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European Journal
of Organic Chemistry

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Recent Progress in Nickel-Catalyzed Biaryl Coupling

Junichiro Yamaguchi,*[a] Kei Muto,[a] and Kenichiro Itami*[a]

Nickel catalysis for biaryl coupling reactions has received significant attention as a less expensive and less toxic alternative to "standard" palladium catalysis. Here we describe recent developments in nickel-catalyzed biaryl coupling methodology, along with mechanistic studies and applications. In particular we focus on nickel-catalyzed coupling reactions in which "unreactive" bonds such as C–H, C–O, and C–C bonds are converted into biaryl moieties.

Introduction

Nickel-catalyzed cross-coupling reactions have recently been receiving significant attention from the synthetic community as a way to construct carbon–carbon bonds or carbon–heteroatom bonds, because nickel catalysts are less expensive and less toxic than palladium catalysts.[1] An epoch-making discovery by the groups of Kumada, Tamao, and Corriu opened up the field of modern cross-coupling.[2] In

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1972, they independently found that nickel complexes or salts can catalyze cross-coupling of Grignard reagents and aryl halides (C–M/C–X coupling; M = metal, X = halogen). On the basis of this discovery, cross-coupling methodology for organometallic reagents and organohalides in the presence of various transition metal catalysts has been developed.[3] So far, however, palladium still reigns as the most widely used transition metal for cross-coupling reactions, with nickel regarded as a "minor" metal.

Nickel and palladium, though, share common chemical features. Both metals, for example, belong to the d^{10} transition metal group, and can have oxidation numbers of 0 and +2 (in the case of nickel, oxidation numbers of +1 and +3 are also known). These features indicate that they should be amenable to general cross-coupling reactions, because

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Kenichiro Itami was born in Pittsburgh, USA (1971) and raised in Tokyo. Educated in chemistry at Kyoto University, Japan, under the guidance of Prof. Yoshihiko Ito, he received his Ph.D. in 1998. From 1997 to 1998 he was a predoctoral researcher in the group of Prof. Jan-E. Bäckvall at Uppsala University, Sweden. In the fall of 1998 he began his academic career at Kyoto University as an Assistant Professor (with Prof. Jun-ichi Yoshida). He moved to Nagoya University to become an Associate Professor (with Prof. Ryoji Noyori) in 2005 and was promoted to Full Professor in 2008. Representative awards include the German Innovation Award (2012), the Novartis–MIT Lectureship Award (2012), the Nozoe Memorial Award for Young Organic Chemists (2011), the Merck–Banyu Lectureship Award (2008), the Minister Award for Distinguished Young Scientists (2006), the Mitsui Chemicals Catalysis Science Award of Encouragement (2005), and the Chemical Society of Japan Award for Young Chemists (2005).

these reactions proceed through sequences of oxidative addition (oxidation change from 0 to +2), transmetalation, and reductive elimination (oxidation change from +2 to 0). Nickel, however, is more nucleophilic and smaller in atomic radius than palladium, so "unreactive" bonds such as C–H, C–O, and even C–C bonds can often undergo oxidative addition to nickel. Furthermore, as an alternative to the use of organometallic reagents (C–M bonds) or organohalides (C–X bonds) as cross-coupling partners, the use of more convenient partners such as esters (C–C bonds) in nickel-catalyzed cross-coupling has recently been attracting much attention from the synthetic chemistry community.

Here we describe recent developments in nickel-catalyzed biaryl coupling methodology, along with mechanistic studies and applications. In particular we focus on nickel-catalyzed coupling reactions in which "unreactive" bonds such as C–H, C–O, and C–C bonds are converted into biaryl moieties.

Ar–M/Ar–O Coupling

Cross-coupling reactions using metalloarenes as nucleophiles and phenol derivatives as electrophiles (Ar–M/Ar–O coupling; Ar = arenes and heteroarenes) have been reported in many instances. Because arenes containing C–O bonds (such as phenols and naphthols) are readily available and less expensive than their aryl halide counterparts, nickel-catalyzed Ar–M/Ar–O couplings have been attracting interest. Although aryl triflates (Ar–OTf) are generally inferior to aryl halides (Ar–X) in terms of reactivity, they were first found to be useful as coupling partners in transition-metal-catalyzed reactions because they have relatively "reactive" C–O bonds.[4] Later, biaryl couplings between metalloarenes and aryl sulfonates such as aryl tosylates (Ar–OTs)[5] and aryl mesylates (Ar–OMs)[6] were reported. Through extensive efforts, nickel-catalyzed cross-coupling reactions involving unconventional electrophilic coupling partners such as aryl carbonates and even aryl ethers have been made possible.

In 1979, Wenkert and co-workers reported nickel-catalyzed cross-coupling reactions involving Grignard reagents and aryl ethers rather than aryl halides (Ar–M/Ar–O coupling).[7] This pioneering work indicated that oxidative addition of C–O bonds to nickel(0) species can occur readily. However, this 1979 discovery was not followed by others until several decades later, when nickel-catalyzed cross-coupling reactions began to attract renewed attention.

In 2004, Dankwardt developed a Ni/PCy$_3$ (PCy$_3$ = tricyclohexylphosphane) catalytic system for cross-coupling between aryl Grignard reagents and aryl methyl ethers.[8] Several chemists later reported transformations of aromatic C–O bonds with the aid of the robust Ni/PCy$_3$ catalyst. In 2008, for example, Chatani and co-workers demonstrated nickel-catalyzed cross-couplings between aryl methyl ethers and aryl boronates.[9] Simultaneously, the groups of Garg and Shi also discovered similar types of coupling reactions.[10] Subsequently, aryl carbamates,[11] carbon-

ates,[11b,12] sulfamates,[11c,13] and even phenolate salts[14] were found to react with arylmetal reagents under similar conditions (Scheme 1).
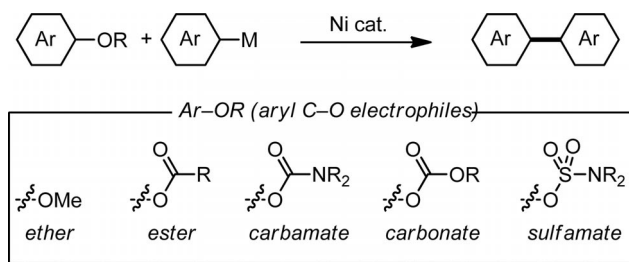
Scheme 1. Recently discovered modes of nickel-catalyzed cross-coupling between metalloarenes and aryl C–O electrophiles.

Aryl C–O bonds are stable under the general reaction conditions for cross-coupling between metalloarenes and aryl halides (Ar–M/Ar–X coupling), so orthogonal arylation strategies can lead to multiply arylated compounds (Scheme 2 and Schemes 3 and 4, below). Garg's group, for example, demonstrated the utility of nickel-catalyzed cross-coupling (Ar–B/Ar–O coupling) when combined with palladium-catalyzed Suzuki–Miyaura cross-coupling (Scheme 2).[10a] Treatment of 4-bromonaphthalen-1-yl pivalate (**1**) with indole-3-boronate **2** in the presence of a palladium catalyst afforded the corresponding coupling product **3** in 90% yield without the loss of the pivalate group. Subsequently, cross-coupling of **3** with phenylboronic acid under nickel catalysis conditions was performed to give triaryl product **4** in 88% yield.
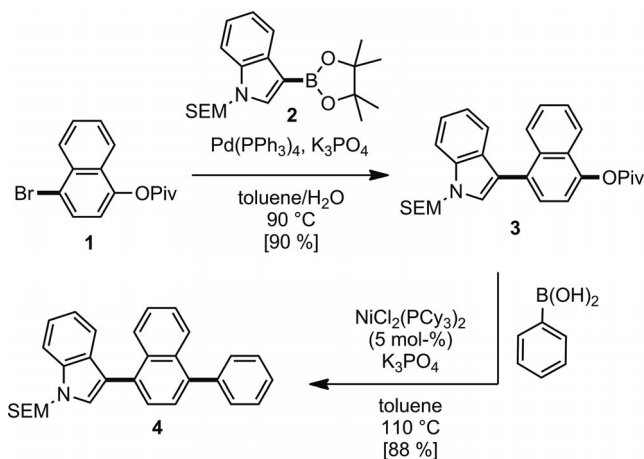

Scheme 2. Orthogonal arylation of 4-bromonaphthalen-1-yl pivalate (**1**).

Garg also achieved the concise synthesis of flurprofen (**9**), a well-known non-steroidal anti-inflammatory drug (NSAID), through nickel-catalyzed cross-coupling (Scheme 3).[11b,11f] Aryl iodide **6**, readily prepared from arylboronic acid **5** by Ritter fluorination[15] and *para*-selective iodination (48% over two steps), was coupled with methyl 2-chloropropanoate in the presence of a NiBr$_2$(bipy) (bipy = 2,2′-bipyridyl) catalyst and manganese metal to give sulfamate **7** in 70% yield. Treatment of **7** with phenylboronic acid in the presence of catalytic NiCl$_2$(PCy$_3$)$_2$, followed by

hydrolysis of methyl ester **8**, completed the synthesis of flurprofen (**9**) in 84 % yield over two steps. Although two types of nickel-catalyzed C–C bond formation are used in this synthesis, the sulfamate group did not disturb the nickel-catalyzed α-arylation step, but did react with phenylboronic acid when desired.
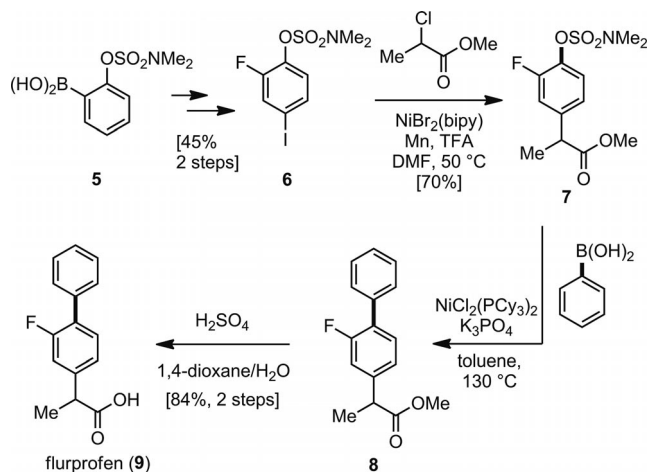
Scheme 3. Concise synthesis of flurprofen (**9**).

