 1:1 ratio (Scheme 7). The ligand probably acts as a bidentate chelate during the catalysis, and retards β-hydride elimination by occupying an additional coordination site on the nickel.[23] The addition of a base was shown to be crucial as it probably helps to generate the carbene complex. Under these conditions, the coupling of tertiary alkyl

Scheme 7. Ni(NHC)-Catalyzed KTC Coupling of Tertiary Alkyl Grignard Reagents[23,24]

X = Br, OTf
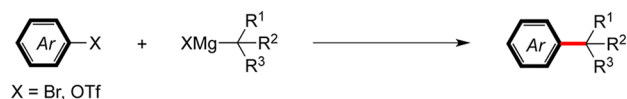
Glorius [ref. 23]		68 - 85%
Ni(acac)$_2$ (5 mol%), LiOt-Bu (1.5 equiv.), THF, 0 °C to RT, 3 - 12 h	**4** (5 mol%)	22 examples
Biscoe [ref. 24]		47 - 86%
NiCl$_2$(H$_2$O)$_{1.5}$ (10 mol%), ICy·HBF$_4$ (10 mol%) THF, -10 °C, 90 min		28 examples

magnesium chlorides with aryl bromides and triflates was achieved at room temperature with moderate to good yields (Scheme 7). Control experiments run with radical scavengers suggested that radical intermediates are implied in the reaction, as the catalytic activity was totally inhibited in their presence.

The same year Biscoe et al. reported another system able to achieve the selective coupling of tertiary substrates.[24] In this case, no base was necessary, but the nature of the ligand, the degree of hydration of the nickel source, the temperature, and the substrate concentration were all critical factors. Thus, using $NiCl_2 \cdot (H_2O)_{1.5}$/ICy·HBF$_4$ (1:1; 10 mol %) in THF at −10 °C allowed the coupling of a broad scope of aryl bromides, as well as some aryltriflates, vinyl chlorides, and vinyl bromides with alkylmagnesium halides. On the basis of literature precedents with nickel-bypyridine[25] and -terpyridine[26] systems, where activation of the electrophiles was shown to be performed by alkyl−Ni(I) complexes, formed by transmetalation with alkylzinc halides, the authors favored a similar Ni(I)/Ni(III) cycle (Scheme 8). Nevertheless, no experimental data were given to support this assumption.

Scheme 8. Ni(I)/Ni(III) Proposed Catalytic Cycle for the Biscoe KTC Coupling of Tertiary Alkyl Grignard Reagents[24]
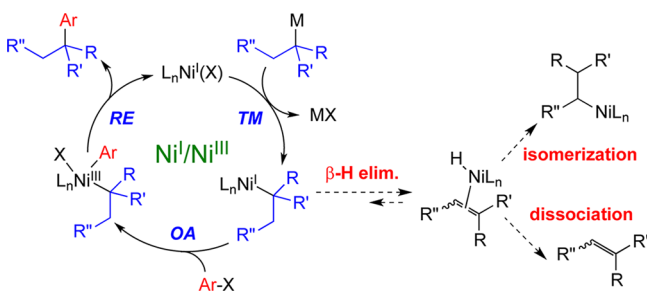
2.2. Well-Defined Ni(NHC) Complexes with Monodentate NHCs.
Although in situ generated metal catalysts are often preferred, due to their facile synthetic use, they can give rise to "cocktail-type systems" with different metal species present in solution, and thus sometimes decreased selectivity.[27] The use of well-defined Ni(NHC) complexes addresses this problem, and many efforts has been devoted to the development of monodentate Ni(II)-NHC, Ni(I)-NHC, and Ni(0)-NHC complexes (Chart 1).

The mixed diphosphine/carbene complexes **5a−e**,[28] **6**, and **7**[29] were prepared by the oxidative addition of either Ni(COD)$_2$ in the presence of PPh$_3$ (2 equiv) or Ni(PPh$_3$)$_4$, to the corresponding 2- or 4-chloroazolium salt. The resulting species were briefly evaluated in the KTC coupling of electron-rich aryl Grignard reagents with aryl chlorides and bromides. The catalytic activities however did not exceed those observed with Herrmann's initial system,[14] or even those observed with Matsubara's mixed phosphine/NHC complex Ni(IPr)(PPh$_3$)Cl$_2$ (**8**): the latter allowed one to observe quantitative yields with a few aryl iodides and bromides within 30 min with only 0.5 mol % of precatalyst.[30] This mixed phosphine/carbene system is actually better than its analogues Ni(IPr)$_2$Cl$_2$ (**9b**) or Ni-(PPh$_3$)$_2$Cl$_2$,[30] and Ni(IPr)(IiPr)X$_2$ (X = Br, Cl) or Ni(IMes)-(IiPr)Br$_2$.[31]

Considering the mechanism, at the end of 2010, Matsubara[32] and Louie[33] concurrently described the synthesis of the paramagnetic 15e nickel(I)−NHC species **11a,b** by reaction of aryl halides with the related zerovalent Ni(NHC)$_2$ complexes

10a,b (Scheme 9). These T-shaped complexes were obtained instead of the expected oxidative addition product Ni-(NHC)$_2$(Ar)X, and they show similar activities in the KTC coupling of aryl bromides and chlorides when compared to the related Ni(NHC)$_2$ and Ni(NHC)$_2$Cl$_2$ complexes.[33] Additionally, stoichiometric reactions between these species and the cross-coupling partner suggested that cross-coupling reactions are initiated by a transmetalation reaction between Ni^I(NHC)$_n$X and the transmetalating reagent.[33] The mechanism depicted in Scheme 10 was therefore proposed.

Complex **11b** could also be synthesized by addition of one equivalent of IPr to the dinuclear complex **12**.[32,34] However, when two equivalents of PPh$_3$ were added to **12**, the Y-shaped species **13** was obtained quantitatively (Scheme 9). Moreover, in the presence of an excess of phosphine (2.5 equiv), the latter proved to be a significantly better catalyst than **11b**, as reaction times could be decreased from 18 to 3 h with the same catalyst loading of 1 mol % in THF at room temperature.[34] More recently, a comparative study conducted with the ring-expanded-NHC−nickel(I) complexes **14** and **15** has shown that the NHC ring size has a dramatic influence on catalysis.[35] Thus, although the six-membered NHC complex **14a** showed equivalent performances to **13**, further increase of the ring size proved highly detrimental to the catalytic activity.

In 2010, Huynh et al. reported the synthesis of diisothiocyanato bis-NHC complexes **16** and **17** via ligand substitution of the trans-dibromo or -diodo precursors.[36] Surprisingly, depending on the size of the N-substituents of the carbene ligands, either trans- or cis-diisothiocyanato complexes **16** or **17** were obtained. Comparison of their activities in KTC coupling predictably revealed that the cis-complexes **16** were more efficient than the trans-complexes **17**. Several (hetero)aryl bromides and chlorides could be coupled with moderate to excellent yields (49−94%) in 24 h at room temperature in the presence of 1 mol % of complex **16a**, which indicates that these results are good in terms of catalyst loading but rather moderate in terms of TOFs.

Significant improvement in the Ni(NHC)-catalyzed KTC biaryl coupling was demonstrated by Snieckus et al. with the use of the η^5-cyclopentadienyl complex [Ni(IMes)ClCp] (**18a**) under remarkably mild conditions (1−2.5 mol % of **18a** in Et$_2$O at 0 to 40 °C) for the coupling of aryl O-sulfamates with arylmagnesium bromides (Scheme 11).[37] Similarly, the related 16-electron η^3-allyl complex **19** remarkably allowed the use of aryl ethers, as well as of challenging heteroaryl chlorides (20 examples) as the electrophiles, under relatively mild conditions (Scheme 11).[38] To the best of our knowledge, these are the only two examples of Ni(NHC)-catalyzed KTC coupling process that involve C$_{Ar}$−O bond activation. The observed catalytic activity with **19** could be explained by the ease of generating an active nickel(0) intermediate starting from a nickel(II)−allyl complex,[39] as reduction of the latter probably occurs in a similar manner to that proposed for palladium(II) analogues.[40]

Another breakthrough has been achieved with the use of the naphtoquinimidazolidene complex **20** that can be electronically modified by an external redox stimulus.[41] Impressively, catalysis can be arrested at anytime by reduction of the electronically active NHC by addition of CoCp$_2$. The active state can be restored by simple oxidation with [FeCp$_2$][BF$_4$] (Scheme 12). This system represents significant practical and conceptual progress toward the use of redox-switchable control as an effector of tandem catalysis.

2.3. Well-Defined Ni(NHC) Complexes with Multidentate NHCs.
Compared to monodentate complexes, chelate

**Chart 1. Monodentate Ni(NHC) Complexes Applied in KTC Coupling**
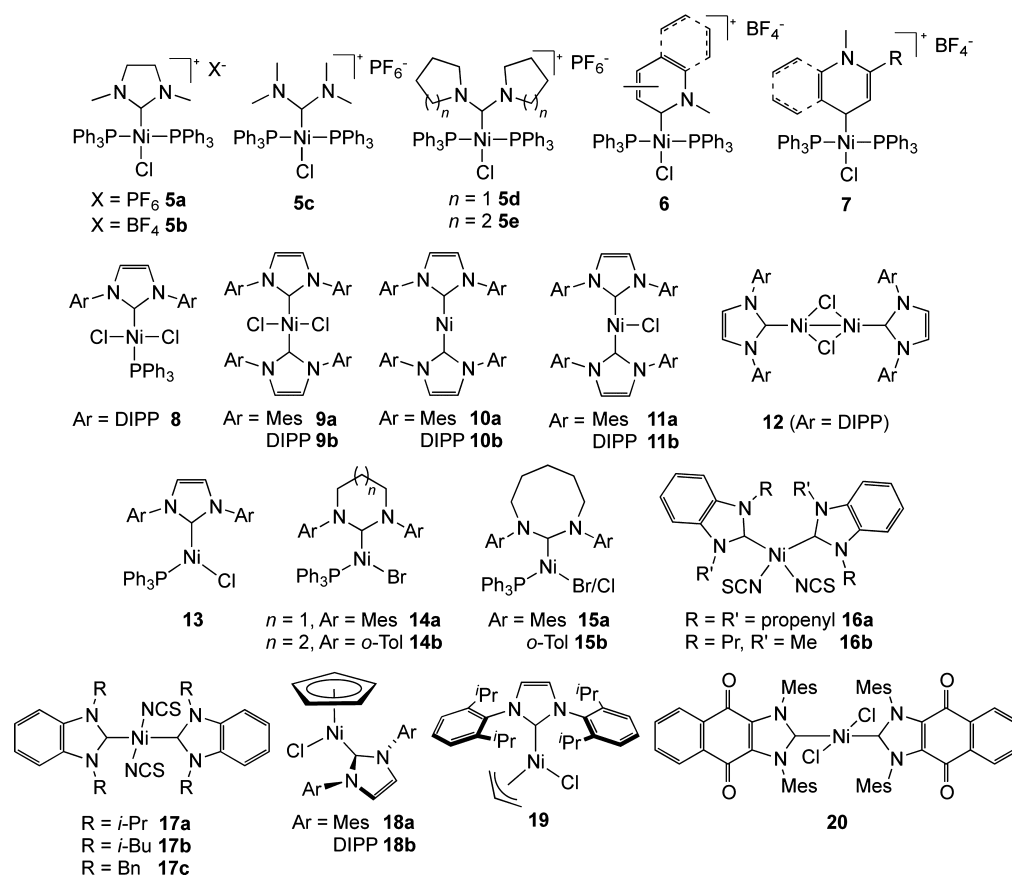
Scheme 9. Synthesis of the T-Shaped 15e Ni(I)-NHC Complexes 11[32,33]
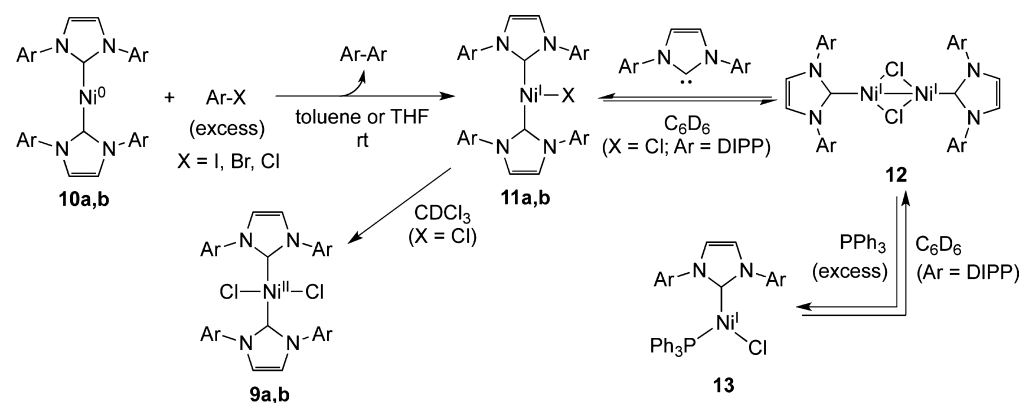
complexes often give rise to more stable, and sometimes more active, metal species. This was confirmed by the performances in KTC coupling of the well-defined Ni(NHC) chelate complexes depicted in Chart 2, which are globally better than those of the monodentate Ni(NHC) complexes, and generally allow one to avoid high reaction temperatures and precatalyst loadings.

