

Cross-Couplings Using Aryl Ethers via C–O Bond Activation Enabled by Nickel Catalysts

Published as part of the *Accounts of Chemical Research* special issue “Earth Abundant Metals in Homogeneous Catalysis”.

Mamoru Tobisu^{*,†,‡} and Naoto Chatani^{*,†}

[†]Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

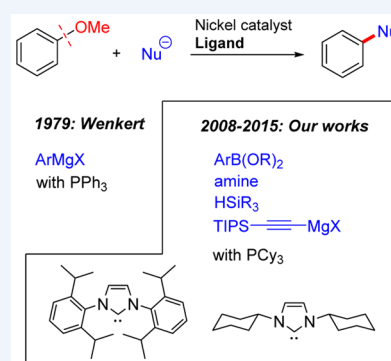
[‡]Center for Atomic and Molecular Technologies, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

CONSPECTUS: Arene synthesis has been revolutionized by the invention of catalytic cross-coupling reactions, wherein aryl halides can be coupled with organometallic and organic nucleophiles. Although the replacement of aryl halides with phenol derivatives would lead to more economical and ecological methods, success has been primarily limited to activated phenol derivatives such as triflates. Aryl ethers arguably represent one of the most ideal substrates in terms of availability, cost, safety, and atom efficiency. However, the robust nature of the C(aryl)–O bonds of aryl ethers renders it extremely difficult to use them in catalytic reactions among the phenol derivatives.

In 1979, Wenkert reported a seminal work on the nickel-catalyzed cross-coupling of aryl ethers with Grignard reagents. However, it was not until 2004 that the unique ability of a low-valent nickel species to activate otherwise unreactive C(aryl)–O bonds was appreciated with Dankwardt’s identification of the Ni(0)/PCy₃ system, which significantly expanded the efficiency of the Wenkert reaction. Application of the nickel catalyst to cross-couplings with other nucleophiles was first accomplished in 2008 by our group using organoboron reagents. Later on, several other nucleophiles, including organozinc reagents, amines, hydrosilane, and hydrogen were shown to be coupled with aryl ethers under nickel catalysis. Despite these advances, progress in this field is relatively slow because of the low reactivity of benzene derivatives (e.g., anisole) compared with polyaromatic substrates (e.g., methoxynaphthalene), particularly when less reactive and synthetically useful nucleophiles are used. The “naphthalene problem” has been overcome by the use of N-heterocyclic carbene (NHC) ligands bearing bulky N-alkyl substituents, which enables a wide range of aryl ethers to be coupled with organoboron nucleophiles. Moreover, the use of N-alkyl-substituted NHC ligands allows the use of alkynylmagnesium reagents, thereby realizing the first Sonogashira-type reaction of anisoles.

From a mechanistic perspective, nickel-catalyzed cross-couplings of aryl ethers are at a nascent stage, in particular regarding the mode of activation of C(aryl)–O bonds. Oxidative addition is one plausible pathway, although such a process has not been fully verified experimentally. Nickel-catalyzed reductive cleavage of aryl ethers in the absence of an external reducing agent provides strong support for this oxidative addition process. Several other mechanisms have also been proposed. For example, Martin demonstrated a new possibility of the involvement of a Ni(I) species, which could mediate the cleavage of the C(aryl)–O bond via a redox-neutral pathway.

The tolerance of aryl ethers under commonly used synthetic conditions enables alkoxy groups to serve as a platform for late-stage elaboration of complex molecules without any tedious protecting group manipulations. Aryl ethers are therefore not mere economical alternatives to aryl halides but also enable nonclassical synthetic strategies.



INTRODUCTION

Recent concern over the shortage of some metallic elements is likely to affect the future directions of scientific research.¹ In the field of synthetic organic chemistry, the development of synthetic methods that use nonprecious, earth-abundant metals instead of precious metals has been accelerated in the past decade, managing to offer sustainable alternatives to the conventional catalysts that now face diminishing supply. Even more important are the fundamental aspects of base-metal catalysts because the use of abundant but less-explored metals coupled with contemporary knowledge of homogeneous catalysis can often lead to new reactivities that have not been

achieved with precious-metal catalysts. One such example is the cross-coupling of aryl ethers using a nickel-based catalyst.

Cross-coupling reactions have long been recognized as one of the most powerful tools in organic synthesis because they can couple organic halides and a range of organic or organometallic nucleophiles, thereby forming a range of carbon–carbon and carbon–heteroatom bonds.² One of the earliest reported cross-coupling reactions was achieved with copper³ and iron⁴ catalysts. The cross-coupling of organic

Received: January 30, 2015

Published: June 3, 2015

halides with Grignard reagents was subsequently developed in 1972 using a nickel catalyst, a reaction that is currently known as the Kumada–Tamao–Corriu reaction.⁵ Also in the 1970s, Wenkert reported the unique reactivity of a nickel catalyst in the Kumada–Tamao–Corriu-type cross-coupling in which aryl ethers react via carbon–oxygen bond cleavage (Scheme 1).⁶

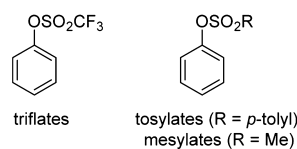
Scheme 1. A Pioneering Study on Cross-Coupling of Aryl Ethers: The Wenkert Reaction⁶



However, this intriguing reactivity of a nickel catalyst did not attract significant attention at that time, probably for two reasons. First, the synthetic community at that time was more focused on the development of cross-couplings using functional-group-tolerant nucleophiles, such as organozinc and organoboron reagents, which were accomplished with palladium-based catalysts.² Second, aryl triflates were soon after found to be more reactive phenolic electrophiles in cross-couplings, which rendered anisole derivatives less appealing as aryl halide surrogates.