Shi's group demonstrated the synthetic utility of their own nickel-catalyzed Ar–B/Ar–O coupling methodology in a triaryl synthesis (Scheme 4).[10b] Treatment of aryl pivalate **10** with (p-methoxyphenyl)boroxin in the presence of catalytic $NiCl_2(PCy_3)_2$ furnished biphenyl **11** in 75 % yield. Baeyer–Villiger oxidation of **11**, followed by hydrolysis of the acetyl group and pivalation of the resulting hydroxy group, afforded aryl pivalate **12** in 62 % yield over three steps. The synthesis of triaryl **13** was completed by Ar–B/Ar–O cross-coupling of **12** with p-tolylboroxin under nickel catalysis conditions (64 % yield).
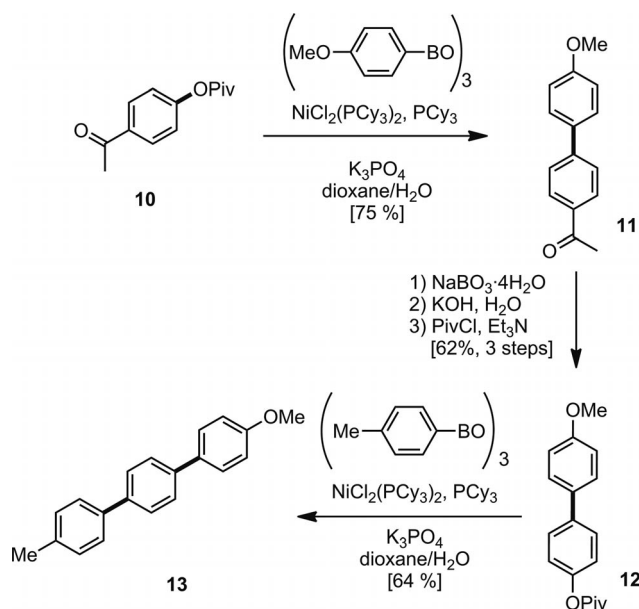

Scheme 4. Triaryl synthesis through nickel catalysis.

Direct C–H Coupling

Ar–H/Ar–X Coupling

Transition-metal-catalyzed direct C–H bond functionalization has been attracting increased attention in the context of streamlined chemical synthesis because carbon–carbon or carbon–heteroatom bonds can be derived from ubiquitous C–H bonds without the need for use of stoichiometric metal reagents.[16,17] In 2009, Itami's and Miura's groups independently reported the first nickel-catalyzed C–H arylations of azoles with aryl halides (see Schemes 5, 6 and 7, below).[18]
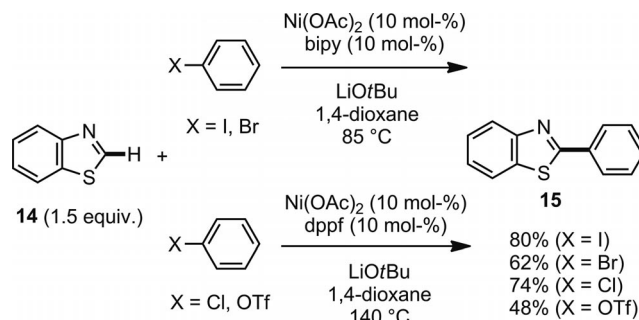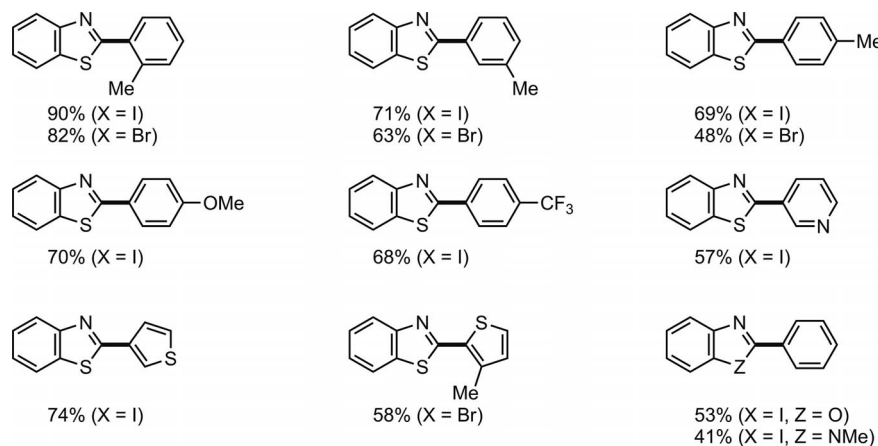

Scheme 5. Itami's nickel-catalyzed direct arylation of azoles with aryl halides and triflates.

Itami's group reported that 1,3-azoles can be cross-coupled with aryl iodides or bromides in the presence of $Ni(OAc)_2$/bipy catalyst and stoichiometric LiOtBu in 1,4-dioxane at 85 °C (see Schemes 5 and 6).[18a] Benzothiazole (**14**, 1.5 equiv.), for example, can be coupled with iodobenzene or bromobenzene under nickel catalysis conditions [$Ni(OAc)_2$/bipy] to afford 2-phenylbenzothiazole (**15**) in 80 % (X = I) and 62 % (X = Br) yields, respectively. On the other hand, 1,1′-bis(diphenylphosphanyl)ferrocene (dppf) is the most suitable ligand for the reactions using chlorobenzene and phenyl triflate, providing **15** in 74 % (X = Cl) and 48 % (X = OTf) yields, respectively (Scheme 5).
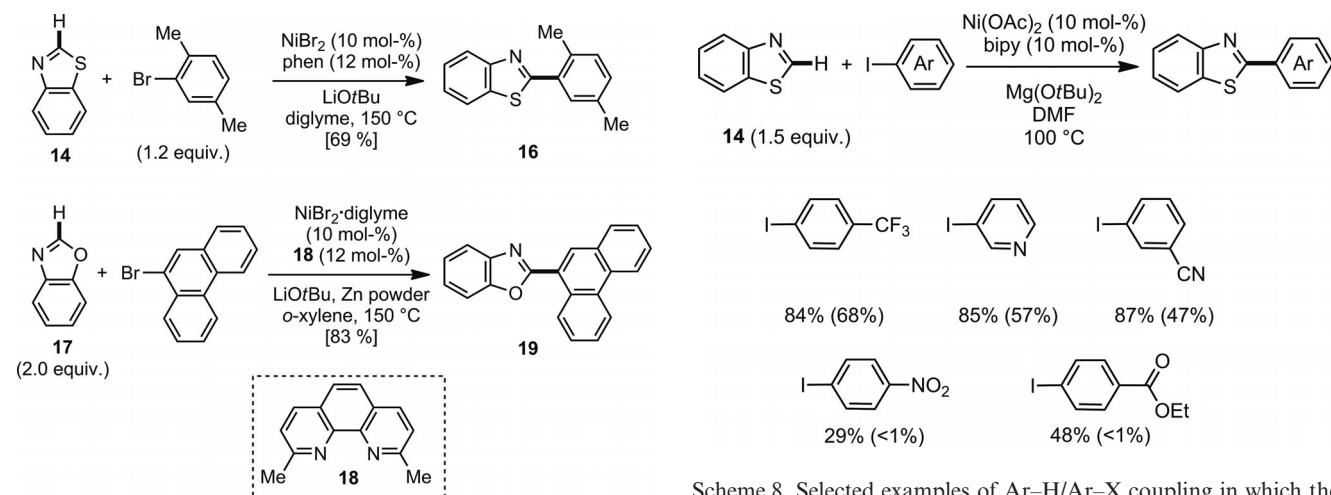
A number of structurally diverse 1,3-azoles and aryl halides are reactive under nickel catalysis conditions (Scheme 6). Benzothiazoles, benzoxazoles, benzimidazoles, oxazoles, and thiazoles can be arylated. Aryl halides substituted in their ortho-, meta-, and para-positions are viable substrates, as are both electron-rich and electron-deficient aryl halides. Additionally, heteroaryl halides such as thiophenes and pyridines can also be used.

At the same time, Miura also reported similar conditions for direct coupling between 1,3-(benzo)azoles and aryl bromides (Scheme 7).[18b] Various (benzo)azoles can be coupled with aryl bromides with the aid of $NiBr_2$/phen (phen = 1,10-phenanthroline) or $NiBr_2$/**18** as the catalyst and LiOtBu as the base in diglyme or o-xylene at 150 °C. ortho-Substituted bromoarenes are particularly suitable coupling partners, giving products such as **16** and **19** in excellent yields. Additionally, when benzoxazole (**17**) is used as a substrate, the addition of Zn powder is effective in increasing the yield of product, presumably by functioning as a reductant to produce an active Ni^0 species.