Thus, complexes **21–25** bearing ter- or tetradentate CN-ligands were all shown to efficiently catalyze the coupling of aryl chlorides with aryl Grignard reagents at room temperature. In particular, the NCCN-complexes **21a–c** were shown to couple a large array of aryl chlorides, heteroaryl chlorides, and vinyl chlorides; the best activity was observed with 2–4 mol % of **21a** for 12 h, (32 examples, 62–99%, including *ortho*-substituted and nitrile-functionalized chloroarenes).[42] The CNN-complexes

22[43] and **23**,[44] bearing, respectively, a rigid phenanthroline and an amido-amine arm, displayed comparable results (1 mol % **22** or 2 mol % **23** for 24 h), but their reaction scopes were not as broad as those of **21a**. Finally, the use of the NCN- and CNC-pincer complexes **24**[45] and **25**[46] allowed, respectively, a reduction in the precatalyst loading to 0.5 mol % (0.5–1 mol % **24**, 12 h, 7 examples, 44–72%) and enabled the coupling of aryl fluorides (5 mol % **25**, 4–6 h, 15 examples, 60–99%). According to the authors, the higher activity of the latter complexes may arise from the ease of generating vacant sites compared to complexes **21a–c**. This is however probably not the sole reason as structurally related neutral and cationic complexes **26** and **27**, which bear *bis*(benzimidazolin-2-ylidene)pyridine

Scheme 10. Plausible Mechanism Involving the T-Shaped 15e Ni(I)-NHC Intermediates in the KTC Reaction[33]
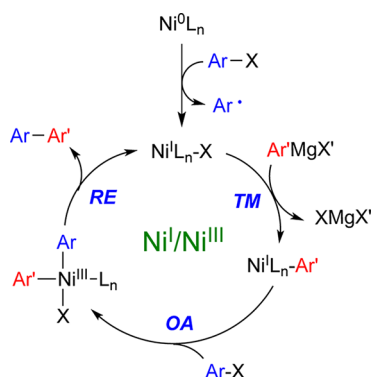
Scheme 11. KTC Coupling of Aryl O-Sulfamates and Aryl Ethers Catalyzed by 18a and 19[37,38]
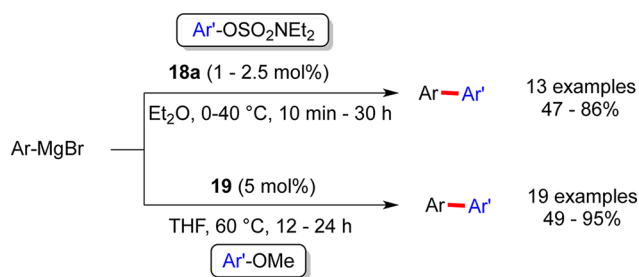
pincer ligands, showed only moderate activity under similar conditions.[47]

The CC′C-pincer like complexes **28**, which were obtained by transmetalation and intramolecular chloronickelation of a bridging triple bond, were also found to be highly efficient for the KTC coupling of a large array of aryl halides at room temperature (0.5–1 mol % **28**, 3–24 h, 27 examples), including *ortho*-substituted aryls, heteroaromatics, cyano-functionalized aryls, and fluoroaryls.[48]

In contrast, the structurally related CNN- and CNP-chelate complexes **29a–c** were all shown to catalyze the KTC coupling of a few aryl chlorides with arylmagnesium bromides with only moderate efficiencies when compared to the previous complexes: relatively high loadings (4 mol %) and/or heating to 80 °C were required in some cases to observe satisfying yields.[49]

The neutral **30**[50] and cationic **31**[51] benzimidazole-tethered Ni(NHC) complexes are structurally similar. Nevertheless, owing to their diverse electronic characters, they behave rather differently during the reaction: the neutral complex **30** allowed the use of aryl chlorides and even fluorides with much shorter reaction times (12−150 min) as compared to the cationic complex **31**. This activity difference could result from the possible decoordination of the anionic benzimidazole arms of **30**,

which would then be stabilized by coordination to the liberated [MgCl]⁺ resulting from the transmetalation step (Scheme 13).[50]

Finally, the bimetallic complex **32a** is among the best well-defined Ni(NHC) precatalysts for KTC coupling, as it could be used with loadings as low as 0.1 mol % with a large array of aryl chlorides at room temperature (Scheme 14).[52] This high activity was attributed to possible bimetallic cooperation as the Ni−Ni distance of 3.22 Å, bridged by a hydroxyl-group, is relatively short.

cis-Chelating *bis*-NHC complexes of nickel are also of interest, as shown by the use of the carbonato complexes **33**[53] and of the *cis*-chelating *bis*-benzimidazolinylidene complexes **34**.[54,55] Loadings of only 1 mol % of **33c** and **34b** led to good to excellent yields for the coupling of aryl bromides and chlorides with arylmagnesium bromides at room temperature. In particular, complex **34b** showed interesting results, as it converted a vast array of substrates including heteroaromatic halides and di-*ortho*-substituted aryl bromides in 12 h (20 examples, 43−99%).

Finally, Kobayashi elegantly described the use of nickel nanoparticles **35** stabilized by NHC ligands embedded on cross-linked polymers.[56] This heterogeneous system competes with the best homogeneous Ni(NHC) catalysts and allows the coupling of a large range of aryl, alkyl, and vinyl halides (including aryl fluorides) with a significant variety of aryl and alkyl Grignard reagents (Scheme 15). Whereas the coupling of iodides and bromides proceeded very smoothly (0 °C or rt), heating at 65 or 100 °C was required with chlorides and fluorides in order to obtain good conversions. Remarkably, even ester-functionalized Grignard reagents were found to be suitable substrates, and **35** could be reused up to 10 times without notable loss of activity.

3. SUZUKI-MIYAURA COUPLING

The Suzuki−Miyaura[13e,57,58] (SM) cross coupling is undoubtedly one of the most powerful methodologies available for the formation of aryl−aryl bonds. The most frequently encountered catalysts are palladium-based. However, significant progress has been made in the recent years with nickel-based systems.[59] In this context, Ni(NHC)-based systems have shown interesting activities, in particular with the use of in situ generated monodentate NHC complexes.

In a first approach, one may consider the reaction mechanism to be similar to that of the KTC coupling with oxidative addition of the aryl halide or pseudohalide to a M(0) complex [M⁰L$_n$] to form [ArM^{II}XL$_n$] as the first step of the cycle. This would be followed by transmetalation with the arylboronic acid Ar′B-(OH)$_2$ to afford [ArMAr′L$_n$] as the second step, and reductive elimination of the coupling product ArAr′ to regenerate the M(0) catalyst as the final step (see Scheme 1). However, such a mechanism does not take into account the necessary presence in all SM couplings of a base, whose role is poorly understood. Thus, in the case of hydroxide, alkoxide, carbonate, or phosphate ions as bases, it is commonly accepted that they would, among