However, method development based on the unique reactivity of low-valent nickel in the activation of otherwise unreactive C(aryl)–O bonds has emerged as a topic of active research in the past decade, in recognition of the earth-abundant nature of nickel and the diverse advantages of using less reactive phenol derivatives over aryl halides or triflates, including availability, stability, atom-efficiency, safety, and application to orthogonal cross-couplings (see Synthetic Applications).⁷ Figure 1 summarizes the representative

a) reactive under Pd catalysis



b) inert (or much less reactive) under Pd catalysis but reactive under Ni catalysis

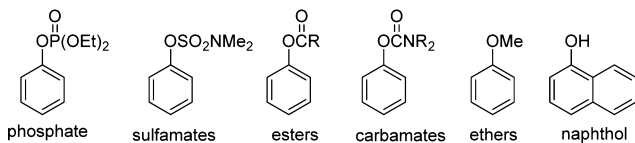


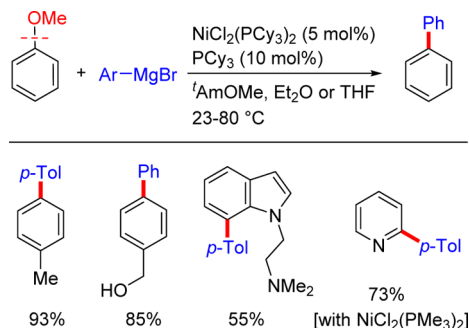
Figure 1. Phenol-based electrophiles used in cross-coupling reactions.

phenolic electrophiles that can be used in cross-coupling reactions with nickel catalysts. In this Account, we present a comprehensive overview of the new advanced methods developed around the Wenkert reaction, with particular emphasis on the nickel-catalyzed transformations of aryl ethers. The C(aryl)–O bond in aryl ethers is one of the most inert among those in phenol derivatives^{7f} and therefore posed a daunting challenge.

REVISITING THE WENKERT REACTION

It was not until 25 years after Wenkert's work that the unique reactivity of nickel toward aryl ethers was re-explored. In 2004, Dankwardt at DMS Pharmaceutical Chemicals documented that the use of alkylphosphine ligands, such as PCy₃ and P^{*i*}Pr₃, significantly improves the activity of the nickel catalyst.⁸ One of the critical limitations of the Wenkert reaction is the low reactivity of anisole derivatives compared with naphthyl ethers. In contrast, the modified nickel catalyst allows the cross-coupling of a broad range of anisole derivatives (Scheme 2).

Scheme 2. Dankwardt's Modified System⁸



Dankwardt's finding clearly demonstrated that aryl ethers can behave like aryl halides if an appropriate catalyst is used, thereby paving the way for the development of nickel-catalyzed transformations of inert phenolic electrophiles.⁷

Several years after Dankwardt's work, two other ligand types were reported to be efficient for the cross-coupling of aryl ethers with Grignard reagents. One is modified trialkylphosphines,⁹ and the other is an N-heterocyclic carbene (NHC) ligand bearing bulky aryl groups, i.e., IPr¹⁰ (Figure 2). The common features of the ligands reported to date for the Wenkert reaction include being monodentate, being a strong σ donor, and having significant steric bulk.

BEYOND THE KUMADA–TAMAO–CORRIU COUPLING

In view of the tremendous advancements in palladium-catalyzed cross-coupling reactions of aryl halides with various nucleophiles, it was natural to envision that aryl ethers could be coupled with nucleophiles that are less reactive than Grignard reagents under similar nickel-catalyzed conditions. Nevertheless, long after Wenkert's report in 1979,⁶ such reactions had not been reported. Therefore, in 2007 our group decided to explore the cross-coupling of aryl ethers with a series of nucleophiles. Given the widespread use of the Suzuki–Miyaura reaction,¹¹ we set organoboron reagents as our initial target and immediately found that the Ni(cod)₂/PCy₃ system is suitable for this process (Scheme 3).¹² Several electrophilic functionalities, including ketones and esters, are well-tolerated under these conditions, which is in sharp contrast to the cross-coupling using Grignard reagents.^{6,8–10} The scope of the aryl ethers used revealed that polyaromatic ethers such as naphthalenes and anthracenes successfully undergo the cross-coupling, whereas anisole is completely unreactive. This reactivity difference between phenyl and naphthyl ethers had hindered the apparently simple extension of the Wenkert reaction to organoboron cross-coupling for nearly 30 years.¹³ Although the inertness of anisoles was a serious limitation of the Ni(0)/PCy₃ catalyst system, it allows regioselective

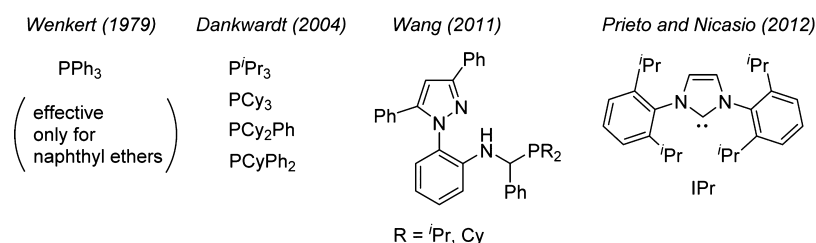
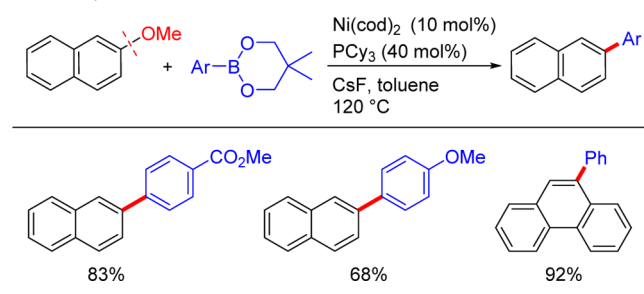


Figure 2. Effective ligands for the Kumada–Tamao–Corriu reaction of aryl ethers.

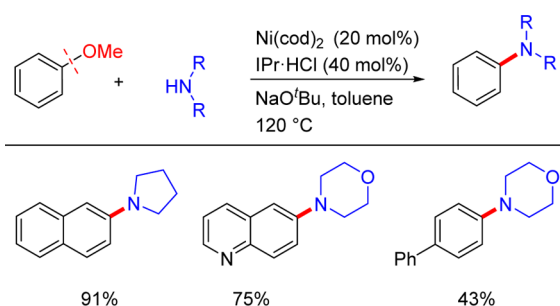
Scheme 3. Nickel-Catalyzed Cross-Coupling of Aryl Ethers with Arylboronic Esters¹²



arylation between two different methoxy groups, as demonstrated in the second example of Scheme 3.