90% (X = I)
82% (X = Br)

71% (X = I)
63% (X = Br)

69% (X = I)
48% (X = Br)

70% (X = I)

68% (X = I)

57% (X = I)

74% (X = I)

58% (X = Br)

53% (X = I, Z = O)
41% (X = I, Z = NMe)

Scheme 6. Substrate scope of nickel-catalyzed C–H/C–X coupling.

Scheme 7. Miura's protocol for nickel-catalyzed heterobiaryl synthesis.

84% (68%)

85% (57%)

87% (47%)

29% (<1%)

48% (<1%)

Scheme 8. Selected examples of Ar–H/Ar–X coupling in which the Ni(OAc)$_2$/bipy/Mg(OtBu)$_2$/DMF system gives better results than the first-generation Ni(OAc)$_2$/bipy/LiOtBu/1,4-dioxane system. The yields obtained with the first-generation catalytic systems are shown in parentheses.

The studies discussed above clearly demonstrated the potential of nickel catalysis to allow rapid access to a range of 2-arylazoles. However, both nickel-catalyzed Ar–H/Ar–X coupling reactions require the use of LiOtBu; otherwise, the reaction does not proceed. In 2011, Itami's group reported a new protocol in which Mg(OtBu)$_2$ (in DMF) is employed as a base (Scheme 8).[19] As a result, two useful sets of coupling conditions based on the Ni(OAc)$_2$/bipy catalytic system were established. Whereas the LiOtBu/1,4-dioxane system generally works well for robust substrates, the Mg(OtBu)$_2$/DMF system is in many cases superior for substrates containing base-sensitive functional groups such as nitro and ester moieties. It is of note that Mg(OtBu)$_2$ is milder and also less expensive than LiOtBu.

Although the mechanisms of nickel-catalyzed arylations of azoles with aryl halides are not clear, a number of experiments are consistent with the proposed Ni^0/Ni^{II} catalytic cycle shown in Scheme 9. The proposed Ni^0/Ni^{II} redox catalysis consists of: 1) production of Ar–Ni–X (**A**) through oxidative addition of Ar–X to Ni^0, 2) azole nickelation to produce Ar–Ni–Het (**B**), and 3) reductive elimination, generating heterobiaryl product Het–Ar (**C**) and Ni^0. It is of

note that LiOtBu and Mg(OtBu)$_2$ most likely play a critical role in the azole nickelation step and are probably involved both in the product-generating catalytic cycle and in the generation of catalytically active Ni^0 species from Ni-(OAc)$_2$.

Nickel-catalyzed direct arylation can be applied to the synthesis of biologically active compounds (Scheme 10). With the Ni(OAc)$_2$/bipy system, the rapid synthesis of febuxostat (Uloric®, **22**), an inhibitor of xanthine oxidase developed by Teijin Pharma as a new drug for the treatment of gout and hyperuricemia, is possible. Thiazole **20** and iodoarene **21** undergo Ar–H/Ar–X coupling in 1,4-dioxane to furnish the corresponding coupling product. Subsequent treatment with CF$_3$CO$_2$H affords **22** in 62–67% overall yield. This methodology has also been implemented in the synthesis of tafamidis (Vyndaqel®, **25**, effective for the treatment of TTR amyloid polyneuropathy) and texaline (**28**, natural product with antitubercular activity).

Yamakawa and co-workers reported direct couplings of simple arenes and aryl halides in the presence of a nickel catalyst (Scheme 11).[20] With Cp$_2$Ni as a catalyst precursor

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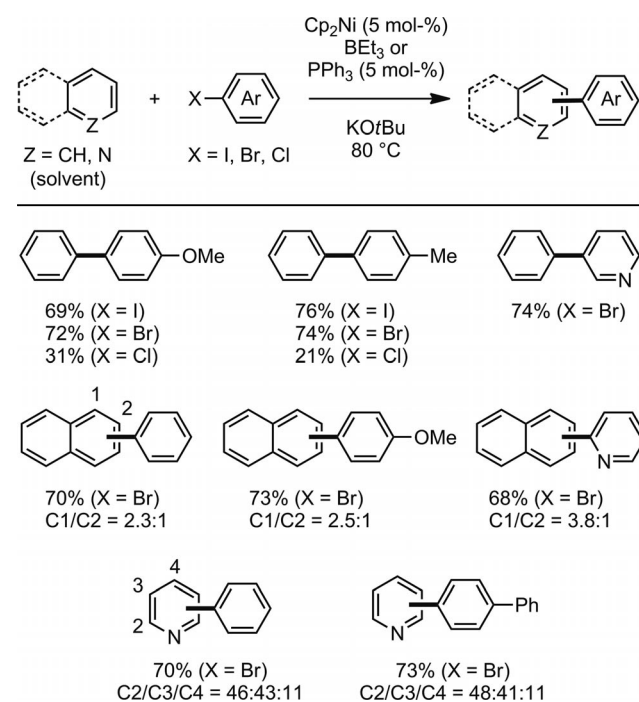*European Journal of Organic Chemistry*
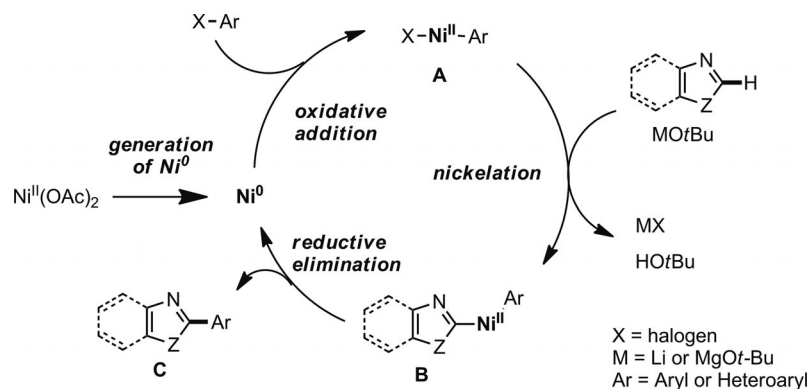
Scheme 9. Proposed mechanism for nickel-catalyzed heterobiaryl synthesis.
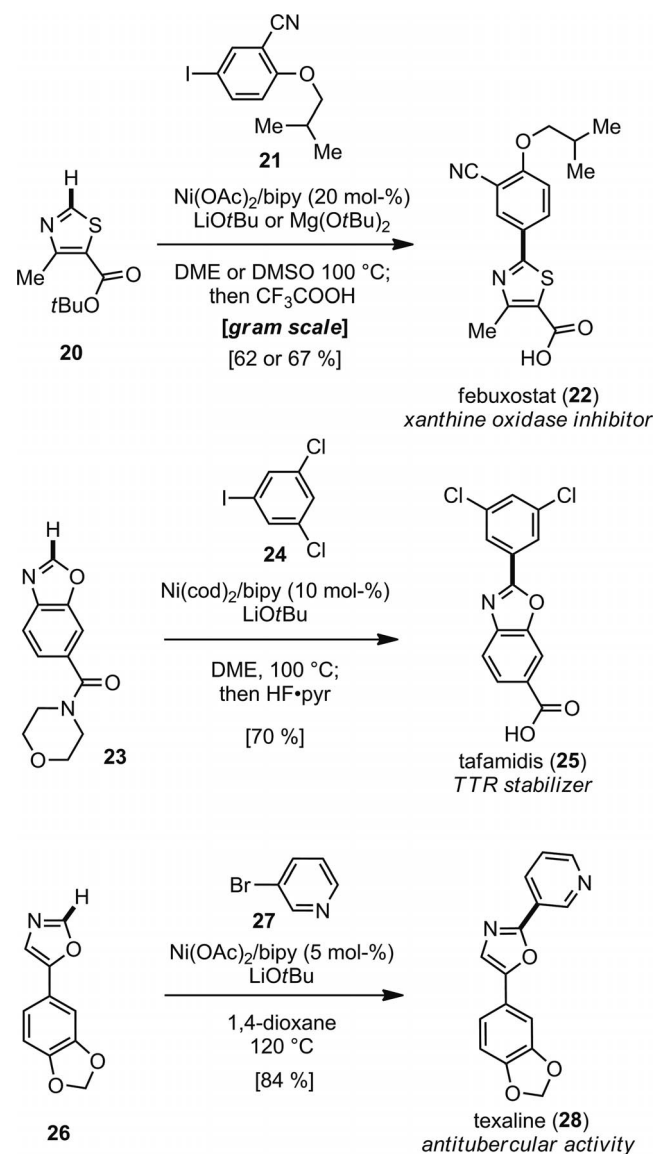
Scheme 10. Application to the synthesis of biologically active compounds.

haloarenes take place in moderate to good yields. Because these reactions produce regioisomers, however, their mechanisms are presumed to be a radical-type pathway.

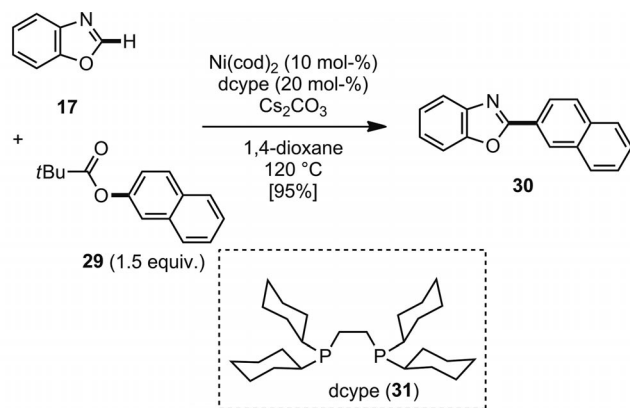Scheme 11. Yamakawa's nickel-catalyzed biaryl coupling method.