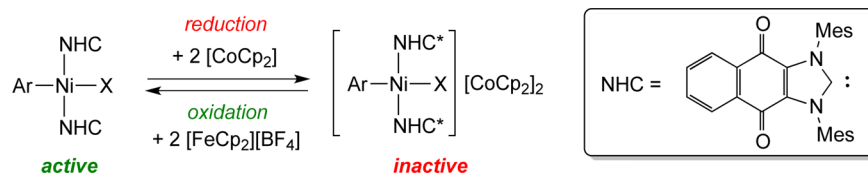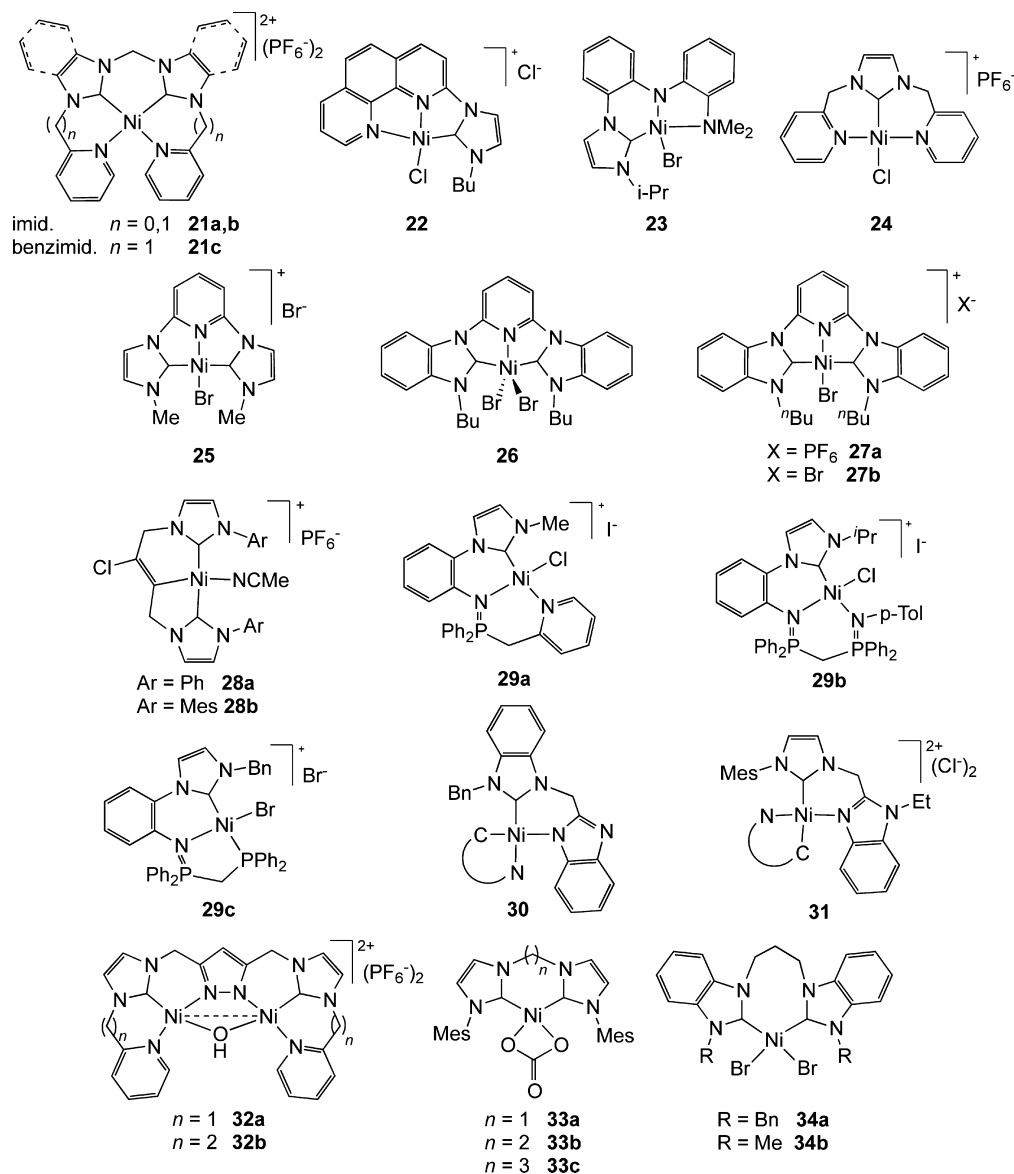**Scheme 12. Redox Control of the Catalytically Active Species Derived from 20[41]**
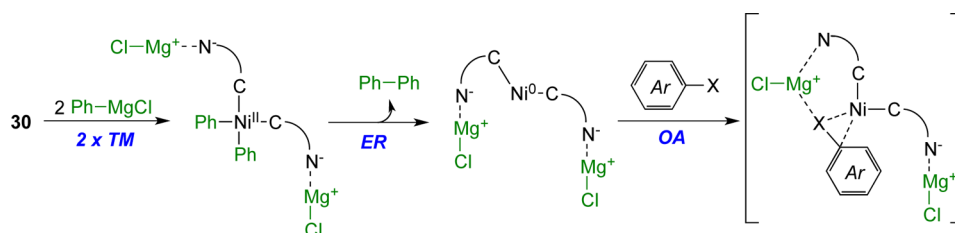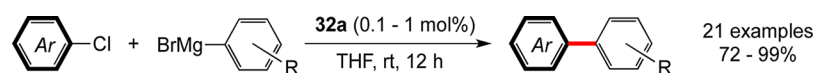
Chart 2. Multidentate Ni(NHC) Complexes Applied in KTC Coupling

imid. $n = 0,1$ **21a,b**
benzimid. $n = 1$ **21c**

22

23

24

25

26

X = PF_6 **27a**
X = Br   **27b**

Ar = Ph   **28a**
Ar = Mes   **28b**

29a

29b

29c

30

31

$n = 1$ **32a**
$n = 2$ **32b**

$n = 1$ **33a**
$n = 2$ **33b**
$n = 3$ **33c**

R = Bn   **34a**
R = Me   **34b**

Scheme 13. Proposed Intermediates and Transition State in the KTC Reaction Catalyzed by 30[50]

Scheme 14. KTC Coupling Catalyzed by 32a under Mild Conditions[52]

others, undergo a ligand exchange reaction with the halide or pseudohalide of $[ArM^{II}XL_n]$ prior to the transmetalation step to generate a more reactive metal-oxo $[ArM^{II}(base)L_n]$ intermediate.[60,61] Nevertheless it is hazardous to draw a general scheme,

especially in the case of nickel, which can shuttle between either Ni(0)/Ni(II) or Ni(I)/Ni(III) oxidation states.[59]

3.1. In Situ Generated Ni(NHC) Complexes. In contrast to KTC coupling for which various nickel sources could be used (vide supra), Ni(COD)$_2$ appeared to be best nickel source for

Scheme 15. NHC-Stabilized Ni-NPs as a Heterogeneous Catalyst for the KTC Reaction[56]
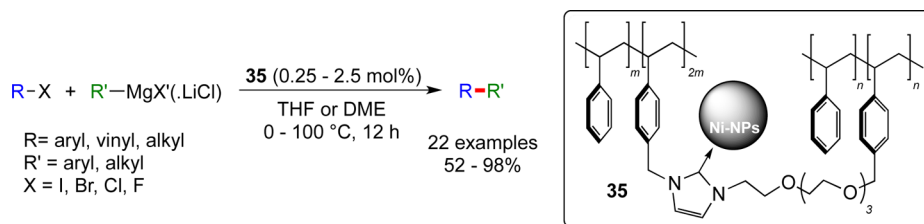
Scheme 16. Aryltrimethylammonium Salts as Electrophiles in the SM Reaction[62]
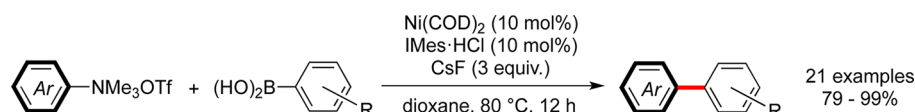
Scheme 17. Azoles and Fluorine as SM Leaving Groups[63]
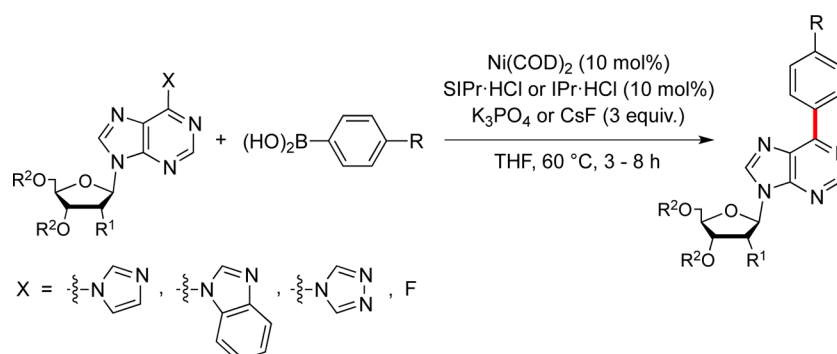
Scheme 18. Stereoselective Synthesis of Triarylmethanes[64]
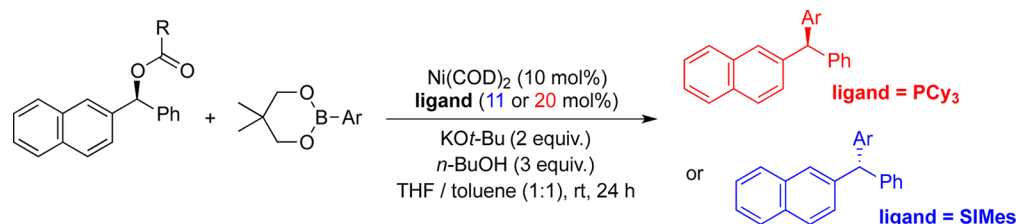
Suzuki coupling, and this precursor allowed for the coupling of uncommon electrophiles. For instance, aryltrimethylammonium salts could be used for the first time as coupling partners to give biaryl products in good to excellent yield with a Ni(COD)$_2$/IMes·HCl (1:1) catalytic system (Scheme 16).[62] Moreover, this system promoted the coupling of mono- and di-*ortho*-substituted coupling partners without significant yield decreases.

Robins et al. described the use of Ni(COD)$_2$/SIPr·HCl or IPr·HCl (1:1) combinations in the presence of K$_3$PO$_4$ or CsF for the synthesis of 6-arylpurine nucleosides from 6-(imidazol-1-yl)-, 6-(benzimidazol-1-yl)-, 6-(1,2,4-triazol-4-yl)- and 6-fluoro-purine derivatives (i.e., the use of azoles[63a] and fluorine[63b] as SM leaving groups, Scheme 17).
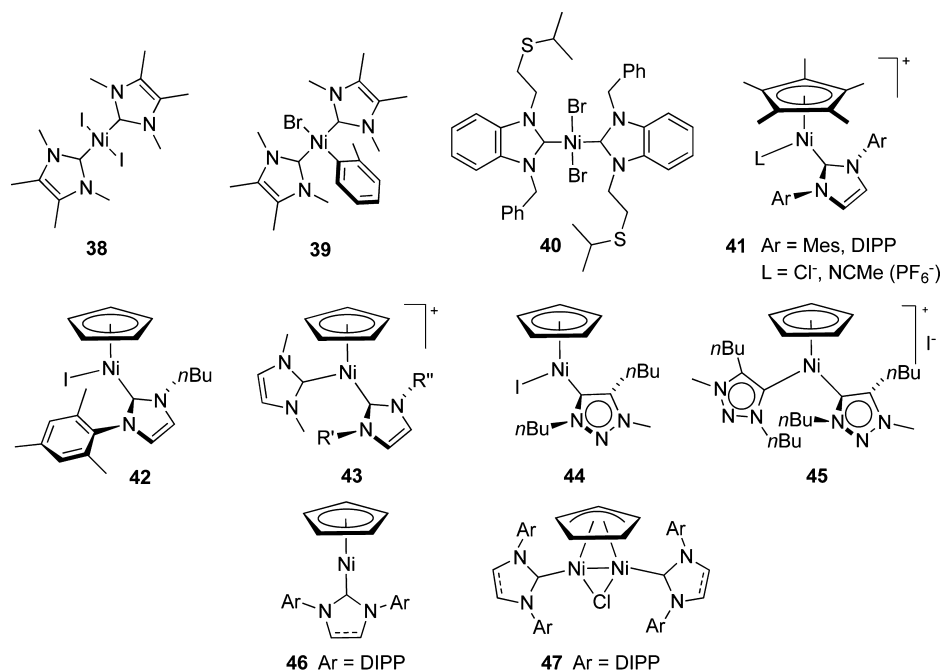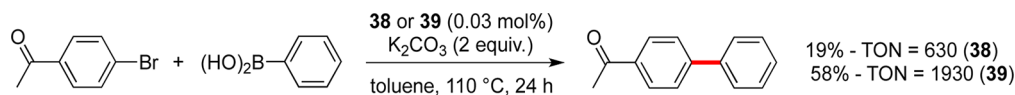
With a similar catalytic system, benzylic carbamates and pivalates could also be employed as electrophiles for the efficient synthesis of enantioenriched triarylmethanes by coupling with arylboronic esters.[64] Remarkably, the stereospecificity of the reaction could be modulated with achiral ligands. Whereas inversion took place with a Ni/SIMes (1:1) catalyst, the retention product was predominantly obtained with a Ni/PCy$_3$ (1:2) catalytic system (Scheme 18).