We subsequently examined amines as potential nucleophiles in nickel-catalyzed cross-coupling of aryl ethers on the basis of the catalytic amination chemistry primarily established by Buchwald and Hartwig.¹⁴ Although the PCy₃ ligand, which was thus far the most effective for cross-couplings with Grignard and organoboron nucleophiles, was less effective for the amination reaction, the use of IPr led to the realization of the first protocol for the amination of aryl ethers (Scheme 4).¹⁵

Scheme 4. Nickel-Catalyzed Amination of Aryl Ethers¹⁵

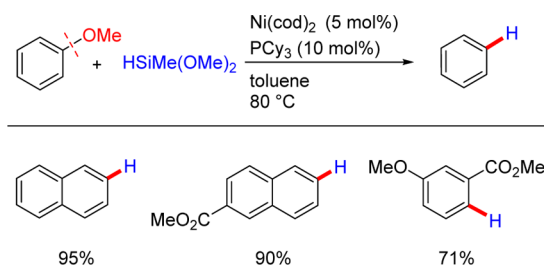


This amination does not occur in the absence of the nickel catalyst, which excludes a mechanistic pathway via direct nucleophilic aromatic substitution and suggests that nickel-mediated C(aryl)–O bond activation is involved under these conditions. Importantly, the scope of aryl ethers in this amination is slightly broader than that in the organoboron cross-coupling (Scheme 3), with electron-deficient heteroaryl and phenyl ethers being aminated in moderate to good yields. The broadened scope cannot be attributed to the IPr ligand, because replacement of PCy₃ with IPr in the Suzuki–Miyaura-type reaction (Scheme 3) gave none of the arylated product. The nature of the nucleophile has a profound impact on the efficiency of C(aryl)–O bond cleavage (see Mechanistic Considerations).

The Ni(0)/PCy₃ system was also found to facilitate cross-coupling with hydrosilane, resulting in substitution of an alkoxy

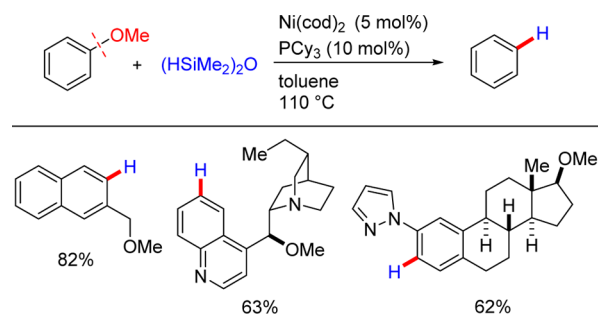
group by a hydrogen atom. This apparently simple transformation promises widespread application in organic synthesis, ranging from the preparation of deoxygenated analogues of biologically active phenol derivatives to the use of alkoxy groups as removable activating groups in arene functionalization reactions. Our group found that HSiMe₂(OMe)₂ functions as a particularly effective hydride donor in this reductive cleavage reaction, probably because of its relatively high Lewis acidity (Scheme 5).¹⁶ The scope of the substrates is again limited to polyaromatics, and simple anisoles are unreactive unless they contain a directing group, such as an ester or N-heteroarene.

Scheme 5. Nickel-Catalyzed Reductive Cleavage of Aryl Ethers¹⁶



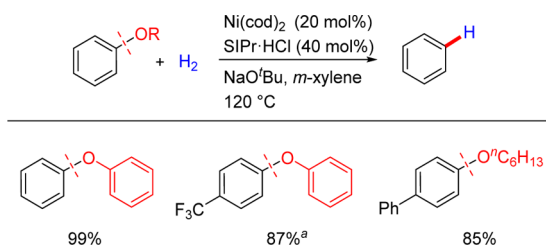
Virtually the same outcome was independently documented by Martin using hydrosiloxane (HSiMe₂)₂O (Scheme 6).¹⁷ Notably, the usefulness of the method was demonstrated by successful execution with a range of elaborated substrates.

Scheme 6. Martin's Nickel-Catalyzed Reductive Cleavage of Aryl Ethers¹⁷



Hartwig's group revealed that hydrogen could be used as a suitable reductant in the nickel-catalyzed reductive cleavage reaction (Scheme 7).¹⁸ The key difference in the catalytic system compared with the reductive cleavage using hydrosilane (Schemes 5 and 6) is that the SIPr ligand is optimal. Importantly, substrates that have no fused rings can be used successfully.¹⁹

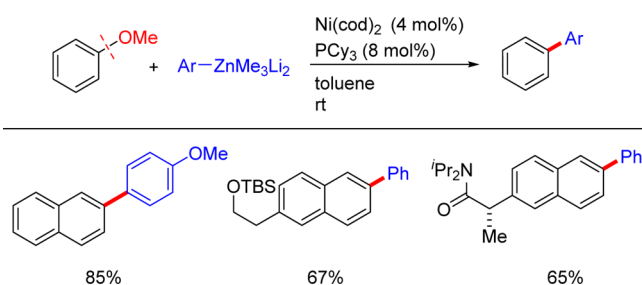
Scheme 7. Hartwig's Nickel-Catalyzed Reductive Cleavage of Aryl Ethers with H₂¹⁸



^aWith 10 mol % catalyst. A mixture of benzotrifluoride (68%) and toluene (19%) was obtained.

Wang and Uchiyama reported that the Ni(0)/PCy₃ system can also catalyze cross-coupling reactions with organozinc reagents (Scheme 8).²⁰ The use of the dianionic zincate

Scheme 8. Wang and Uchiyama's Nickel-Catalyzed Cross-Coupling of Aryl Ethers with Organozinc Reagents²⁰



ArZnMe₃Li₂ is crucial, whereas ArZnX and ArZnMe₂Li fail to participate in this reaction. Functional groups, including enolizable amides, remained untouched under these conditions, although the scope of aryl ethers is again primarily limited to naphthalene derivatives.

■ TACKLING THE “NAPHTHALENE PROBLEM”