Ar–H/Ar–O Coupling

Nickel-catalyzed Ar–H/Ar–X coupling reactions between (hetero)arenes and aryl halides have been reported, but the requirement for the use of aryl halides as aryl electrophiles is still a drawback. Coupling arenes with phenol derivatives (Ar–H/Ar–O coupling) would be more advantageous because numerous phenols and their derivatives are commercially available and inexpensive.
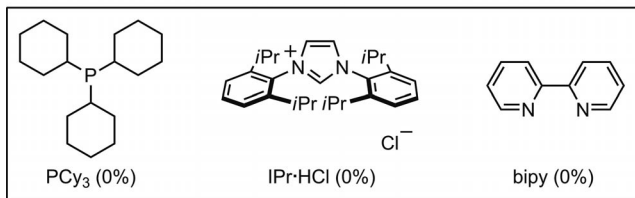
In 2012, Itami's group reported the first Ar–H/Ar–O coupling, with use of Ni(cod)$_2$/dcype [**31**, 1,2-bis(dicyclohexylphosphanyl)ethane] as the catalyst (Scheme 12).[21] In the presence of this catalyst and Cs$_2$CO$_3$ in 1,4-dioxane

and BEt$_3$ or Ph$_3$P as an additive, direct couplings of benzene, naphthalene, and pyridine (used as solvent) with

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Scheme 12. Itami's nickel-catalyzed Ar–H/Ar–O coupling.

at 120 °C, benzoxazole (**17**) can be coupled with naphthalen-2-yl pivalate (**29**) to produce the coupling product **30** in excellent yield. Notably, the reaction displays dramatic ligand effects; the use of dcype (**31**) is essential. PCy$_3$ and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr·HCl), which are known to be able to activate aryl C–O bonds, for example, are entirely ineffective in Ar–H/Ar–O coupling. Bipyridine, a standard ligand for Ar–H/Ar–X coupling as mentioned above, is also not effective.

The Ni(cod)$_2$/dcype catalyst is active for the coupling of other phenol derivatives such as carbamates, carbonates, sulfamates, triflates, tosylates, and mesylates (80–99% yields, Scheme 13). When naphthalene-1-yl, pyridin-3-yl, and quinolin-6-yl pivalates are used, coupling products are obtained in excellent yields, whereas phenyl derivatives react better when triflates are used instead of pivalates. This protocol is also effective for the direct arylation of oxazoles, benzothiazoles, and thiazoles (Scheme 13).

Syntheses based on more complex phenol derivatives such as estrone and quinine triflates are also possible with this catalyst (Scheme 14). Coupling between estrone triflate (**32**) and 5-phenyloxazole (**33**) proceeds smoothly in the presence of Ni(cod)$_2$/dcype to afford heteroarylated estrone
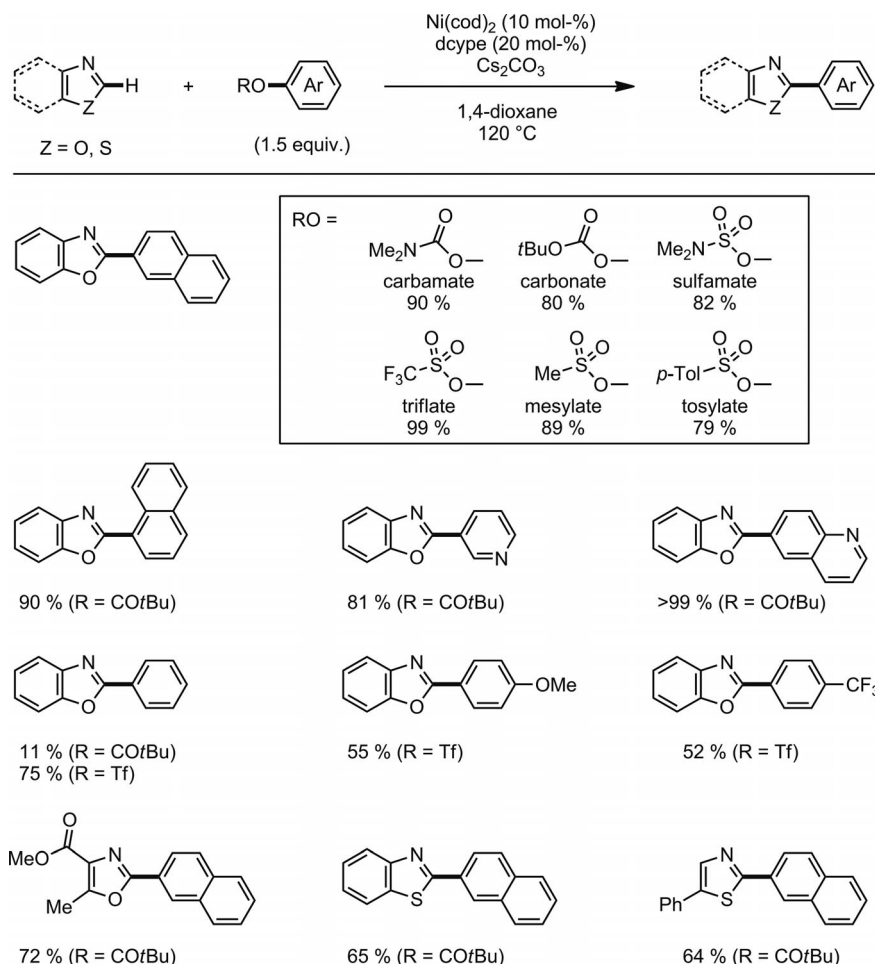
Scheme 13. Nickel-catalyzed Ar–H/Ar–O coupling of azoles and phenol derivatives.

34 in 52% yield. The Ar–H/Ar–O coupling between quinine triflate (**35**) and benzoxazole (**17**) also occurs, to give the quinine-benzoxazole hybrid molecule **36**, albeit with somewhat lower efficiency. Notably, the hydroxy, amino, and olefinic functionalities are tolerated under the coupling conditions.
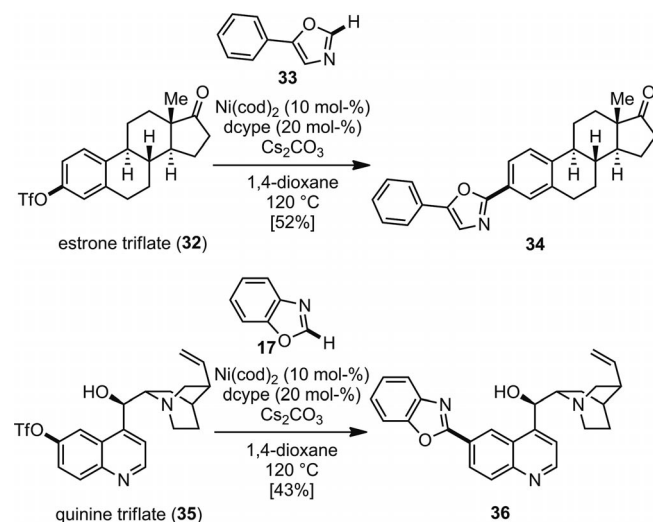

Scheme 14. Nickel-catalyzed arylation of complex steroid and alkaloid scaffolds.

Nickel-catalyzed Ar–H/Ar–O coupling thus has the potential to be extremely useful as an inexpensive coupling method for construction of heterobiaryls, despite having limitations in the scope of heteroarenes.
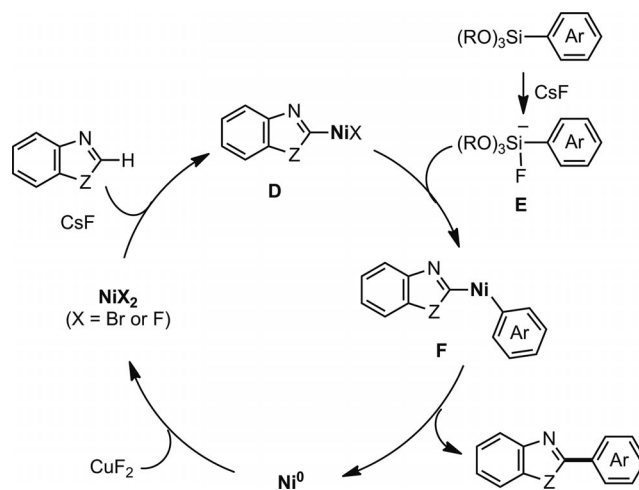
Ar–H/Ar–M Coupling

Nickel-catalyzed oxidative coupling reactions between arenes and metalloarenes (Ar–H/Ar–M; M = B, Si, Mg, Zn) have also been reported recently. In a first report describing Ar–H/Ar–M couplings of arenes, Miura's group disclosed that 1,3-azoles can be arylated at C2 with trimethoxyarylsilanes as the organometallic coupling partners (Scheme 15).[22] In the presence of catalytic amounts of NiBr$_2$·diglyme/bipy and stoichiometric amounts of CsF and CuF$_2$, various 1,3-azoles such as benzoxazoles, oxazoles, benzothiazoles, benzimidazoles, and 1,3,4-oxadiazoles cross-couple with arylsilanes to afford 2-arylazoles. Classifying this C–H coupling into a reaction type is difficult, because oxidative C–H arylation with organosilanes is rare even with other transition metal catalysts.[23]