Finally, the tetrachloronickelate-containing ionic liquid **36** and silica-immobilized ionic liquid **37** (Scheme 19) were used for the

Scheme 19. SM Active NiCl$_4^{2-}$-containing Ionic Liquids 36 and 37[65]
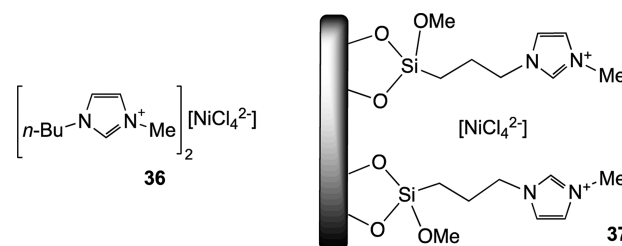
coupling of arylboronic acids with aryl chlorides.[65] In the presence of 2 equiv of PPh$_3$, both systems were very efficient (catalyst loadings as low as 0.5 and 2 mol % for **36** and **37**, respectively), and **37** could be used three times without activity loss.

Chart 3. Monodentate Ni(NHC) Complexes Applied in SM Coupling

38 **39** **40** **41** Ar = Mes, DIPP
L = Cl⁻, NCMe (PF₆⁻)

42 **43** **44** **45**

46 Ar = DIPP **47** Ar = DIPP

Scheme 20. First Example of a Ni(NHC)-Catalyzed SM Coupling[66]

38 or 39 (0.03 mol%)
K₂CO₃ (2 equiv.)
toluene, 110 °C, 24 h

19% - TON = 630 (**38**)
58% - TON = 1930 (**39**)

3.2. Well-Defined Ni(NHC) Complexes with Monodentate NHCs. A number of well-defined monodentate NHC complexes of nickel, which are depicted in Chart 3, were also shown to have interesting activities in SM reactions, though usually with more classical aryl halides.

The first example was described in 1999 by Cavell et al. with the use of the *trans-bis*-NHC complexes [Ni(tmiy)₂I₂] (**38**) and [Ni(tmiy)₂(o-tolyl)Br] (**39**) for the coupling of 4-bromoacetophenone and phenylboronic acid. Impressively, very low catalytic loadings could be used, and these complexes remain to date the most efficient well-defined Ni(NHC) complexes for the SM coupling in terms of TON (Scheme 20).[66] The increased activity observed with **39**, which was obtained by oxidative addition of 2-bromotoluene to Ni⁰(tmiy)₂, sustains the possibility of a Ni(0)/Ni(II) catalytic cycle.

In comparison, the recently reported *trans-bis*-benzimidazolin-2-ylidene nickel(II) complex **40** that bears thioether-functionalized side chains and exists as an inseparable mixture of *trans-syn* and *trans-anti* rotamers, proved much less efficient as the catalyst loading could not be lowered below 1 mol %. Furthermore, it required the use of additional triphenylphosphine (2 mol %).[67]

The Cp-Ni(NHC) complexes **18**, that were demonstrated to be efficient precatalysts for the KTC coupling of aryl O-sulfamates with arylmagnesium bromides (see Scheme 11),[37] showed moderate performances for the SM coupling of activated bromoarenes with phenylboronic acid.[68,69] Interestingly, the more hindered and electron-rich pentamethylcyclopentadienyl (Cp*) derivatives **41** proved much more efficient and even allowed 92−95% conversion in only 10 to 15 min for the coupling of 4′-bromoacetophenone with phenylboronic acid in the presence of 3 mol % precatalyst and of K₃PO₄ as the sole additive, giving TOFs of up to 190 h⁻¹.[68] Fast catalyst

deactivation was however observed when the catalyst loading was reduced to 1 mol %. Nevertheless, encouraged by these results, the authors embraced a study aiming at heterogenizing these complexes.[70] In this investigation, while using *N*-aryl,*N*′-butyl-NHC derivatives as models for complexes immobilized on a solid support via a three carbon linker, they surprisingly discovered that the Cp iodide complex **42** was even more active than the Cp* complexes **41**. The observed TOF of 352 h⁻¹ for the coupling of 4′-bromoacetophenone with phenylboronic acid in the presence of 1 mol % of **42**, is one of the highest observed rates for a nickel(II)-based catalyst in the absence of cocatalyst or reductant. The significant stabilization of the active species compared to those resulting from the other Cp species **18** and the Cp* species **41** was tentatively attributed to the presence of the voluminous iodide ligand, which could play a protecting role for a nickel(0) active species.[70] In comparison, however, the bulky *bis*-NHC complexes **43** did not allow an efficient SM coupling, probably because they are too stable or too congested to react.[71]

Interestingly, the structurally related and recently reported triazolylidene complex **44**, which also bears an iodide ligand and a N-bonded *n*-butyl arm, behaves similarly to **42**. It also allowed the coupling of 4′-bromoacetophenone with phenylboronic acid with a high TOF of 228 h⁻¹ under similar reaction conditions. However, its *bis*-triazolylidene derivative **45** proved to be much less efficient, with an inertness comparable to that of the *bis*-carbene complexes **43**.[72]

Finally, Hazari et al. recently reported that the nickel(I) monomers and dimers **46** and **47**, bearing only Cp and NHC ligands, catalyze the SM coupling of 4-chlorotoluene with phenylboronic acid. Although none of these catalysts were as active as their nickel(II) congeners **41**, **42**, and **43** or as any other
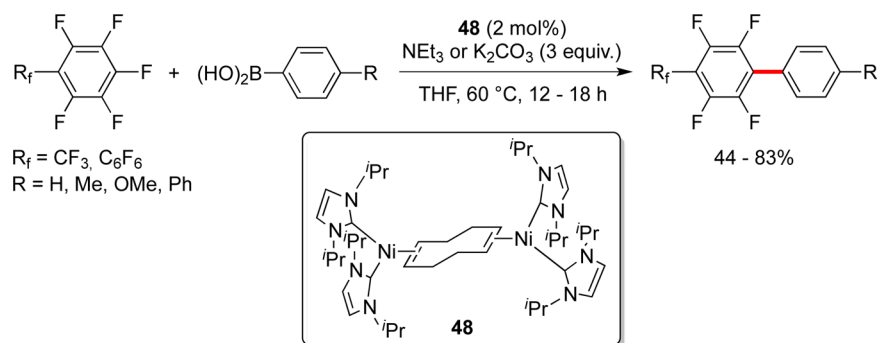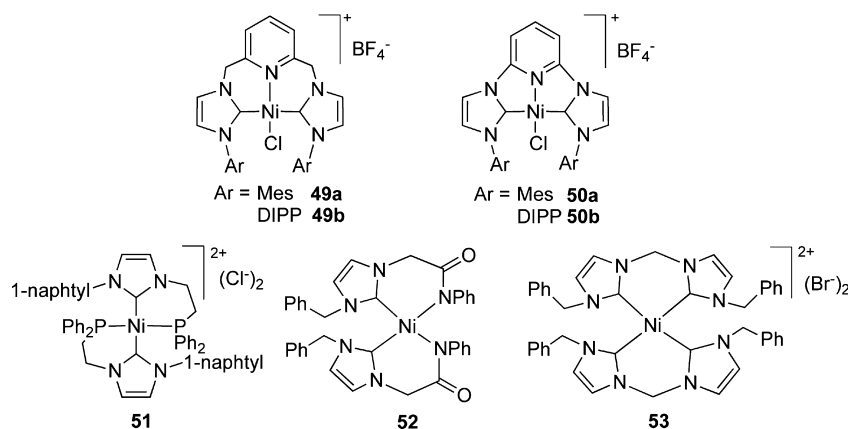
Scheme 21. SM Coupling of Perfluoroarenes Catalyzed by 48 under Mild Conditions[74]

R_f = CF₃, C₆F₆
R = H, Me, OMe, Ph

44 - 83%

Chart 4. Multidentate Ni(NHC) Complexes Applied in SM Coupling

Ni(0) or Ni(II) species described here, these results show that nickel(I) species can act as precatalysts for the SM reaction.[73]

Relatedly, the SM cross-coupling between aryl bromides and phenylboronic acid was also investigated with the *bis*-NHC complexes Ni^{II}(IMes)$_2$Cl$_2$ (**9a**), Ni^0(IMes)$_2$ (**10a**), and Ni^I(IMes)$_2$Cl (**11a**) (see Chart 1).[33] As was observed in the KTC reactions (though with a much higher catalyst loading of 10 mol % in SM coupling vs 3 mol % in KTC coupling), all of the Ni species afforded the biaryl product in comparable yields, regardless of their oxidation state. This allowed Louie et al. to propose a similar Ni(I)/Ni(III) mechanism (see Scheme 10).

Finally, perhaps the most interesting result was obtained with Radius' Ni(0) homobimetallic compound **48**, which acts as a source for the electron-rich Ni^0(IiPr)$_2$ complex and allowed the first selective SM coupling of perfluoroarenes under relatively mild conditions (Scheme 21).[74] Interestingly, **48** (2.4 mol %) was also recently demonstrated to catalyze the almost quantitative SM coupling of chlorobenzene with phenylboronic acid in 16 h in refluxing toluene with 3 equiv of KOt-Bu as base.[75] Stoichiometric reactions of **48** with perfluoro-,[74] polyfluoro-[76] and chloroarenes[75] always yielded complexes of the type *trans*-[Ni(IiPr)$_2$(Ar)X]. These results are in agreement with Cavell's synthesis of [Ni(tmiy)$_2$(o-tolyl)Br] (**39**) from the oxidative addition of 2-bromotoluene to Ni^0(tmiy)$_2$ (*vide supra*),[66] and contrast with Matsubara's[32,34] and Louie's[33] syntheses of the T-shaped species [Ni(IMes)$_2$Cl] (**11a**) and [Ni(IPr)$_2$Cl] (**11b**) from the reactions of aryl chlorides with the corresponding zerovalent complexes **10a,b** (see Scheme 9). They suggest that Ni(0)/Ni(II) catalytic cycles could occur with small NHCs, whereas Ni(I)/Ni(III) cycles would be more likely with more sterically demanding NHCs.

Well-Defined Ni(NHC) Complexes with Multidentate NHCs. Multidentate chelate Ni(NHC) complexes were also employed for SM coupling (Chart 4). This often resulted in good activities with relatively low precatalyst loadings, albeit the use of harsher conditions and/or additional triphenylphosphine was generally required. For instance, the cationic tetradentate NCCN-complexes **21a–c** (see Chart 2) catalyzed the coupling of phenylboronic acid with *para*-substituted aryl iodides, bromides, and chlorides at catalyst loadings of 1 to 3 mol %.[77,78] However, except for activated aryl bromides, the addition of 1–2 equiv of triphenylphosphine, relative to the nickel precursor, was crucial in order to obtain good yields of the coupled products.