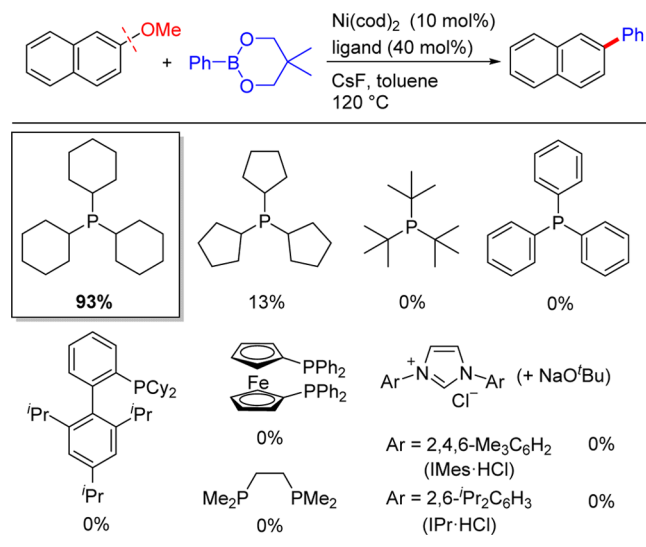
As discussed earlier, the range of nucleophiles that can be coupled with aryl ethers has been expanded significantly over the past decade. However, the maturity of the methodology lags far behind the powerful palladium-based cross-coupling technology in terms of both the efficiency and the scope of the aryl ethers and nucleophiles. A critical issue that has hampered further development is the considerably lower reactivity of anisole derivatives compared with naphthalene and higher π -extended aromatic substrates (the “naphthalene problem”). The discrepancy in reactivity between aromatic systems is seemingly less pronounced in the palladium-catalyzed cross-couplings but becomes apparent under nickel catalysis. One reason for the sensitivity of the nickel catalysis to the nature of the substrate π system might be the increased importance of the formation of π -arene nickel intermediates, which can be formed more facily with π -extended arenes, prior to a bond activation event.²¹ The naphthalene problem is prevalent throughout the nickel-catalyzed cross-couplings of inert aromatic electrophiles, including aryl fluorides,²² aryl amides,²³ aryl esters,²⁴ and phenols.²⁵ Thus, finding a solution to this problem will contribute extensively to the advancement of nickel-catalyzed aromatic transformations.

In the cross-coupling of aryl ethers, a closer look at the substrate scope revealed that the extent of the naphthalene problem is highly dependent on the nature of the nucleophile

employed. Although the reactivity difference between phenyl and naphthyl ethers was pronounced under the classical Wenkert conditions,⁶ this limitation was apparently overcome by the development of the modified catalysts (Figure 2)^{8–10} when Grignard reagents were used. In contrast, anisoles cannot efficiently undergo cross-coupling with less reactive but more useful nucleophiles, including organoboron (Scheme 3),¹² organozinc (Scheme 8),²⁰ amines (Scheme 4),¹⁵ and hydrosilanes (Schemes 5 and 6).^{16,17}

A possible solution to the naphthalene problem is the generation of a more electron-rich nickel species through tuning of the nature of the ligand, which is expected to facilitate the postulated oxidative addition process of C(aryl)–O bonds of aryl ethers. It is well-known that the impact of the nature of the ligand is enormous in palladium-catalyzed cross-couplings, and tremendous knowledge on ligand design has accumulated over the past two decades.²⁶ However, this knowledge has not readily translated to nickel catalysis, in particular with aryl ether substrates. As shown by our initial ligand screening in 2008 (Scheme 9),¹² several other ligands capable of promoting

Scheme 9. Initial Screening of the Ligand in Ni-Catalyzed Cross-Coupling of Aryl Ethers with Organoboron Reagents

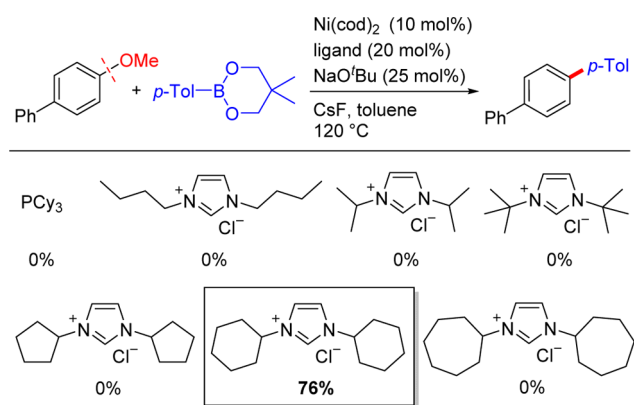


palladium-catalyzed Suzuki–Miyaura reactions, including P^tBu₃, XPhos, IMes, and IPr, were all found to be ineffective, and PCy₃ was solely active. Although some bidentate phosphines, such as bis(diphenylphosphino)ferrocene, are known to promote the activation of C(aryl)–O bonds of aryl esters,²⁷ aryl ethers are completely inert with these ligands. Thus, the scope of efficient ligands for organoboron cross-coupling is severely limited compared with that for Grignard cross-coupling (Figure 2). The narrow window of structural variations of active ligands highlights the difficulty in designing improved catalysts for the nickel-catalyzed Suzuki–Miyaura-type cross-coupling of aryl ethers.

Our search for a new ligand to overcome the naphthalene problem began with a careful examination of the substrate scopes of the aforementioned nickel-catalyzed cross-coupling reactions of aryl ethers. Apart from Grignard reagents, amines (Scheme 4)¹⁵ and hydrogen (Scheme 7)¹⁸ are the only reagents that can be coupled with nonfused anisole derivatives (although not very efficiently), and both cases use a nickel catalyst ligated with an NHC ligand (IPr for amines, SiPr for hydrogen). These

findings prompted us to thoroughly evaluate a series of NHC-based ligands for their ability to promote the cross-coupling of anisole derivatives, although IPr and SIPr had already been determined to be inactive for organoboron cross-coupling in our previous studies.¹² In addition to IMes and IPr, NHC ligands bearing *n*-butyl, isopropyl, or *tert*-butyl groups on the nitrogen atoms failed to deliver the arylated product under the same conditions (Scheme 10). We were delighted to find that a

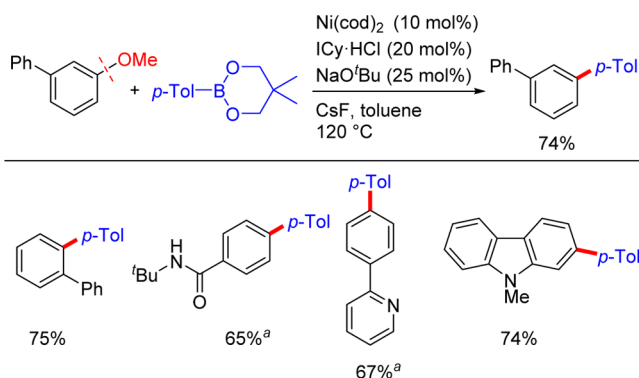
Scheme 10. Detailed Screening of NHC Ligands in Ni-Catalyzed Cross-Coupling of Aryl Ethers with Organoboron Reagents



cyclohexyl-substituted NHC ligand (ICy) allowed the Suzuki–Miyaura-type cross-coupling of anisoles that cannot be used with the original Ni(0)/PCy₃ system.²⁸ Replacing the cyclohexyl groups with cyclopentyl or cycloheptyl groups resulted in a complete loss of activity, highlighting the sensitivity of this catalytic system to subtle changes in the ligand structure.