A plausible mechanism for the Ar–H/Ar–Si coupling is illustrated in Scheme 16. Initial nickelation of the heteroarene substrate, through the action of basic CsF, could afford the Het–Ni–X intermediate **D**. Subsequent transmetalation with aryl or alkenyl silicate **E** (generated in situ with CsF), and an ensuing reductive elimination from intermediate **F**, could furnish the biaryl product and the Ni^0 species. Reoxidation of Ni^0 with CuF$_2$ would regenerate the divalent NiX$_2$ to complete the catalytic cycle.
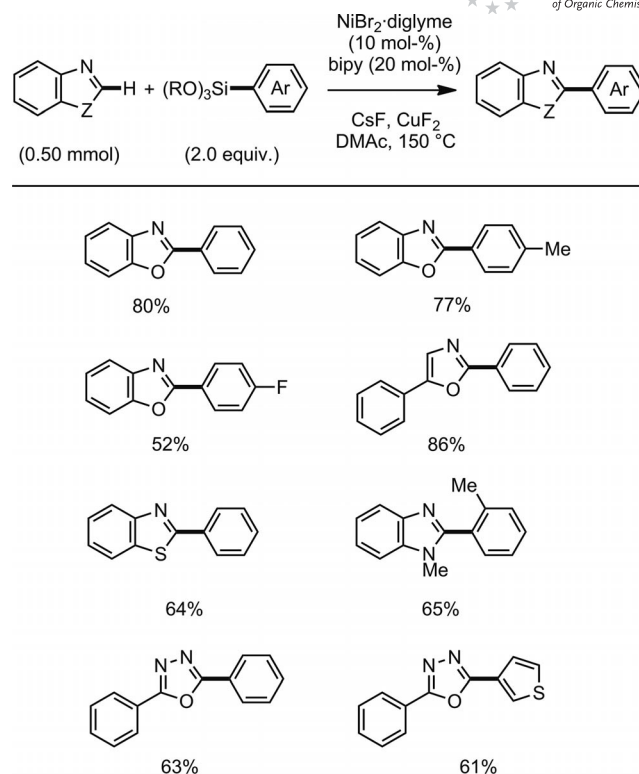
Scheme 15. Miura's nickel-catalyzed Ar–H/Ar–Si couplings of azoles and trimethoxyarylsilanes.


Scheme 16. A plausible mechanism for nickel-catalyzed Ar–H/Ar–Si coupling.

Oxidative C–H coupling requires a stoichiometric amount of oxidant, for which oxygen (air) is ideal. In 2010, Miura discovered nickel-catalyzed C–H arylations of azoles with arylboronic acids (Ar–H/Ar–B) that operate under air (Scheme 17).[24] Treatment of benzoxazole (**17**) with *m*-tolylboronic acid in the presence of catalytic NiBr$_2$/bipy and K$_3$PO$_4$ in DMAc at 120 °C affords the corresponding coupling product **37** in 76% yield. With 5-phenyloxazole (**33**), a Ni/phen/NaO*t*Bu catalytic system gives the coupling product **38** in a better yield.

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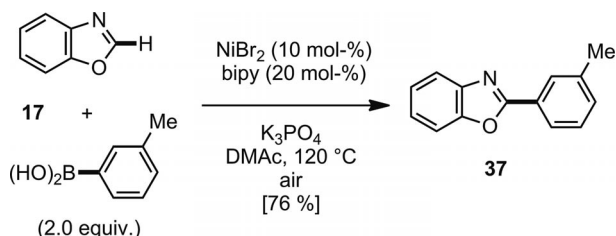
Scheme 17. Miura's nickel-catalyzed Ar–H/Ar–B couplings of azoles and arylboronic acids.

Additionally, a one-pot borylation/arylation sequence based on this nickel-catalyzed direct coupling has also been accomplished (Scheme 18). After conversion of hexafluoro-*m*-xylene into the corresponding arylboronate **39** by Hartwig–Miyaura borylation,[25] **39** can be directly coupled with oxadiazole **40** (Ar–H/Ar–M coupling) under nickel catalysis conditions to afford 2-arylated azole **41** in 73% overall yield.
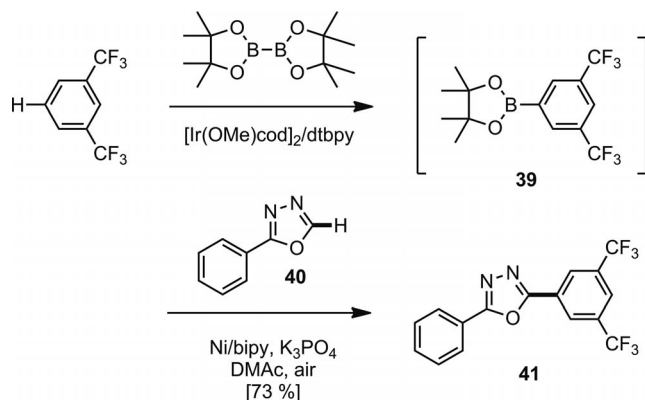
Scheme 18. A one-pot sequence of C–H borylation and Ar–H/Ar–B coupling.

The stoichiometric reaction with isolated [PhNiCl(bipy)] complex **42** (Scheme 19) sheds light on the reaction mechanism. Upon exposure of **42** to a mixture of 5-phenyloxazole (**33**), NaOtBu, and phen in DMAc under nitrogen, product **43** is detected in 27% GC yield. This result suggests that the active species in the catalytic cycle is [Ar–Ni^{II}–X] (X = bromide or alkoxide).

Miura proposed a reaction mechanism for the Ar–H/Ar–B coupling that is in agreement with the above results (Scheme 20). Initial transmetalation of NiX$_2$ with arylboronic acid, or its borate generated by the action of base (K$_3$PO$_4$ or NaOtBu), could afford arylnickel intermediate **G**, which is the equivalent of **42** in Scheme 19. Subsequent
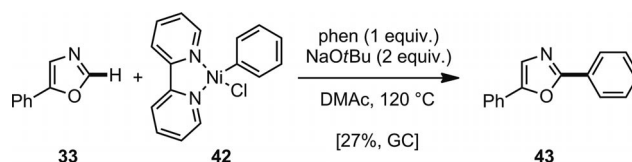

Scheme 19. Stoichiometric reaction between an azole and the [PhNiCl(bipy)] complex.

base-assisted nickelation of the azole partner followed by reductive elimination from intermediate **H** could lead to the desired biaryl product along with Ni^0. Reoxidation with molecular oxygen would complete the catalytic cycle. However, other possibilities such as pathways involving alternative reaction orders (e.g., azole then boronic acid) cannot be ruled out at this stage.
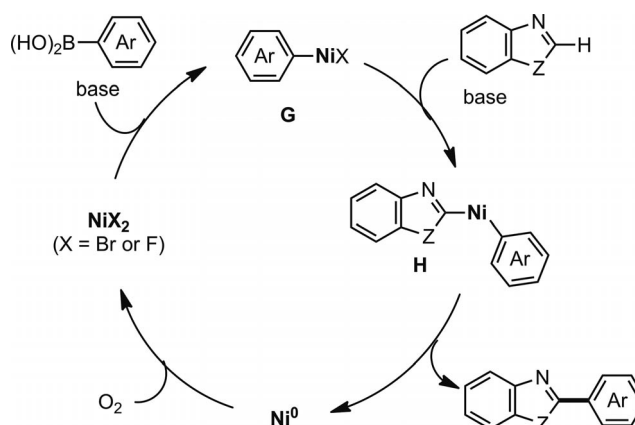
Scheme 20. A possible catalytic cycle for direct arylation of 1,3-azoles with arylboronic acids.
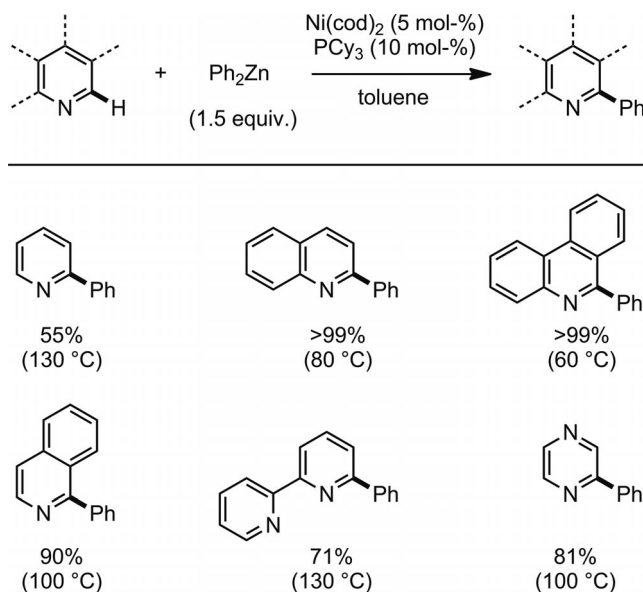
In 2011, nickel-catalyzed C–H arylations of azoles (purine) with aryl Grignard reagents (Ar–H/Ar–Mg coupling) were reported by Qu and Gao (Scheme 21).[26] Various purine derivatives can be coupled with aryl Grignard reagents in the presence of NiCl$_2$(dppp) at room temperature.
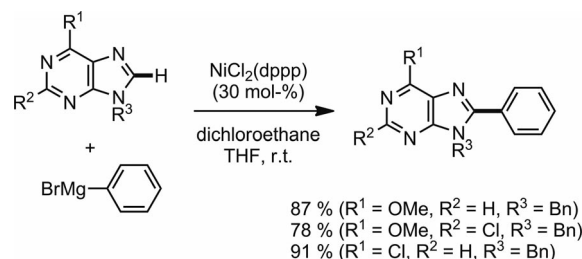
Scheme 21. Ni-catalyzed Ar–H/Ar–Mg couplings.