In comparison, the pyridine-bridged CNC-systems **25**,[46,79] **49**, and **50**[80] catalyze the SM coupling of a wider range of substrates, and most importantly, allow one to avoid the addition of PPh$_3$ in most cases. These systems, that have initially been applied to the coupling of simple bromo- and chloroarenes with aryl/alkenylboronic acids (typically with 1 mol % of precatalyst and K$_3$PO$_4$ (2 equiv) as base at 100 °C in s-BuOH),[46,79,80a] were later used with more challenging electrophiles such as aryl/alkenyl tosylates, and aryl mesylates (typically with 5 mol % of precatalyst and K$_3$PO$_4$ (2–3 equiv) as base at 120 °C in DME or dioxane).[80b] Interestingly comparative studies between complexes **49**, possessing six-membered metalacycles, and complexes **50**, possessing five-membered metalacycles, showed a better activity with the most rigid systems for aryl halides, and a better activity with the less rigid systems for aryl tosylates and mesylates. This observation plausibly indicates that the rate-determining step would be different for the reactions of aryl halides and aryl tosylates/mesylates.[80]

Scheme 22. Formation of (Hetero)Aryl-Substituted Anthracene Derivatives with 27b[82]

Reactivity: OPiv ~ OC(O)NEt$_2$ > OC(O)Ph ~ OC(O)Et > OC(O)Me ~ OC(O)^{i}Pr >> OC(O)Mes >> OC(O)Bn
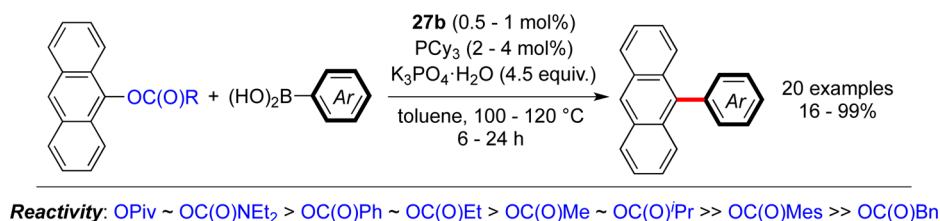
Scheme 23. SM Coupling of Aryl Fluorides with 53[85]
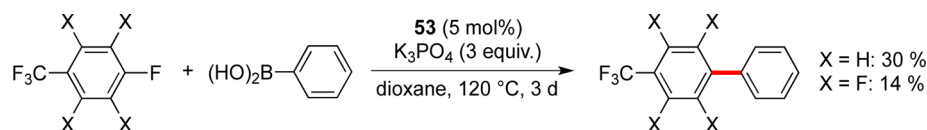
Scheme 24. Ni(NHC)-Catalyzed MH Coupling[79,85,89]
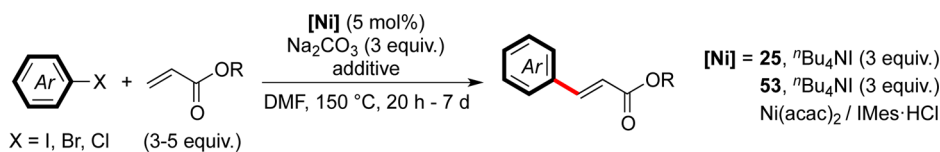
Scheme 25. Negishi Cross-Coupling Catalyzed by 21a, 29b, and 32a[49,92]
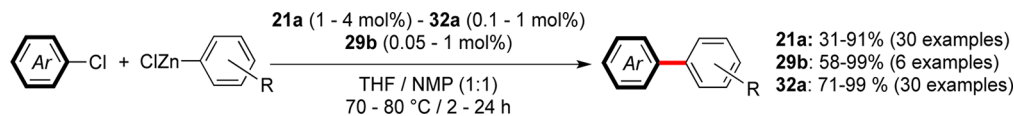
Later studies in the design of appropriate ligands showed that the benzimidazolinylidene derivative **27b** (see Chart 2) also allows the use of aryl tosylates and mesylates as coupling partners (typically with 2 mol % of **27b**, 10−20 mol % of PPh$_3$, and K$_3$PO$_4$ as base at 100 °C in dioxane),[81] as well as that of anthracenyl carboxylates to form (hetero)aryl-substituted anthracene derivatives (with a slightly lower catalyst loading, Scheme 22),[82] though the use of additional phosphine was required in these cases.

Other chelate complexes such as the *bis*-bidentate CP- or CN-complexes **51**[83] and **52**[84] also displayed good activities for the coupling of a few de-, un-, and activated aryl bromides and chlorides with 1 to 3 mol % of the precatalyst. However, such complexes still suffer from the requirement of an excess of triphenylphosphine (2 equiv/Ni) to observe optimal yields. It is noteworthy that complex **53**[85] also allowed the coupling of a couple of aryl fluorides, though relatively harsh conditions were required (Scheme 23). Importantly, this study pointed out the necessity of performing blank tests, as aryl iodides and bromides could be coupled in the absence of **53** in otherwise unchanged conditions (with lower yields though than in its presence). As observed earlier by Leadbeater et al.,[86] sub ppm levels of Pd found in commercial bases are likely to be responsible for catalyzing the reaction in these cases.

Finally, as observed in KTC coupling, the homobimetallic complex **32a** (see Chart 2) was one of the most active complexes for the SM coupling of aryl chlorides and bromides, probably due to a bimetallic cooperative effect.[52] Thus, precatalyst loadings as low as 0.04 mol % for aryl bromides and as low as 0.2 mol % for aryl chlorides could be used with very good efficiency and applicability (21 examples, 78−99%). In addition, as for KTC coupling, the catalytic system tolerates hindered substrates and is selective in the presence of other functional groups such as ketones, aldehydes and nitriles. However, the major drawback of this catalyst was, again, the requirement of additional triphenylphosphine (up to 5 equivalents relative to nickel!).

4. MIZOROKI−HECK COUPLING

Ni(NHC) catalysts have scarcely been applied to Mizoroki−Heck[13e,58a,87,88] (MH) coupling, and only a few examples with the use of acrylates as the sole olefinic substrates have been reported. Moreover, harsh reaction conditions were required to obtain reasonable yields of the *trans*-cross-coupling product (Scheme 24).[79,85,89]

Inamoto's in situ generated catalytic system from Ni(acac)$_2$/IMes·HCl was the first reported example.[89] It allowed the efficient coupling of aryl iodides and bromides with acrylates with yields ranging from 65 to 91% in only 20 h (Scheme 24). Interestingly, the long induction periods observed with the latter system, as well as with the CNC-pincer complex **25**, and the total inhibition of the reaction in the presence of mercury suggested the participation of a heterogeneous nickel(0) catalyst in both cases.[79] Nevertheless, **25** behaved differently from the in situ system and allowed the coupling of activated aryl chlorides, though the required reaction times were much longer (3−5 days), and an iodide salt was required.[79] Finally, the more recent cationic complex **53** proved to be the least active.[85]

5. NEGISHI COUPLING

Ni(NHC) systems have rarely been applied in Negishi coupling,[13e,58a,90,91] and to the best of our knowledge, only a couple of examples describing the use of well-defined Ni(NHC) complexes for the coupling of aryl chlorides have been reported.

Scheme 26. Homocoupling of Aryl Bromides Catalyzed by Complexes 54 and 55[95,96]
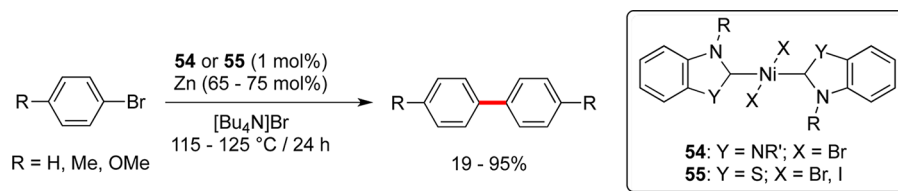
Scheme 27. Homocoupling of Aryl Chlorides and Fluorides Catalyzed by 56[97]
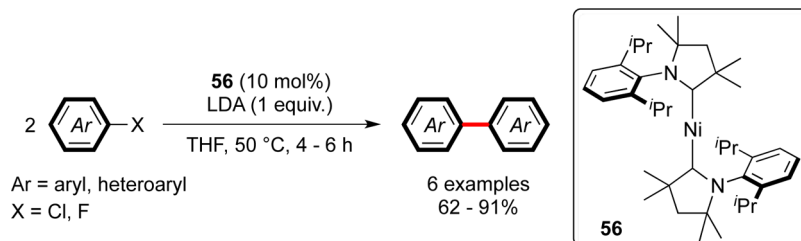
The NCCN-tetracoordinated complex **21a** and the versatile bimetallic complex **32a** (see Chart 2) were shown to catalyze the Negishi coupling of a variety of unactivated aryl chlorides, heteroaryl chlorides, aryl dichlorides, and vinyl chlorides under mild conditions (Scheme 25).[92] Both complexes were found to be highly efficient, but the binuclear complex **32a** shows higher activities than **21a** with all aryl chlorides. Again, bimetallic cooperativity was proposed to be responsible for the higher activity of **32a** (see Scheme 14).

The structurally related CNN- and CNP-chelate complexes **29a−c** (see Chart 2) were also shown to be highly active for the Negishi coupling of some activated and unactivated aryl chlorides with *p*-tolylzinc chloride under similar reaction conditions.[49] Among these, **29b** exhibited the highest catalytic activity and allowed catalyst loadings as low as 0.05 mol % for a few substrates (Scheme 25).

6. ULLMANN COUPLING

The timeless Ullmann homocoupling reaction[93,94] has also seen only a small number of successful Ni(NHC)-based catalysts. The reported examples concern the exclusive use of monodentate *bis*-NHC complexes of nickel. Whereas 1 mol % of the nickel(II) complexes **54**[95] and **55**[96] in the presence of a large excess of Zn powder allowed the coupling of simple aryl bromides in molten [Bu₄N]Br at 125 °C (Scheme 26), employing the zerovalent nickel complex **56** bearing a cyclic (alkyl)(amino)carbene (cAAC) ligand in the presence of 1 equiv of LDA resulted in more interesting activity: the more challenging aryl chlorides and fluorides could be coupled under milder reaction conditions (Scheme 27).[97] Unfortunately, this latter methodology suffers from high catalyst loadings.

7. OTHER CROSS-COUPLINGS

Alternatives to organomagnesium, -boron, and -zinc cross-coupling agents with Ni(NHC) catalysts have received very little attention. We are thus aware of only two reports, which are already dated. In 2006, a Ni(acac)₂/IPr·HCl (1:2) combination was demonstrated by Schneider and Fort to provide, with a loading of 5 mol %, an efficient catalyst for the cross-coupling of aryl bromides with organomanganese reagents under very mild conditions (Scheme 28).[98] Interestingly, the procedure tolerates a relatively large variety of functional groups and works well with

Scheme 28. Other Cross-Coupling Methodologies to Form Biaryl Compounds[98,99]
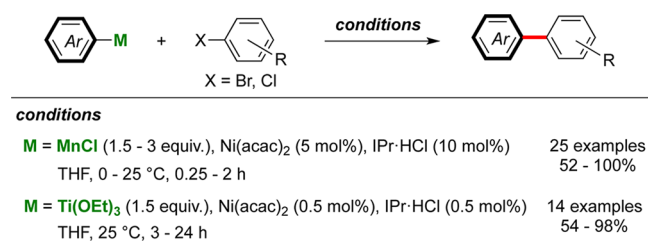
electron-deficient and electron-rich aryl bromides, as well as with sterically hindered ones. It is however less active with aryl chlorides, and electron-rich aryl chlorides notably gave poor results. One year later, Knochel et al. reported that a similar combination of Ni(acac)₂/IPr·HCl, in a 1:1 ratio though, constituted an efficient catalyst for the cross-coupling of aryl titanium(IV) alkoxides and aryl halides (Scheme 28).[99] The reaction works well with various functionalized aryl bromides and chlorides, but the phosphine ligand *tris*(2,4,6-trimethoxyphenyl)phosphine, in a 1:2 ratio, gave superior results with electron-rich substrates. A much lower catalyst loading is required in this reaction (0.5 mol %) as compared to the previous one. It is astonishing that despite their interesting performances, these two reports have not been followed by any other examples.

Other alternatives to traditional cross-coupling reactions involve the use of other electrophiles to the traditional organo halides or pseudohalides, such as organo chalcogenide compounds. In spite of the seminal publications of Wenkert[100] and Takei,[101] this has also received very little attention, and to our knowledge, there are only a couple of such examples.