The Ni(0)/ICy catalyst has proved effective for the Suzuki–Miyaura-type cross-coupling of an expanded array of aryl ether substrates. It is noteworthy that the examples shown in Scheme 11 are completely inactive with the Ni(0)/PCy₃ catalyst. A

Scheme 11. Ni(0)/ICy-Catalyzed Cross-Coupling of Aryl Ethers with Organoboron Reagents²⁸



^aWith 20 mol % Ni(cod)₂ and 40 mol % ICy-HCl.

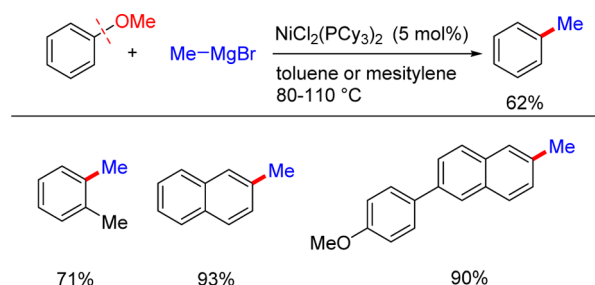
range of anisole derivatives, including those with steric bulk and functional groups, can be coupled successfully. The Ni(0)/ICy catalyst also overcomes the key limitation that heteroaryl ethers are unreactive, allowing for the arylation of pyridines and carbazoles. Unfortunately, however, electron-rich anisoles do not react with the Ni(0)/ICy system, posing a remaining challenge for further development of universally active catalysts.

■ CROSS-COUPINGS WITH C(SP³)- AND C(SP)-BASED NUCLEOPHILES

As discussed earlier, the arylation methods for aryl ethers via nickel-catalyzed cross-coupling have been advanced using several arylating reagents. However, efforts in method development for alkylation and alkynylation of aryl ethers using C(sp³)- and C(sp)-based nucleophiles, respectively, have met with limited success.

Shi demonstrated that methylation of anisoles is possible using a Ni(0)/PCy₃ catalyst and MeMgBr (Scheme 12).²⁹

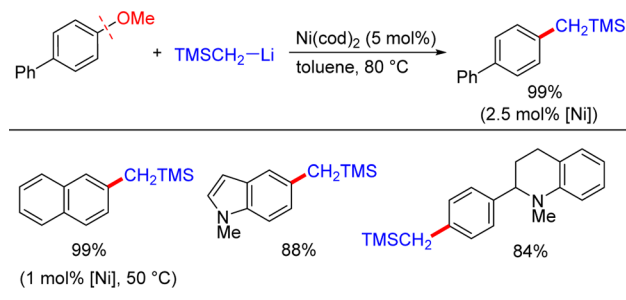
Scheme 12. Shi's Ni(0)/PCy₃-Catalyzed Methylation of Aryl Ethers with MeMgBr²⁹



Although both phenyl and naphthyl ethers can be methylated successfully, phenyl ethers require harsher conditions, permitting a regioselective methylation of two different methoxy groups.

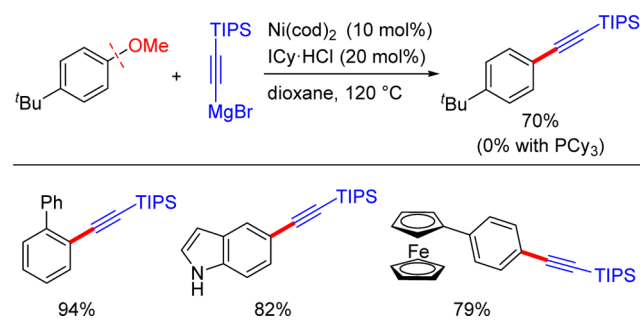
The introduction of a TMSCH₂ group via nickel-catalyzed C(aryl)–O bond cleavage of aryl ethers was reported by Rueping (Scheme 13).³⁰ Although the scope of the substrates is

Scheme 13. Rueping's Ligand-Free Ni(0)-Catalyzed Alkylation of Aryl Ethers with TMSCH₂Li³⁰



limited by the strong nucleophilicity of TMSCH₂Li, the nucleophile required in this reaction, the resulting products ArCH₂TMS are versatile synthetic intermediates for further elaboration. A notable feature of this reaction is that the C(aryl)–O bond activation occurs in the absence of a ligand. An anionic nickelate species, which could be generated by the reaction of Ni(cod)₂ with TMSCH₂Li, might be involved and mediate the C(aryl)–O bond activation via a nonclassical mechanism (see Mechanistic Considerations).

Our group reported the first method for the alkynylation of anisoles via nickel-catalyzed cross-coupling (Scheme 14).³¹ Despite the apparent similarity, alkynylMgX is less nucleophilic than ArMgX by a factor of more than 10, based on the pK_a values of benzene (43) and acetylene (25). Indeed, simple application of the catalytic conditions for ArOMe/ArMgX cross-coupling (10 mol % Ni(cod)₂, 20 mol % PCy₃, 120 °C, 18 h) afforded none of the alkynylated product. In contrast, our

Scheme 14. Ni(0)/ICy-Catalyzed Alkynylation of Aryl Ethers with Grignard Reagents³¹

second-generation catalyst Ni(0)/ICy successfully promoted the cross-coupling of anisoles with alkynylMgX. The use of triisopropylsilyl (TIPS)-protected alkyne is essential for an efficient reaction, presumably to suppress the undesired interaction of the alkyne moiety with a nickel species. This alkynylation reaction is free from the naphthalene problem, allowing access to a range of aromatic and heteroaromatic alkynes from readily available aryl ethers.