Ar–H/Ar–M couplings of azoles, which are electron-rich heteroarenes, with organometallic reagents are described above. Electron-deficient heteroarenes such as azines can also be arylated directly with organometallic reagents. Although nickel-catalyzed C–H arylations of azines were reported by Yamakawa and co-workers as an early example in this field (see Scheme 11), they require excess amounts of azines and the regioselectivity is difficult to control.

In 2009, Chatani, Tobisu, and co-workers demonstrated nickel-catalyzed Ar–H/Ar–M couplings of azines and diarylzinc reagents (Scheme 22).[27] With use of a diarylzinc reagent as an aryl nucleophile and Ni(cod)₂/PCy₃ as a catalyst, various azines such as pyridines, quinolines, phenanthridines, and pyrazines can be arylated regioselectively at C2 in good to excellent yields.


Scheme 22. Chatani's nickel-catalyzed direct arylations of azines with diarylzinc reagents.

Chatani and Tobisu extensively investigated the substrate scope and mechanisms of these Ar–H/Ar–M coupling reactions (see Schemes 23, 24 and 25, below).[28] To this end, various quinolines bearing functional groups at C6 were treated with diphenylzinc reagents under the standard conditions at elevated temperature (Scheme 23). Reactive functional groups such as chloro, methoxy, amine, and ester groups are tolerated, to afford the corresponding coupling products in good to excellent yields.

The mechanisms of these coupling reactions are assumed to consist of addition of the aryl nucleophile under nickel catalysis conditions, followed by in situ rearomatization to form the coupling product. To support this hypothesis, the rearomatization reaction was specifically studied by Chatani's group (Scheme 24). Treatment of 2-phenyl-1,2-dihydroquinoline (**44**, prepared by nucleophilic addition of phenyllithium onto quinoline) with diphenylzinc at room temperature produces rearomatized product **46** without nickel catalyst in 75% yield. According to this result, loss of the C2-hydrogen atom of **44** proceeds through the intermediacy of an organozinc species such as **45**.

On the basis of this investigation, a reaction mechanism for the nickel-catalyzed C–H arylation of azines with diarylzinc has been proposed (Scheme 25). Nickel(0) species **I** could initially react with diarylzinc–pyridine adduct **J** to form azanickelacyclopropane **K**. An intramolecular aryl transfer could afford a nickel species **L**, which could subsequently liberate Ni⁰ catalyst **I** along with zinc amide **M**
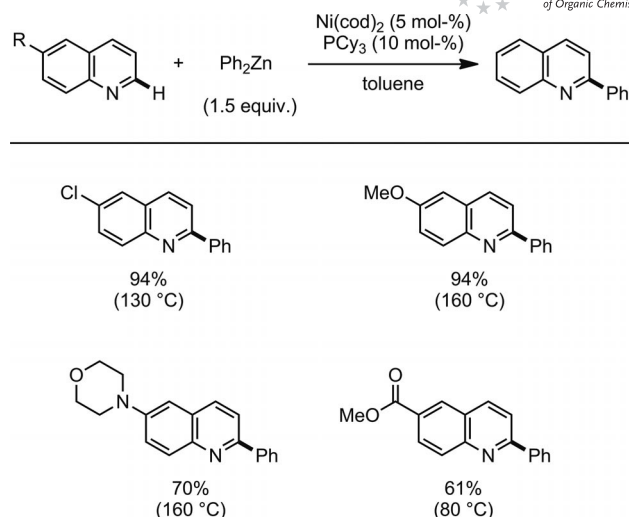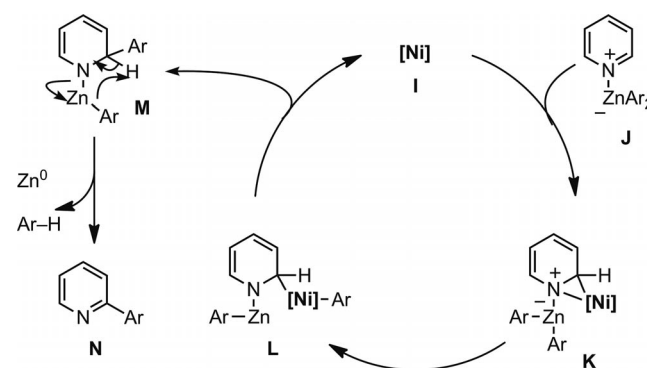

Scheme 23. Functional group tolerance of nickel-catalyzed C–H arylations of quinolines.
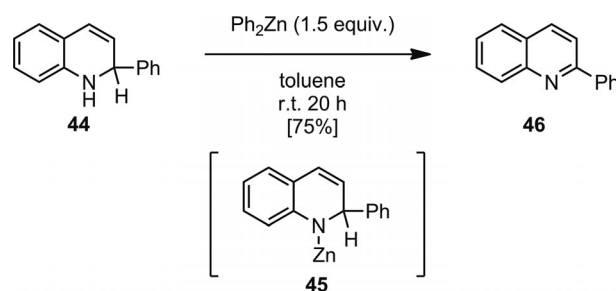
Scheme 24. Rearomatization of dihydroquinoline with Ph₂Zn.

by reductive elimination. The zinc amide species **M** should then undergo rapid oxidative rearomatization, leading to arylated product **N**.

Scheme 25. A plausible reaction mechanism for nickel-catalyzed direct couplings of azines with diarylzinc reagents.

In 2011, Chatani and Tobisu also discovered regioselective C–H arylations of acridines at C4 (Scheme 26).[29] In the presence of a catalytic amount of Ni(cod)₂, SIPr·HCl [1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride], and a stoichiometric amount of NaOtBu, acridines cross-couple with excess amounts of diarylzinc reagents to afford C4-arylated products regioselectively.

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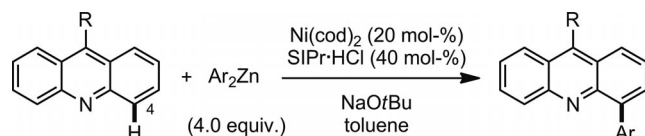
Scheme 26. Nickel-catalyzed C–H arylations of acridines with di-arylzinc regents.

Decarbonylative C–H Coupling

Aroyl compounds such as aromatic carboxylic acids, acid chlorides, anhydrides, and esters have received significant attention as useful aryl sources in metal-catalyzed decarboxylative or decarbonylative biaryl coupling reactions.[30] In comparison with typical cross-coupling partners such as metalloarenes or haloarenes, aroyl compounds are usually inexpensive, stable, and readily available. Typically, these types of coupling reactions are accomplished with palladium catalysts for decarboxylative coupling[31] and rhodium catalysts for decarbonylative coupling;[32] only a few reports of nickel-mediated (stoichiometric nickel) decarbonylative biaryl formation are known.[33] Although decarboxylative and decarbonylative C–H couplings between (hetero)arenes and aroyl compounds have recently received much attention in the context of "green" methods, these reactions also require expensive palladium and rhodium catalysts.[34,35]

In 2012, Itami's group discovered the first nickel-catalyzed decarbonylative C–H biaryl couplings of azoles and aryl esters (Scheme 27).[36] In the presence of a catalytic system similar to that used in the previously mentioned nickel-catalyzed Ar–H/Ar–O coupling (see Schemes 12 and 13), a decarbonylative C–H coupling between benzoxazole (**17**) and phenyl thiophenecarboxylate (**47**) proceeds smoothly to furnish the corresponding coupling product **48** in 96% yield. Various esters, particularly heteroaromatic esters such as furans, thiophenes, thiazoles, pyridines, and quinolones, can be used in this reaction to give the corresponding coupling products.
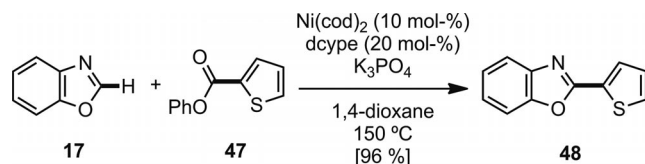
Scheme 27. Itami's nickel-catalyzed decarbonylative C–H coupling.

A plausible mechanism for these decarbonylative C–H arylation reactions is shown in Scheme 28. It is proposed that the reactions involve Ni^0/Ni^{II} redox catalysis, consisting of: i) oxidative addition of the ester C–O bond in **O** to Ni^0, ii) CO migration onto the nickel center to produce an $Ar–Ni^{II}(CO)_{n+1}–OPh$ species (**P**, $n = 0$ or 1), iii) C–H nickelation of azole (Het–H) with $Ar–Ni^{II}(CO)_{n+1}–OPh$ (**Q**) to generate $Ar–Ni^{II}(CO)_{n+1}–Het$ (**R**), and iv) reductive elimination to release the coupling product Het–Ar (**S**) and to generate a $Ni^0(CO)_{n+1}$ species (**T**). Although a seemingly

inactive nickel dicarbonyl complex **T** would be produced after two turnovers, the active Ni^0 catalyst could be regenerated by thermal extrusion of CO from **T**.
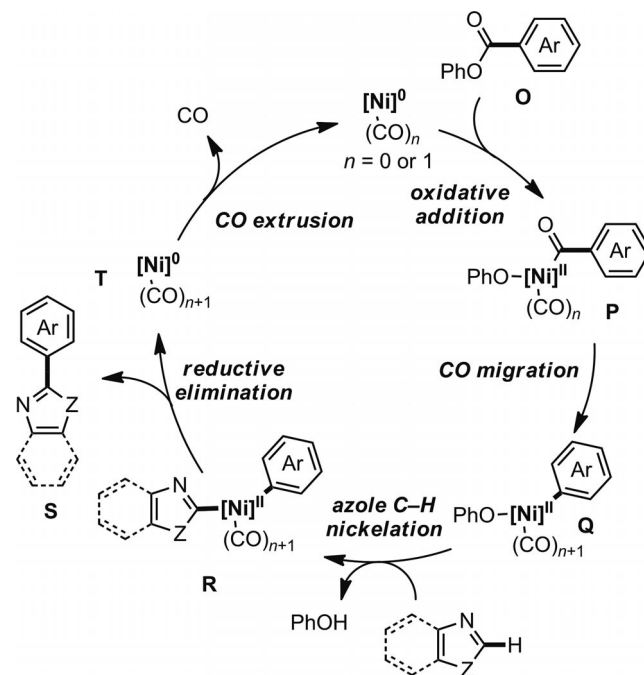
Scheme 28. A plausible mechanism for the decarbonylative C–H arylation reaction.