The first one demonstrates that the use of suitable trialkylphosphines or NHC ligands turned the Wenkert arylation of thiophene into a superior and scalable synthetic method.[102] Thus, the use of Ni(acac)₂/IMes·HCl or IPr·HCl combinations in a 1:2.5 ratio or of NiCl₂(PR₃)₂ (PR₃ = PCy₃ or PBu₃) allowed the selective syntheses of (E,E)-1,4-diaryl-1,3-butadienes by the coupling of thiophene with aryl Grignard reagents in fair to good yields (Scheme 29).

A related C−O arylation of 2,3-dihydrofurans with arylmagnesium bromides in the presence of Ni(COD)₂/SIPr·HCl (1:1) as catalyst and of LiCl as additive was recently

Scheme 29. Ni(NHC)-Catalyzed Wenkert Arylation of Thiophene[102]
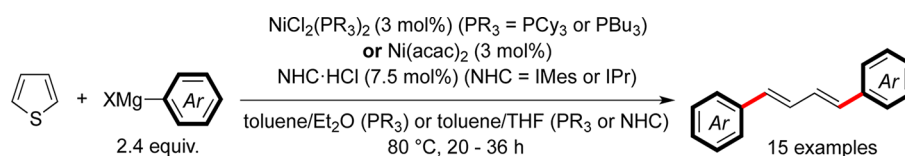
Scheme 30. C−O Arylation of 2,3-Dihydrofuranes[103]
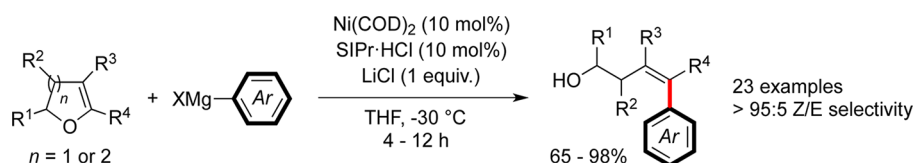
Scheme 31. Proposed Mechanism for the C−O Arylation of 2,3-Dihydrofuranes[103]
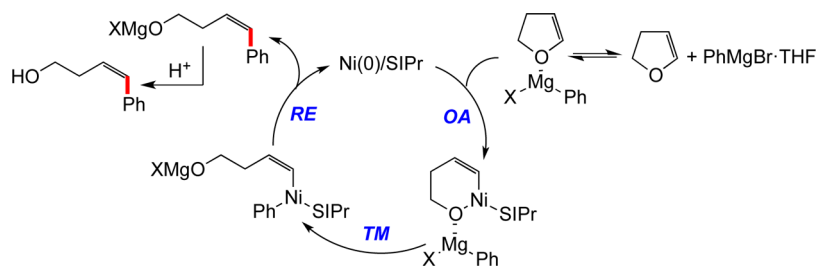
Scheme 32. Alkenylative Cross-Coupling of Alkyl Aryl Sulfides[104]
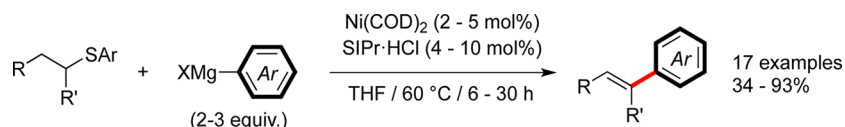

discovered.[103] Remarkably, the reactions proceeded at low temperature, allowing the presence of sensitive functional groups for the highly efficient and selective preparation of (Z)-homoallylic alcohols (Scheme 30). Regarding the mechanism, the stoichiometric reaction of dihydrofurane with Ni(COD)$_2$, SIPr·HCl, and LiCl in THF-d_8 at −30 °C did not result in oxidative addition of the C−O bond onto the Ni(0)/SIPr species, even after prolonged reaction times. In sharp contrast, the addition of phenylmagnesium bromide to this reaction mixture resulted in rapid formation of the expected coupling product. On the basis of these observations, the authors suggested a Lewis acid-aided oxidative addition of the C−O bond onto the Ni(0)/SIPr active species takes place before rapid transmetalation and reductive elimination (Scheme 31).

The last example is a remarkable Ni(COD)$_2$/SIPr·HCl (1:2)-catalyzed dehydrogenative coupling of alkyl aryl sulfides with aryl magnesium bromides, that gives access to a variety of olefinic compounds in good yields under fairly mild conditions (Scheme 32).[104] A plausible mechanism, based on experimental results, computational studies, and related literature, which justifies the requirement of 2 equiv of aryl Grignard reagent, was proposed by the authors.

8. C−C BOND FORMATION *VIA* C−H BOND FUNCTIONALIZATION

The use of Ni(NHC) systems for the functionalization of C−H bonds has up to now mainly involved in situ generated catalytic systems for the addition of C−H bonds onto unsaturated substrates.

An earlier example in this domain came again from Cavell's group, who described the catalytic annulation of N-butenyl- or N-pentenyl-substituted imidazolium and thioazolium salts in the presence of a Ni(COD)$_2$/NHC (1:2) catalytic system (NHC = IPr, SIPr, IMes or SIMes) (Scheme 33).[105] Most probably, the

Scheme 33. Annulation of N-Butenyl- or N-Pentenyl-Substituted Azolium Salts[105a]
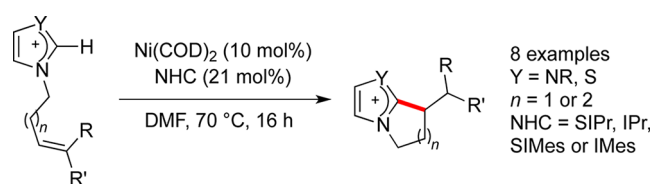
reaction proceeds through C−H oxidative addition to Ni(0)[105c] followed by intramolecular insertion of an N−alkenyl bond into the Ni−hydride bond to afford a carbene−alkyl−nickelacycle, which then gives the fused-ring products after reductive elimination.

An intermolecular version of this reaction was later reported by Hiyama et al., who described a Ni(COD)$_2$/IMes (1:1)-catalyzed hydroheteroarylation of vinylarenes that selectively affords 1-aryl-1-heteroarylethane compounds (Scheme 34).[106] Interestingly, the Ni(COD)$_2$/IMes catalytic system showed a wide tolerance for both vinylarenes (which could contain both electron-rich and electron-poor substituents) and heteroarenes (including indoles, benzimidazole, (benz)oxazole, benzothia-

Scheme 34. Hydroheteroarylation of Vinylarenes[106,107]

a: E = C(CO₂Me), C(COMe), C(CN), N
Y = NMe, O, S
18 examples, 41 - 100%

b: E = N, Y = NR
15 examples, 50 - 99%

16 examples
55 - 99%
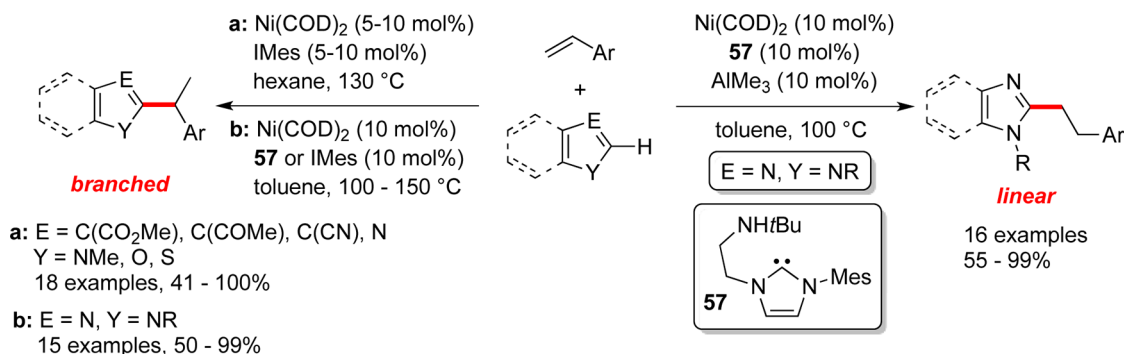
Scheme 35. C4-Alkylation[109] or -Alkenylation[111] of Pyridines and C6-Alkylation of 2-Pyridones[110]

a: R² = H, 14 examples
**b:** R¹ = R² = Pr, 10 examples

17 examples
45 - 95%
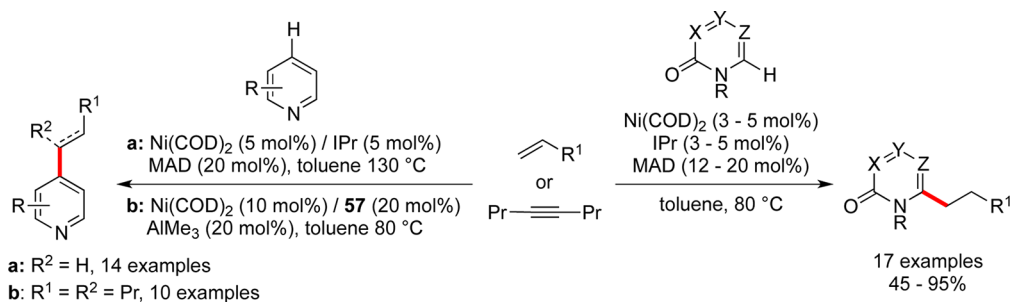
zole, and benzofuran). The proposed mechanism was similar to that of Cavell's intramolecular reaction with azolium salts and included initial oxidative addition of an heteroaryl−H bond to a Ni(0)/IMes species, followed by hydronickelation of the vinylarene and reductive elimination of the 1,1-diarylethane. Deuterium labeling experiments suggested that all steps, except the reductive elimination, were reversible.

A related catalytic system consisting of Ni(COD)₂ and of the amino-NHC ligand **57** in a 1:1 ratio was recently shown to similarly catalyze the hydroalkenylation of benzimidazole derivatives with various electron-rich, -neutral, and -poor styrenes to give 1-aryl-1-heteroarylethanes (Scheme 34).[107] Addition of AlMe₃ as a cocatalyst induced a cooperative effect that allowed complete reversal of the regioselectivity of the reaction to give the linear isomers (Scheme 34). Mechanistic investigations by ¹H NMR and X-ray crystallography indicated the formation of a Lewis pair adduct, in which AlMe₃ is datively coordinated to the benzimidazole nitrogen. The latter would impose a steric control that would lead to the 1-aryl-2-heteroarylethane compounds.[107]

A similar Lewis acid-driven regioselective switch was recently applied with a Ni(COD)₂/NHC (1:1)−AlMe₃ (NHC = IMes or IPr) cooperative catalytic system to the 1,2- or 1,3-hydroheteroarylation of allylarenes.[108] Remarkably, the formation of the branched product (in the absence of AlMe₃) yielded the 1,3-addition product, resulting from a tandem C−H bond functionalization/alkene isomerization process.