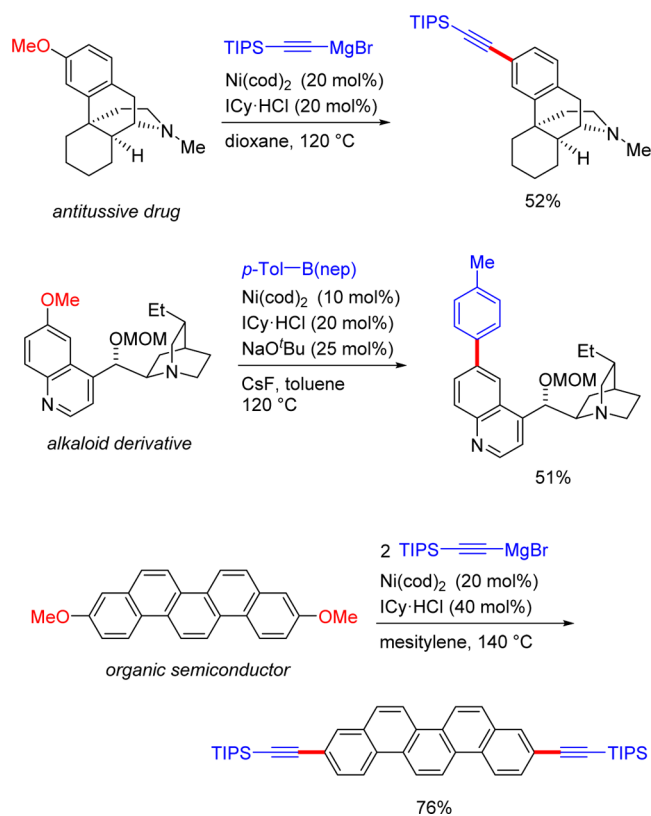
■ SYNTHETIC APPLICATIONS

The use of anisole derivatives instead of aryl halides or triflates is beneficial in terms of availability, cost, atom efficiency, and avoidance of potential toxicity. In addition, the direct transformation of a methoxy group streamlines the synthesis of elaborate aromatic compounds, enabling postsynthetic derivatization of molecules relevant to biology and materials (Scheme 15)^{28,31,32}.

A very important aspect of anisole cross-couplings is that the robust nature of a methoxy group allows for new synthetic strategies by combination with existing methods. For example, the inertness of a methoxy group is best represented by its tolerance under the conditions using BuLi, yet it is reactive under suitable nickel-catalyzed conditions, enabling the synthesis of polysubstituted arenes without the need for protective groups (Scheme 16a).³¹ A methoxy group is absolutely stable under palladium- or copper-catalyzed conditions for the transformations of aryl halides, which makes the sequence of C–X and C–OMe transformations a reliable strategy (Scheme 16b,c).^{12a,15b} Moreover, fine-tuning of the ligand allows two nickel-catalyzed reactions to occur in a sequential manner. For example, a pivaloxy group is a poor leaving group in palladium-catalyzed cross-coupling reactions but can be arylated with the Ni(0)/PCy₃ catalyst using an organoboron nucleophile with a methoxy group remaining intact. The significantly less reactive methoxy group can subsequently be arylated using the Ni(0)/ICy catalyst (Scheme 16d).²⁸ The inability of the Ni(0)/PCy₃ system to promote the arylation of quinolones allows the arylation of a C–H bond of methoxyquinoline using this nickel catalyst.³³ The remaining methoxy group can be modified using a Ni(0)/NHC-based catalyst (Scheme 16e).

■ MECHANISTIC CONSIDERATIONS

Progress in the nickel-catalyzed cross-coupling of aryl ethers has been guided by a working mechanism involving a sequence of oxidative addition/transmetalation/reductive elimination, which is generally accepted for cross-couplings of aryl halides (Scheme 17a). However, neither experimental nor theoretical evidence to support the mechanism for each step, in particular,

Scheme 15. Late-Stage Elaboration of Aryl Ether Moieties via Nickel Catalysis^a

^aTop: ref 31. Middle: ref 28. Bottom: ref 32.

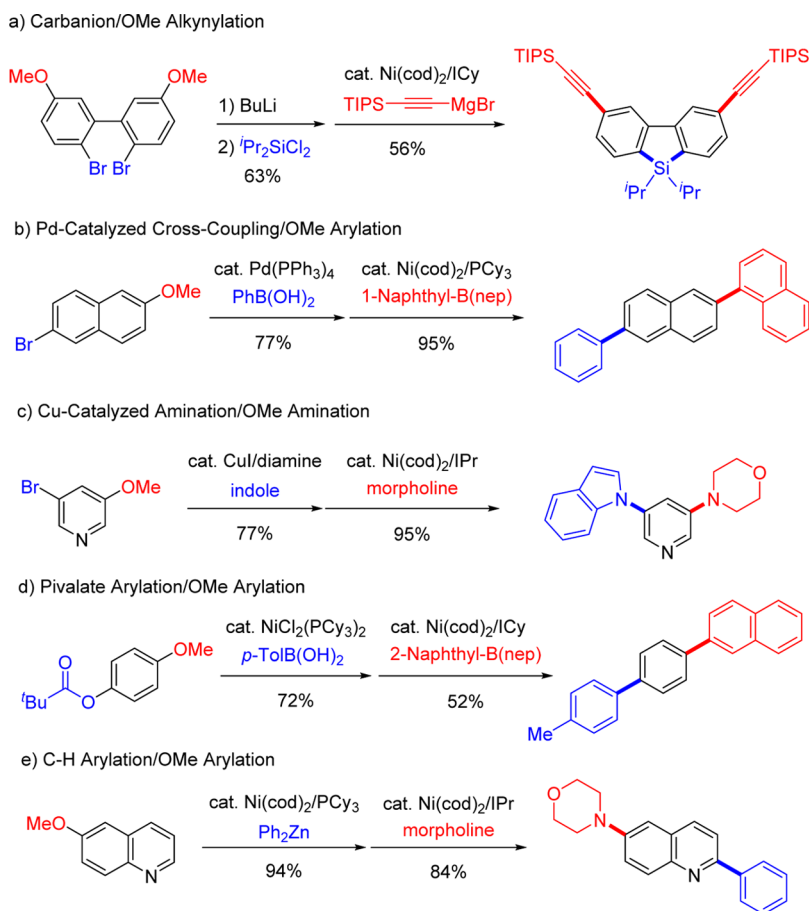
regarding the critical oxidative addition process (A → B),³⁴ had been reported.

Although this postulated mechanism can explain many of the outcomes reported to date, several questions arise. For example, the observed impact of the nature of the nucleophile (i.e., Grignard reagents vs other less reactive nucleophiles) on the scope of the aryl ether substrates is apparently puzzling if the mechanism shown in Scheme 17a is operative. Under such simplified circumstances, the oxidative addition step is the most likely to be a turnover-limiting step on the basis of the inertness of C(aryl)–OMe bonds, but the oxidative addition is unlikely to be affected by the identity of the nucleophile.