The assumed intermediate $Ni(dcype)(CO)_2$ (**49**) is indeed a competent catalyst: **48** can be obtained in 96% yield from the reaction between **17** and **47** in the presence of a catalytic amount of **49** (Scheme 29). The use of the stable and less expensive $NiCl_2$ in combination with zinc powder also promotes the decarbonylative C–H coupling (Scheme 29).
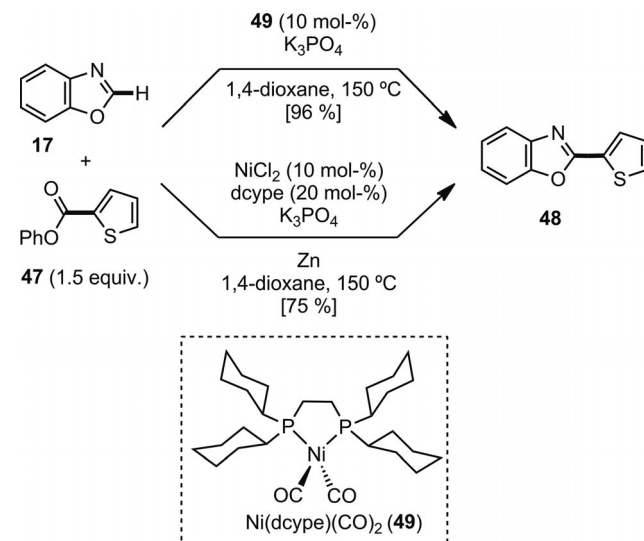
Scheme 29. Alternative protocols for the decarbonylative C–H coupling.

This newly developed decarbonylative C–H arylation is useful in the synthesis of muscoride A (**55**), a natural product with antibacterial activity (Scheme 30).[37] The two

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azole esters **51** and (–)-**52** are coupled under Ni/dcype catalysis conditions to furnish the corresponding coupling product (–)-**53** in 39% yield. The conversion of (–)-**53** into (–)-**55** has been described previously, so a formal synthesis of (–)-muscoride A (**55**) has been completed. If the synthesis were instead planned and executed with typical cross-coupling substrates (aryl halides and organometallic reagents), it would become much less efficient, with many additional steps.
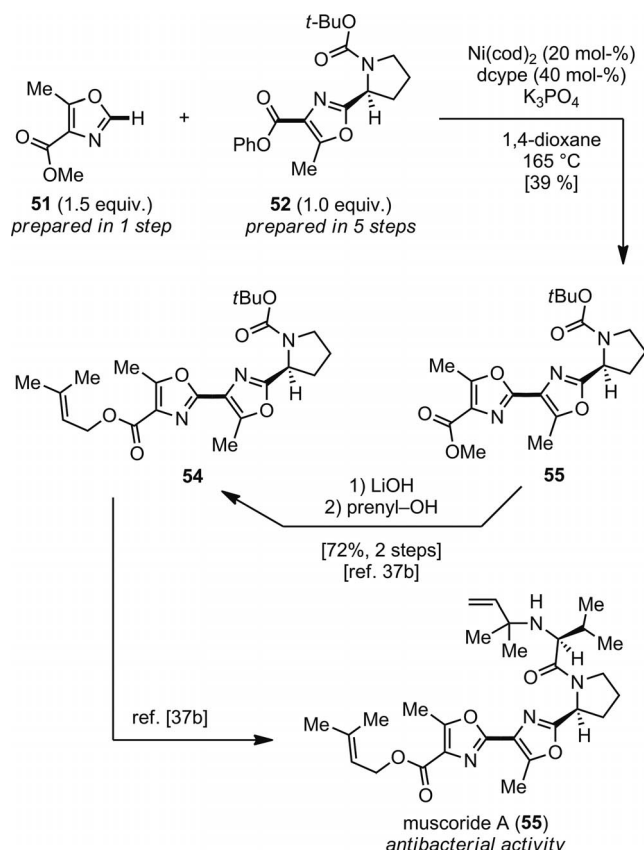
Scheme 30. Formal synthesis of muscoride A through nickel-catalyzed decarbonylative C–H coupling.

Conclusions

Forty years ago, nickel-catalyzed cross-coupling was an uncharted territory open to exploration by pioneering chemists. Now, in the 21st century, this catalytic reaction has been expanded to provide new types of cross-coupling methodology for the construction of biaryls, such as Ar–M (M = B, Mg)/Ar–O, Ar–H/Ar–X, Ar–H/Ar–O, Ar–M (M = B, Si, Mg, Zn)/Ar–H, and decarbonylative C–H coupling. These nickel-catalyzed coupling reactions not only turn traditional cross-coupling (Ar–M/Ar–X coupling) into a method that is less expensive, easily available, and less toxic, but also allow for new types of C–C bond connection yet to be achieved with palladium or other transition metal catalysts. Additionally, orthogonal strategies in cross-coupling and applications toward the synthesis of useful arene-assembled molecules have begun to appear. It is now an op-portune moment to re-evaluate nickel-catalyzed biaryl coupling and to expand its chemistry further.

[1] For a review on nickel-catalyzed cross-coupling reactions, see: a) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg, V. Percec, *Chem. Rev.* **2011**, *111*, 1346–1416.

[2] a) K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 4374–4376; b) R. J. P. Corriu, J. P. Masse, *J. Chem. Soc., Chem. Commun.* **1972**, 144; c) K. Tamao, *J. Organomet. Chem.* **2002**, *653*, 23–26.

[3] a) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1470; b) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, Germany, **2004**; c) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4516; *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489.

[4] a) For a review, see: K. Ritter, *Synthesis* **1993**, 735–762; b) A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.

[5] For selected examples of biaryl coupling reactions of aryl tosylates, see: a) V. Percec, J.-Y. Bae, D. H. Hill, *J. Org. Chem.* **1995**, *60*, 1060–1065; b) D. Zim, V. R. Lando, J. Dupont, A. L. Monteiro, *Org. Lett.* **2001**, *3*, 3049–3051; c) A. H. Roy, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 8704–8705; d) H. N. Nguyen, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 11818–11819; e) Z.-Y. Tang, Q.-S. Hu, *J. Am. Chem. Soc.* **2004**, *126*, 3058–3059; f) L. Zhang, J. Wu, *J. Am. Chem. Soc.* **2008**, *130*, 12250–12251.

[6] For a review on cross-coupling reactions of aryl mesylates, see: C. M. So, F. Y. Kwong, *Chem. Soc. Rev.* **2011**, *40*, 4963–4972.

[7] a) E. Wenkert, E. L. Michelotti, C. S. Swindell, *J. Am. Chem. Soc.* **1979**, *101*, 2246–2247; b) E. Wenkert, E. L. Michelotti, C. S. Swindell, M. Tingoli, *J. Org. Chem.* **1984**, *49*, 4894–4899.

[8] J. W. Dankwardt, *Angew. Chem.* **2004**, *116*, 2482; *Angew. Chem. Int. Ed.* **2004**, *43*, 2428–2432.

[9] M. Tobisu, T. Shimasaki, N. Chatani, *Angew. Chem.* **2008**, *120*, 4944; *Angew. Chem. Int. Ed.* **2008**, *47*, 4866–4869.

[10] a) K. W. Quasdorf, X. Tian, N. K. Garg, *J. Am. Chem. Soc.* **2008**, *130*, 14422–14423; b) B.-T. Guan, Y. Wang, B.-J. Li, D.-G. Yu, Z.-J. Shi, *J. Am. Chem. Soc.* **2008**, *130*, 14468–14470.

[11] a) S. Sengupta, M. Leite, D. S. Raslan, C. Quesnelle, V. Snieckus, *J. Org. Chem.* **1992**, *57*, 4066–4068; b) K. W. Quasdorf, M. Riener, K. V. Petrova, N. K. Garg, *J. Am. Chem. Soc.* **2009**, *131*, 17748–17749; c) A. Antoft-Finch, T. Blackburn, V. Snieckus, *J. Am. Chem. Soc.* **2009**, *131*, 17750–17752; d) L. Xu, B.-J. Li, Z.-H. Wu, X.-Y. Lu, B.-T. Guan, B.-Q. Wang, K.-Q. Zhao, Z.-J. Shi, *Org. Lett.* **2010**, *12*, 884–887; e) M. Baghbanzadeh, C. Pilger, C. O. Kappe, *J. Org. Chem.* **2011**, *76*, 1507–1510; f) K. W. Quasdorf, A. Antoft-Finch, P. Liu, A. L. Silberstein, A. Komaromi, T. Blackburn, S. D. Ramgren, K. N. Houk, V. Snieckus, N. K. Garg, *J. Am. Chem. Soc.* **2011**, *133*, 6352–6363.

[12] R. Kuwano, R. Shimizu, *Chem. Lett.* **2011**, *40*, 913–915.

[13] T. K. Macklin, V. Snieckus, *Org. Lett.* **2005**, *7*, 2519–2522.