Ni(NHC)/Lewis acid cooperative catalysis was also used for the selective hydro-alkenylation or -alkynylation of pyridines and pyridones. Thus, the use of a Ni(COD)₂/IPr (1:1) catalyst in combination with the very bulky Lewis acid MAD allowed the C4-alkylation of pyridines,[109] as well as the C6-alkylation of 2-pyridones[110] (Scheme 35). Use of a Ni(COD)₂/**57** (1:2) catalyst in combination with AlMe₃, for its part, allowed the C4-alkenylation of pyridines with 4-octyne (Scheme 35).[111] In the
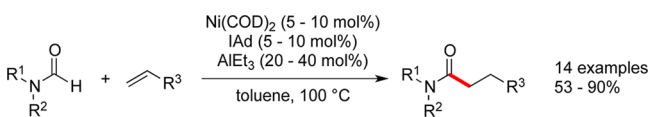
latter case, after reaction of Ni(COD)₂, **57** and AlMe₃, an aluminum N-adduct of a η²-pyridine-nickel(0) complex **58** was isolated (Scheme 36), which proved to be catalytically active for

Scheme 36. Pyridine Alkenylation Intermediate Complex 58[111]
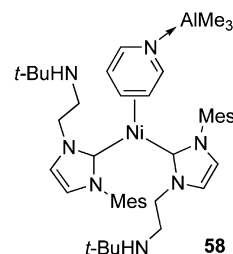
the alkenylation of pyridine: this supports a bimetallic catalysis mechanism. In the proposed mechanisms,[109−111] such η¹,η²-substrate Ni(0)−Al(III) intermediates would precede the C−H bond oxidative addition step, which would then be followed by alkene or alkyne insertion into the Ni−H bond and reductive elimination of the coupling product.

A last example of Ni(NHC)/Al cooperative catalysis concerned the regioselective hydrocarbamoylation of 1-alkenes. Thus, in the presence of a Ni(COD)₂/IAd (1:1) catalyst in combination with AlEt₃, various N-alkyl-substituted formamides and 1-alkenes could be coupled to afford selectively linear alkanamides in good yields (Scheme 37).[112] A limitation of this methodology is the use of N-aryl-substituted formamides, for which the reaction was sluggish.

Related hydrocarbonylation reactions of alkenes could also be achieved in the absence of a Lewis acid cocatalyst. Thus, an intramolecular alkene hydroacylation could be achieved in the presence of a Ni(COD)₂/I*t*Bu (1:1) catalyst with 2-allyl- and 2-homoallylbenzaldehydes to furnish indanone and tetralone

Scheme 37. Regioselective Hydrocarbamoylation of 1-Alkenes[112]

Ni(COD)$_2$ (5 - 10 mol%)
IAd (5 - 10 mol%)
AlEt$_3$ (20 - 40 mol%)
toluene, 100 °C

14 examples
53 - 90%

Scheme 39. Tail-To-Tail Hydroalkenylation of Vinylarenes with 1-Alkenes[114]

Ni(COD)$_2$ / IPr (5 mol%)
n-octene (10 mol%)
NEt$_3$ (30 mol%)
p-anisaldehyde (5 mol%)
Et$_3$SiOTf (10 mol%)
toluene, rt

(3 equiv.)
R = Ar, alkyl

Major   *minor*
13 examples, 37 - 95%

derivatives in good to excellent yields (Scheme 38).[113] Remarkably, an enal-coordinated complex **59a** and a dimeric oxanickelacycle **59b** could be isolated and were demonstrated to participate in the hydroacylation reaction, as evidenced by the transformation of **59a** into **59b**, and that of **59b** into the corresponding indanone under both stoichiometric and catalytic conditions (probably via β-H-elimination to yield an alkyl–nickel–hydride ketone complex and reductive elimination, though this was not stated in the report) (Scheme 38).

The first highly selective intermolecular tail-to-tail hetero-hydroalkenylation of vinylarenes with unactivated α-olefins has been reported.[114] In the presence of a Ni(IPr) hydride derivative of type "[(IPr)NiH]OTf" — in situ generated via a Ni(IPr)-mediated alkene/aldehyde/silyltriflate coupling[115] — branched 1,1-disubstituted olefins were predominantly obtained, the only notable byproduct being the homo tail-to-tail 1,1-disubstituted alkene from the vinylarene (Scheme 39). The same catalytic system also proved efficient in the head-to-tail hydroalkenylation of vinylsilanes with α-olefins.[116]

α-Olefins were also shown to add on isocyanates in the presence of a Ni(COD)$_2$/IPr (1:1) catalyst to give acrylamides in which the C−C bond has formed selectively at the tail position of the 1-alkene (Scheme 40).[117] The predominant formation of the 1,1-disubstituted olefins was attributed to steric interactions between a putative azanickelacyclopentanone intermediate and the IPr ligand.
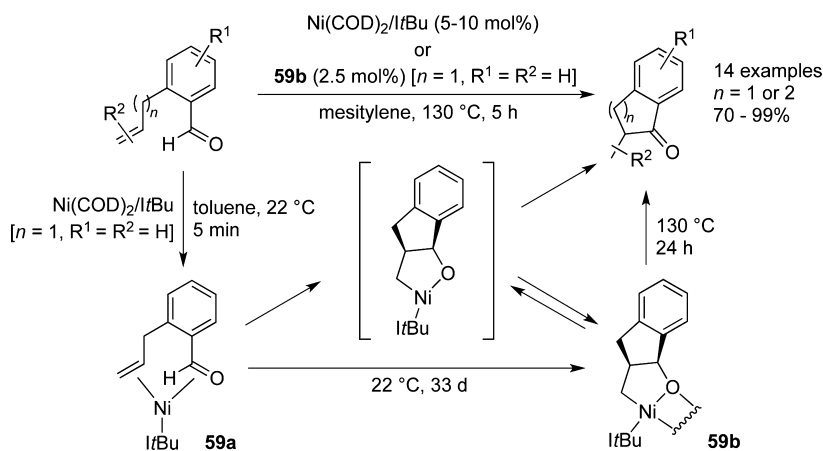
Very recently, Kurahashi and Matsubara developed a remarkable direct coupling of alcohols and alkynes.[118] The reaction yields allylic alcohols without use of any additive such as a reductant or an oxidant (Scheme 41) and thus constitutes an advantageous alternative to the well-known nickel-catalyzed reductive coupling of alkynes and aldehydes in the presence of organosilyl reagents.[11a] Of note, this atom-economical coupling can be applied for the conversion of various benzylic and aliphatic alcohols to the corresponding allylic alcohols in good to moderate yields.
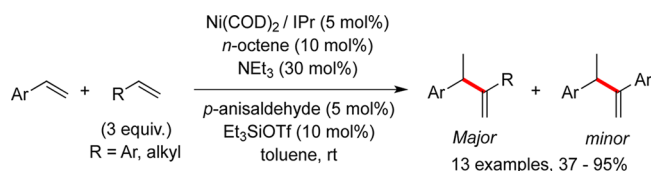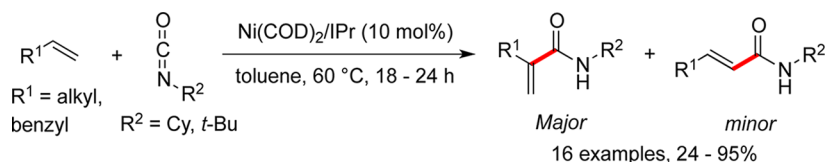
On the basis of (i) the known propensity of aldehydes, alkynes, and Ni(0) to form oxanickelacycles by oxidative cyclization[11a] and (ii) the results of a deuterium labeling experiment conducted with α,α-dideuteriobenzyl alcohol and 7-tetradecyne, which resulted in the formation of the corresponding allylic alcohol with 92% deuterium at the olefinic position and of cis-7-tetradecene in 11% yield with 99% deuterium at the olefinic position as a minor product, the authors proposed the mechanism depicted in Scheme 42. In this mechanism, 7-tetradecyne, which is present in slight excess as compared to the deuterated alcohol, would first act as an hydrogen scavenger to yield deuterio-cis-7-tetradecene and a catalytic amount of α-deuteriobenzaldehyde (induction step). The latter would then participate in the formation of the reactive oxanickelacycle through oxidative cyclization with the alkyne and Ni(0) (catalytic process). In a next step, another molecule of α,α-dideuteriobenzyl alcohol would then protonate the oxanickelacycle with its hydroxy hydrogen atom to afford an acyclic intermediate. Subsequent β-H elimination would then afford: (i) a nickel-deuterio intermediate, which will provide the allylic alcohol and regenerate Ni(0) by reductive elimination, and (ii) α-deuteriobenzaldehyde, which will further react with Ni(0) and an another molecule of 7-tetradecyne to form a new oxanickelacyle.

A few other C−C bond forming reactions via C−H bond activation involve well-defined Ni(II)-NHC complexes.

The oldest example, reported in 2007 by Matsubara et al., involves the monodentate NHC-containing complex **8** (see Chart 1) in an extremely rare example of Ni(NHC)-catalyzed C−H/C−X coupling reaction, namely, the α-arylation of acyclic ketones. Thus, in the presence of 10 mol % of **8** and of NaOtBu as a base, a few propiophenone derivatives could be converted to the corresponding α-aryl ketone in reasonable to high yields by reaction with several aryl bromides and chlorides (Scheme 43).[119] Despite these encouraging results, the second (and last!)

Scheme 38. Catalytic Intramolecular Hydroacylation of Alkenes and Isolated Intermediates[113]

Ni(COD)$_2$/ItBu (5-10 mol%)
or
59b (2.5 mol%) [n = 1, R^1 = R^2 = H]
mesitylene, 130 °C, 5 h

14 examples
n = 1 or 2
70 - 99%

Ni(COD)$_2$/ItBu | toluene, 22 °C
[n = 1, R^1 = R^2 = H] | 5 min

130 °C
24 h

22 °C, 33 d

59a   **59b**

Scheme 40. Hydroalkenylation of Isocyanates with 1-Alkenes[117]

Scheme 41. Direct Coupling of Alcohols and Alkynes[118]
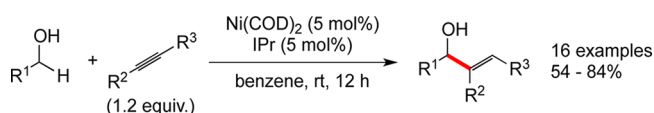
Scheme 42. Plausible Mechanism of the Direct Coupling of Alcohols and Alkynes[118]
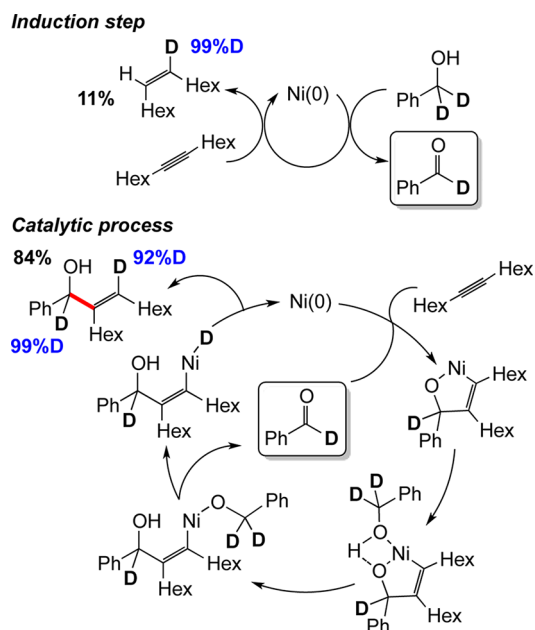
such example only appeared in the literature this year. Thus, the Cp-complex **18b** (see Chart 1), which bears the same IPr ligand as **8**, was also shown to catalyze the α-arylation of acyclic ketones (Scheme 43).[120] Gratifyingly, in this case, the catalyst loading could be lowered down to 1 mol %, and dialkyl ketones could be used in addition to propiophenone derivatives. One drawback, however, was the absence of reaction with aryl chlorides. Interestingly, a mechanistic investigation suggested a radical pathway, though a nickel C-bound ketone enolate generated by base-promoted metalation, may also be involved.[121]