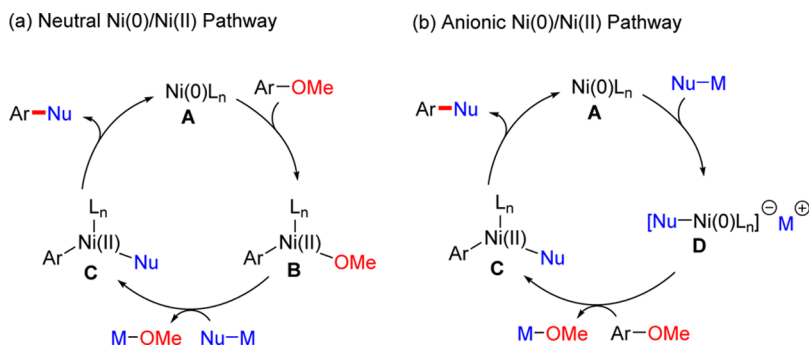
There are several possible scenarios that can account for the wider substrate scope when using Grignard reagents. One possibility is that the Grignard reagent plays a certain role in the oxidative addition process. For example, Martin proposed that a C(sp²)–O bond could be electrophilically activated by coordination to the Lewis acidic magnesium center of the Grignard reagent, thus facilitating its oxidative addition to an electron-rich nickel species.^{35,36} Hartwig also observed that the addition of a stoichiometric amount of AlMe₃ significantly accelerated the nickel-catalyzed reductive cleavage of challenging aryl ether substrates.¹⁸ However, the addition of Lewis acid additives, such as MgX₂, ZnX₂, TiF₄, and ZrX₄, in the Ni(cod)₂/PCy₃-catalyzed cross-coupling of aryl ethers with organoboron reagents was unsuccessful.

Another plausible scenario involves the generation of an anionic nickelate species by reaction of the Ni(0) precursor with ArMgX, potentially serving as the competent catalyst that is more reactive toward anisole activation because of increased

Scheme 16. Sequential Synthetic Modification Enabled by Ni-Catalyzed Cross-Couplings of Aryl Ethers



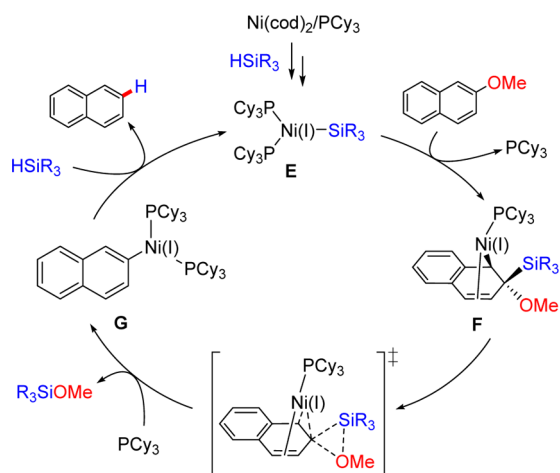
Scheme 17. Possible Mechanisms for Ni-Catalyzed Cross-Coupling of Aryl Ethers



electron density around the nickel center (Scheme 17b).³⁷ Although the formation of anionic nickelate species **D** was experimentally proved when Grignard reagents were used,³⁸ its generation by the reaction with less reactive nucleophiles, such as organoboron reagents, is unlikely. The change in the substrate scope depending on the nature of the nucleophiles might be caused by the switch between these neutral and anionic mechanisms, but further mechanistic studies are required to prove the feasibility of this proposal.

C(aryl)–O bond activation through a mechanism completely different from oxidative addition was put forward by Martin. His group reported extensive mechanistic studies on the Ni(cod)₂/PCy₃-catalyzed reductive cleavage of aryl ethers using hydrosilane.^{17b} On the basis of experimental and theoretical studies, it was proposed that R₃Si–Ni(I) species **E**, which could

be generated by a comproportionation of Ni(0) and HNi(II)–SiR₃ species, is responsible for the catalysis (Scheme 18). Migratory insertion of methoxynaphthalene forms benzylnickel(I) intermediate **F**, which undergoes concerted elimination of R₃SiOMe and [1,2]-migration of the nickel center to generate naphthylnickel(I) species **G**. The reductive cleavage product is produced via σ -bond metathesis between complex **G** and hydrosilane, with concomitant regeneration of **E**. The requirement of a polyaromatic system as the substrate for this reaction is well-rationalized by this proposed mechanism involving a dearomatized intermediate **F**. Martin's work raises concerns that oxidative addition is not always a suitable pathway for the activation of inert C(aryl)–O bonds and suggests that Ni(I) species could play a pivotal role in these reactions.

Scheme 18. Martin's Ni(I) Mechanism for Reductive Cleavage of Aryl Ethers^{17b}

The nickel-catalyzed reductive cleavage reactions of aryl ethers as discussed thus far require an external hydride donor such as hydrosilane¹⁷ or hydrogen.¹⁸ We recently found that the same transformation can be accomplished without using an external reductant (Scheme 19).³⁹ The use of a new NHC ligand bearing a 2-adamantyl group [I(2-Ad)] enables the catalytic removal of an alkoxy group on the aromatic ring. The reductant-free protocol is particularly useful for aryl ether substrates bearing reducible functionalities such as alkenes and ketones.

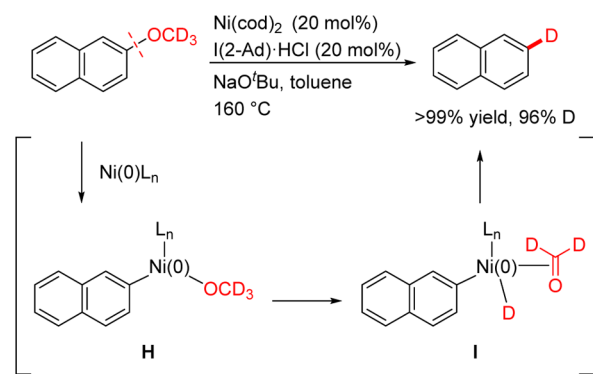
A labeling experiment revealed that the hydrogen of the alkoxy group in the substrate serves as an internal reductant (Scheme 20). This result suggests that oxidative addition of aryl ethers occurs under these conditions, and the subsequent β -hydrogen elimination leads to the formation of a final reduced product.

Although several mechanistic studies have emerged and allowed detailed discussion of the mechanism, current knowledge is still limited. In addition to the simple oxidative addition mechanism, nonclassical modes of activation should be taken into account depending on the nature of the nucleophile and the ligand used.