[14] a) D.-G. Yu, B.-J. Li, S. F. Zheng, B.-T. Guan, B.-Q. Wang, Z.-J. Shi, *Angew. Chem.* **2010**, *122*, 4670; *Angew. Chem. Int. Ed.* **2010**, *49*, 4566–4570; b) D.-G. Yu, Z.-J. Shi, *Angew. Chem.* **2011**, *123*, 7235; *Angew. Chem. Int. Ed.* **2011**, *50*, 7097–7100.

[15] T. Furuya, T. Ritter, *Org. Lett.* **2009**, *11*, 2860–2863.

[16] a) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826; b) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115; c) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238.

[17] For selected recent examples, see: a) D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172–1175; b) J. C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013–1025; c) H.-Q. Do, R. M. K. Khan, O. Daugulis, *J. Am. Chem. Soc.* **2008**, *130*, 15185–15192; d) R. J. Phipps, M. J. Gaunt, *Science* **2009**, *323*,

MICROREVIEW

1593–1597; e) D.-H. Wang, K. M. Engle, B.-F. Shi, J.-Q. Yu, *Science* **2010**, *327*, 315–319; f) M. S. Chen, M. C. White, *Science* **2010**, *327*, 566–571; g) S. Kirchberg, S. Tani, K. Ueda, J. Yamaguchi, A. Studer, K. Itami, *Angew. Chem.* **2011**, *123*, 2435; *Angew. Chem. Int. Ed.* **2011**, *50*, 2387–2391; h) M. A. Bigi, S. A. Reed, M. C. White, *Nat. Chem.* **2011**, *3*, 216–222; i) K. Mochida, K. Kawasumi, Y. Segawa, K. Itami, *J. Am. Chem. Soc.* **2011**, *133*, 10716–10719; j) K. Yamaguchi, J. Yamaguchi, A. Studer, K. Itami, *Chem. Sci.* **2012**, *3*, 2165–2169.

[18] a) J. Canivet, J. Yamaguchi, I. Ban, K. Itami, *Org. Lett.* **2009**, *11*, 1733–1736; b) H. Hachiya, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2009**, *11*, 1737–1740.

[19] T. Yamamoto, K. Muto, M. Komiyama, J. Canivet, J. Yamaguchi, K. Itami, *Chem. Eur. J.* **2011**, *17*, 10113–10122.

[20] O. Kobayashi, D. Uraguchi, T. Yamakawa, *Org. Lett.* **2009**, *11*, 2679–2682.

[21] K. Muto, J. Yamaguchi, K. Itami, *J. Am. Chem. Soc.* **2012**, *134*, 169–172.

[22] H. Hachiya, K. Hirano, T. Satoh, M. Miura, *Angew. Chem.* **2010**, *122*, 2248; *Angew. Chem. Int. Ed.* **2010**, *49*, 2202–2205.

[23] a) S. Yang, B. Li, X. Wan, Z. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 6066–6067; b) W. Li, Z. Yin, X. Jiang, P. Sun, *J. Org. Chem.* **2011**, *76*, 8543–8548; c) Z. Liang, B. Yao, Y. Zhang, *Org. Lett.* **2010**, *12*, 3185–3187; d) W. Han, P. Mayer, A. R. Ofial, *Chem. Eur. J.* **2011**, *17*, 6904–6908; e) K. Kawasumi, K. Mochida, T. Kajino, Y. Segawa, K. Itami, *Org. Lett.* **2012**, *14*, 418–421.

[24] H. Hachiya, K. Hirano, T. Satoh, M. Miura, *ChemCatChem* **2010**, *2*, 1403–1406.

[25] a) T. Ishiyama, N. Miyaura, *Pure Appl. Chem.* **2006**, *78*, 1369–1375; b) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890–931.

[26] G.-R. Qu, P.-Y. Xin, H.-Y. Niu, D.-C. Wang, R.-F. Ding, H.-M. Guo, *Chem. Commun.* **2011**, *47*, 11140–11142.

[27] M. Tobisu, I. Hyodo, N. Chatani, *J. Am. Chem. Soc.* **2009**, *131*, 12070–12071.

[28] I. Hyodo, M. Tobisu, N. Chatani, *Chem. Asian J.* **2012**, *7*, 1357–1365.

[29] I. Hyodo, M. Tobisu, N. Chatani, *Chem. Commun.* **2012**, *48*, 308–310.

[30] a) L. J. Gooßen, G. Deng, L. M. Levy, *Science* **2006**, *313*, 662–664; b) O. Baudoin, *Angew. Chem.* **2007**, *119*, 1395; *Angew. Chem. Int. Ed.* **2007**, *46*, 1373–1375; c) L. J. Gooßen, N. Rodriguez, K. Gooßen, *Angew. Chem.* **2008**, *120*, 3144; *Angew.*

Chem. Int. Ed. **2008**, *47*, 3100–3120; d) W. I. Dzik, P. P. Lange, L. J. Gooßen, *Chem. Sci.* **2012**, *3*, 2671–2678.

[31] a) J.-J. Dai, J.-H. Liu, D.-F. Luo, L. Liu, *Chem. Commun.* **2011**, *47*, 677–679; b) J. Cornella, H. Lahlali, I. Larrosa, *Chem. Commun.* **2010**, *46*, 8276–8278; c) K. Xie, S. Wang, Z. Yang, J. Liu, A. Wang, X. Li, Z. Tan, C.-C. Guo, W. Deng, *Eur. J. Org. Chem.* **2011**, 5787–5790.

[32] L. J. Gooßen, J. Paetzold, *Adv. Synth. Catal.* **2004**, *346*, 1665–1668.

[33] For a nickel-mediated decarbonylative biaryl formation from phthalimides and arylzinc reagents, see: a) S. E. Havlik, J. M. Simmons, V. J. Winton, J. B. Johnson, *J. Org. Chem.* **2011**, *76*, 3588–3593. For other decarbonylative transformations using stoichiometric amounts of nickel, see: b) B. M. Trost, F. Chen, *Tetrahedron Lett.* **1971**, *12*, 2603–2607; c) E. M. O'Brien, E. A. Bercot, T. Rovis, *J. Am. Chem. Soc.* **2003**, *125*, 10498–10499.

[34] For decarboxylative C–H coupling, see: a) A. Voutchkova, A. Coplin, N. E. Leadbeater, R. H. Crabtree, *Chem. Commun.* **2008**, 6312–6314; b) J. Cornella, P. Lu, I. Larrosa, *Org. Lett.* **2009**, *11*, 5506–5509; c) W.-Y. Yu, W. N. Sit, Z. Zhou, A. S.-C. Chan, *Org. Lett.* **2009**, *11*, 3174–3177; d) J. Zhou, P. Hu, M. Zhang, S. Huang, M. Wang, W. Su, *Chem. Eur. J.* **2010**, *16*, 5876–5881; e) K. Xie, Z. Yang, X. Zhou, X. Li, S. Wang, Z. Tan, X. An, C.-C. Guo, *Org. Lett.* **2010**, *12*, 1564–1567; f) F. Zhang, M. F. Greaney, *Angew. Chem.* **2010**, *122*, 2828; *Angew. Chem. Int. Ed.* **2010**, *49*, 2768–2771; g) H. Zhao, Y. Wei, J. Xu, J. Kan, W. Su, M. Hong, *J. Org. Chem.* **2011**, *76*, 882–893; h) P. Hu, M. Zhang, X. Jie, W. Su, *Angew. Chem. Int. Ed.* **2012**, *51*, 227–231; i) C. Li, P. Li, J. Yang, L. Wang, *Chem. Commun.* **2012**, *48*, 4214–4216.

[35] For decarbonylative C–H coupling, see: a) X. Zhao, Z. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 8136–8137; b) W. Jin, Z. Yu, W. He, W. Ye, W.-J. Xiao, *Org. Lett.* **2009**, *11*, 1317–1320; c) Q. Shuai, L. Yang, X. Guo, O. Baslé, C.-J. Li, *J. Am. Chem. Soc.* **2010**, *132*, 12212–12213.

[36] K. Amaike, K. Muto, J. Yamaguchi, K. Itami, *J. Am. Chem. Soc.* **2012**, *134*, 13573–13576.

[37] For isolation and biological activity of muscoride A, see: a) A. Nagatsu, H. Kajitani, J. Sakakibara, *Tetrahedron Lett.* **1995**, *36*, 4097–4100. For the synthesis of muscoride A, see: b) P. Wipf, S. Venkatraman, *J. Org. Chem.* **1996**, *61*, 6517–6522; c) J. C. Muir, G. Pattenden, R. M. Thomas, *Synthesis* **1998**, 613–618; d) P.-Y. Coqueron, C. Didier, M. A. Ciufolini, *Angew. Chem.* **2003**, *115*, 1451; *Angew. Chem. Int. Ed.* **2003**, *42*, 1411–1414.

Recent Progress in Nickel-Catalyzed Biaryl Coupling

Nickel Catalysis

Biaryl coupling through nickel catalysis has been known for a few decades. The topic has recently resurfaced in synthetic chemistry, however, thanks to its use of ideal coupling partners such as simple arenes (Ar–H) and phenol derivatives (Ar–OR). In this microreview, recent achievements in nickel-catalyzed biaryl coupling are summarized.

biaryl and
heterobiaryl
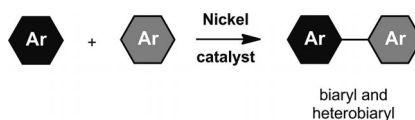
**J. Yamaguchi,* K. Muto,
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Recent Progress in Nickel-Catalyzed Biaryl Coupling