A series of bifunctional Ni(NHC) precatalysts, containing a Lewis acidic metal center and a Lewis basic amido site have been designed for the base-free Michael reaction (the addition of a

nucleophile's C—H bond to an electrophilic olefin). Thus, complexes **60a–c** that bear bidentate amido-functionalized NHCs were shown to catalyze the Michael addition of β-dicarbonyl, β-diester, β-keto ester, and α-cyano ester compounds with α,β-unsaturated carbonyl and cyano compounds in air at room temperature in generally good to high yields (Scheme 44).[122]

Finally, a last example involving a bidentate Ni(NHC) is the Friedel–Crafts reaction of indoles with β-nitrostyrenes catalyzed by the pyridyl- and benzimidazole-functionalized complex **61** under very mild conditions (Scheme 45).[123]

9. MISCELLANEOUS C—C BOND FORMATION REACTIONS

In 2009, Navarro et al. described an anaerobic Ni(COD)$_2$/IPr·HCl (1:1)-catalyzed oxidation of secondary alcohols with chlorobenzene as oxidant.[124] Itami et al. concurrently described the use of a similar Ni(COD)$_2$/IPr·HCl (1:2) catalytic system for the addition of arylboronate esters to aldehydes and ketones to yield secondary and tertiary alcohols, respectively.[125] Consequently, these two groups later, and independently, reported an efficient domino oxidation–addition protocol for the synthesis of tertiary alcohols from primary[126] or secondary[127] alcohols and organoboronates (Scheme 46). Navarro's protocol is incompatible with primary alcohols, but Itami's allows a controlled sequential double oxidation-addition process from primary alcohols. The key of this remarkable reaction seems to be the use of an excess of arylboronate ester and cesium fluoride in a toluene/dioxane medium (Scheme 46).[126] This strategy notably allowed the one-pot synthesis of flumecinol, a hepatic microsomal enzyme reducer.

Finally, in a totally different context, the dinuclear complex **48** (see Scheme 21) has been shown to be able to activate not only C—F[74,76] and C—Cl[75] bonds but also C—C bonds.[128] Thus, the reaction of diphenylacetylene with biphenylene in the presence of 3 mol % of **48** led to the formation of diphenylphenanthrene by alkyne insertion into the strained C—C bond of biphenylene. The reaction is complete in only 19 min in benzene at 60 °C (Scheme 47).

10. CONCLUSION

Since the discovery of NHCs as powerful ligands for transition metal-catalyzed organic transformations, the field of nickel catalysis has increased exponentially. Over the last 15 years,

Scheme 43. α-Arylation of Acyclic Ketones Catalyzed by 8 and 18b[119,120]
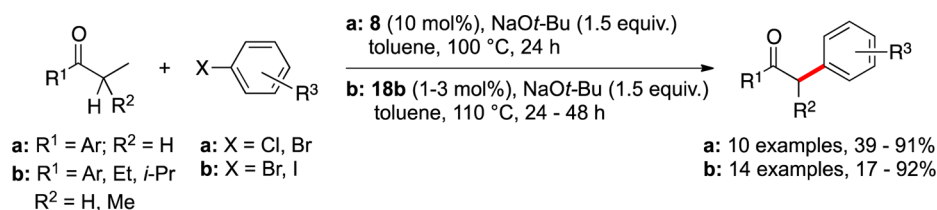
Scheme 44. Base-Free Michael Addition[122]
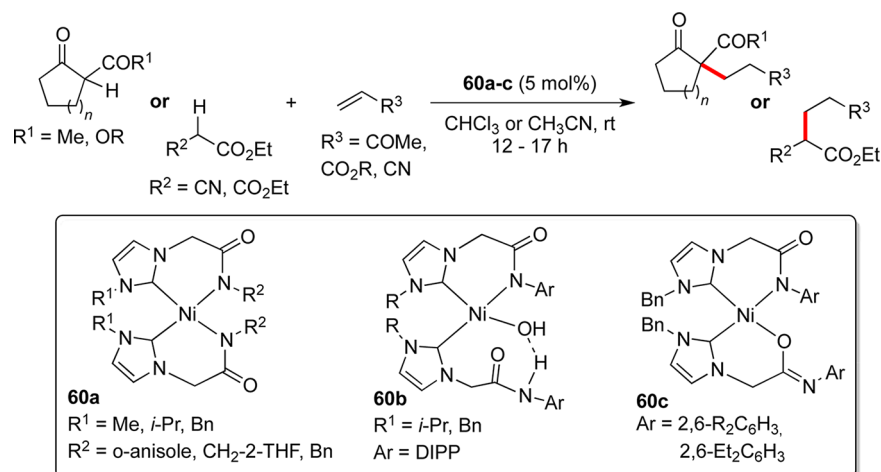
Scheme 45. Friedel−Crafts Alkylation of Indoles with β-Nitrostyrenes[123]
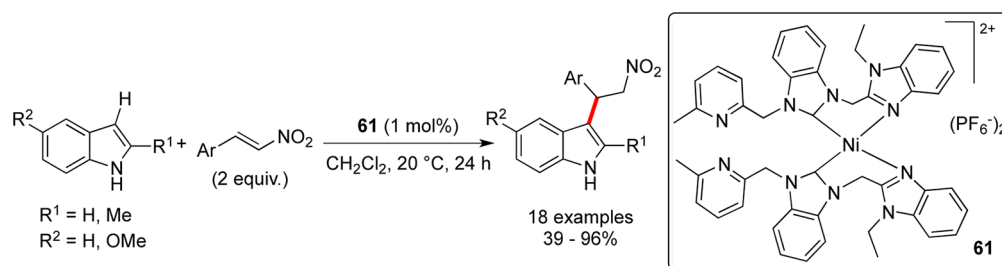
Scheme 46. Domino Synthesis of Tertiary Alcohols from Primary and Secondary Alcohols
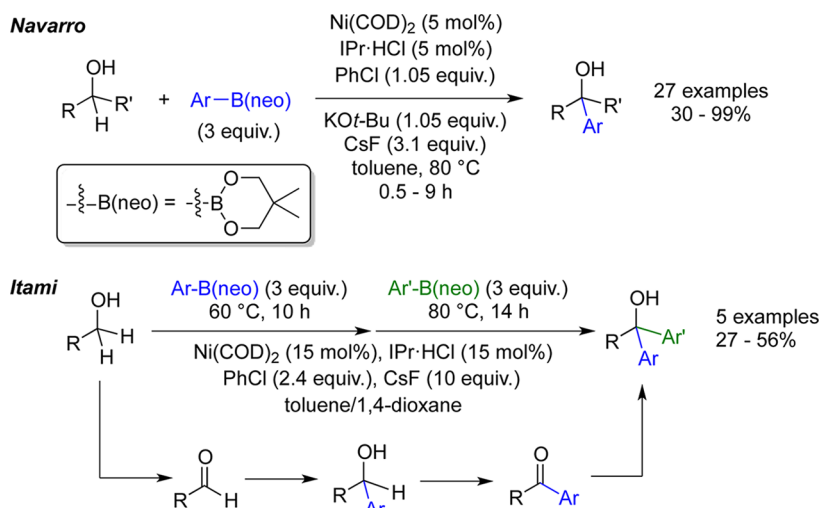
Scheme 47. Catalytic C−C Bond Formation via C−C bond Activation by 48[128]
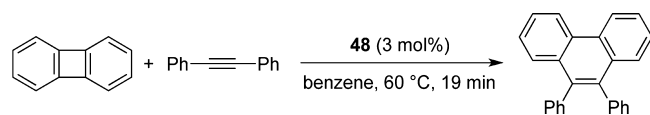
considerable efforts have been directed toward the development of Ni(NHC) systems as cheaper alternatives to noble metal-based catalysts. This review clearly demonstrates the developing potential and breath of application of these Ni(NHC) catalysts as

shown by the diversity of C−C bond-forming reactions described above.

It is not easy to summarize general trends in the catalysts and their associated ligands for all the reactions presented here—a large variety of reactions are catalyzed, and no general themes seem to emerge that cover all catalysis by Ni-NHC complexes. Nevertheless, while mechanistic studies are still in their infancy, the intermediacy of radical species that involve Ni(I) and Ni(III) appears to be important in some examples of Ni(NHC) catalysis, especially in cross-coupling reactions, where there is evidence of reversible shuttling between Ni(I) and Ni(III). In contrast, in the catalysis of C−H functionalization reactions, it appears that the

active species involve Ni(0): this is borne out by the frequent use of Ni(0) species, often Ni(COD)$_2$, together with NHC ligands, as catalytic precursors. Another general point is the extreme scarcity of metallic nickel being formed, even in reactions where it appears that Ni(0) species are involved—to our knowledge there have been only a couple of reports of metallic nickel being formed in these catalyzed reactions (see Mizoroki–Heck coupling). It thus appears that the overwhelming majority of these reactions involve genuine homogeneous catalysis.

Further contributions in metal complex and ligand design are still needed to broaden the scope and improve the yields of many of these reactions. While there have been some interesting ligands designed, the number of distinct NHC species used is not very high. This is not necessarily a disadvantage if the catalysts are efficient and effective, but this is not always the case with some of the catalysis described herein. Nevertheless, very significant progress has been made, with the long-term goal being the availability of systems that are not only inexpensive and versatile but also efficient tools for catalytic C–C bond formation. In a sense, having simple, readily available catalysts of good, though not excellent efficiency, which are effective in the catalytic transformation of a number of different substrates, is arguably better than using highly specific and expensive catalytic systems, with complicated ancillary ligand syntheses.

One major area where there has not been highly significant nickel(NHC) catalysis with respect to C–C bond formation is in the area of chiral induction and stereospecific bond formation. Much remains to be done in what is essentially a wide-open area. Nevertheless, based on the described and ongoing work, the future appears bright for nickel-NHC catalysts in general.

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Notes
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■ ABBREVIATIONS

Acac, acetylacetonate; COD, η^4-cyclooctadiene; Cp, η^5-cyclopentadienyl; Cp*, pentamethylcyclopentadienyl; DIPP, 2,6-diisopropylphenyl; DMF, dimethylformamide; IAd, 1,3-diadamantylimidazol-2-ylidene; ICy, 1,3-dicyclohexylimidazol-2-ylidene; I*i*Pr, 1,3-diisopropylimidazol-2-ylidene; IMes, 1,3-dimesitylimidazol-2-ylidene; IPr, 1,3-*bis*(2,6-diisopropylphenyl)-imidazol-2-ylidene; I*t*Bu, 1,3-di-*tert*-butylimidazol-2-ylidene; KTC, Kumada–Tamao–Corriu (coupling); LDA, lithium diisopropylamide; MAD, methylaluminum-*bis*(2,6-di-*tert*-butyl-4-methylphenoxide); Mes, 2,4,6-trimethylphenyl; NMP, *N*-Methyl-2-pyrrolidone; OA, oxidative addition; RE, reductive elimination; SIMes, 1,3-dimesitylimidazolidin-2-ylidene; SIPr, 1,3-*bis*(2,6-diisopropylphenyl)-imidazolidin-2-ylidene; SM, Suzuki–Miyaura (coupling); THF, tetrahydrofuran; TM, trans-metalation; tmiy, 1,3,4,5-tetramethylimidazol-2-ylidene; TOF, turnover frequency; TON, turnover number

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