SUMMARY AND OUTLOOK

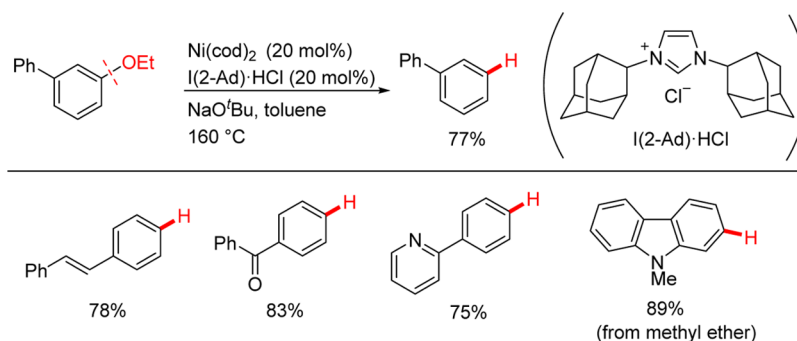
Driven by the concerns of limited availability of precious metals, base-metal catalysis has attracted significant attention in recent years. Aside from such demands from society, the unique reactivities of base metals often allow the development of new

Scheme 20. Experimental Implication of Oxidative Addition of a C(aryl)–OMe Bond to Ni(0)



reactions that have never been achieved with precious-metal catalysts. In this Account, we have described cross-coupling reactions of aryl ethers in which a nickel catalyst plays a key role in activating otherwise unreactive C(aryl)–O bonds. The potential reactivity of low-valent nickel species toward the activation of aryl ethers was exploited by Wenkert as early as 1979 in cross-coupling with Grignard reagents. However, it was only during the past decade that the striking reactivity of nickel was applied to other nucleophiles, including organoboron, organozinc, amines, and hydride reagents. One serious problem that has inhibited widespread use of the cross-coupling of aryl ethers is the much lower reactivity of phenyl ethers compared with polyaryl ethers, such as naphthalenes, especially when synthetically useful less reactive nucleophiles are used. To address the “naphthalene problem”, the use of *N*-alkyl-substituted NHC ligands was demonstrated to be effective, and this option will stimulate the future development of better ligands for even more challenging classes of substrates. Another aspect that has hampered the rapid development of the aryl ether cross-coupling is mechanistic ambiguity, in particular regarding the C(aryl)–O bond activation process. The reactions reported to date indicate that the conventional oxidative addition is not the only mode of activation, and several mechanistic variants are also likely to be operative depending on the ligand and the nucleophile employed. The diversity of the mechanism in turn promises numerous opportunities for new discoveries.

Despite the accumulated knowledge of palladium-catalyzed cross-coupling reactions of aryl halides, its simple extension to nickel-catalyzed cross-coupling of aryl ethers has often met with poor results. In fact, many of the nucleophiles used in the cross-coupling of aryl halides remain unreactive when applied to

Scheme 19. Ni(0)/I(2-Ad)-Catalyzed Reductive Cleavage of Aryl Ethers without an External Reductant³⁹

cross-couplings with aryl ethers. The development of more versatile and efficient catalysts is required to unveil the full potential of this synthetic method. This endeavor is highly rewarding and worthwhile because aryl ethers serve not only as more economical alternatives to aryl halides but also as a robust platform for new synthetic strategies, such as sequential cross-couplings.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: tobisu@chem.eng.osaka-u.ac.jp.

*E-mail: chatani@chem.eng.osaka-u.ac.jp.

Notes

The authors declare no competing financial interest.

Biographies

Mamoru Tobisu received his Ph.D. from Osaka University under the direction of Prof. Shinji Murai (2001). During his Ph.D. study, he also worked with Prof. Gregory C. Fu at the Massachusetts Institute of Technology for 5 months as a visiting scientist (1999). Following a period at the Takeda Pharmaceutical Company (2001–2005), he started his academic career at Osaka University in 2005 as an assistant professor with Prof. Naoto Chatani. He was then appointed as an associate professor at the Center for Atomic and Molecular Technologies at Osaka University in 2011. He received the Thieme Chemistry Journals Award in 2008, the Chemical Society of Japan Award for Young Chemists in 2009, the Young Scientists' Award, a Commendation for Science and Technology from the Minister of Education, Culture, Sports, Science and Technology in 2012, and the Merck–Banyu Lectureship Award in 2012.

Naoto Chatani received his Ph.D. in 1984 under Profs. Noboru Sonoda and Shinji Murai. In 1984 he joined the Institute of Scientific and Industrial Research at Osaka University and worked in the laboratory of Prof. Terukiyo Hanafusa. After postdoctoral studies in 1988–1989 under Prof. Scott E. Denmark at the University of Illinois at Urbana–Champaign, he moved back to Osaka University and was promoted to associate professor in 1992 and to full professor in 2003. He received The Chemical Society of Japan Award for Young Chemists in 1990, The Green & Sustainable Chemistry Award from the Minister of Education, Culture, Sports, Science and Technology in 2005, and The Nagoya Silver Medal in 2013.

ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas “Molecular Activation Directed toward Straightforward Synthesis” from MEXT, Japan, and ACT-C from JST, Japan. We thank Professor Yasushi Nishihara for fruitful discussions.

REFERENCES

- (1) Nakamura, E.; Sato, K. Managing the scarcity of chemical elements. *Nat. Mater.* **2011**, *10*, 158–161.
- (2) *Cross-Coupling Reactions: A Practical Guide*; Miyaura, N., Ed.; Topics in Current Chemistry, Vol. 219; Wiley: Chichester, U.K., 2001.
- (3) For an early review, see: Fanta, P. E. The Ullmann Synthesis of Biaryls, 1945–1963. *Chem. Rev.* **1964**, *64*, 613–632.
- (4) (a) Tamura, M.; Kochi, J. K. Vinylation of Grignard reagents. Catalysis by iron. *J. Am. Chem. Soc.* **1971**, *93*, 1487–1489. (b) Kochi, J. K. Electron-transfer mechanisms for organometallic intermediates in catalytic reactions. *Acc. Chem. Res.* **1974**, *7*, 351–360.
- (5) (a) Tamao, K.; Sumitani, K.; Kumada, M. Selective carbon–carbon bond formation by cross-coupling of Grignard reagents with

organic halides. Catalysis by nickel-phosphine complexes. *J. Am. Chem. Soc.* **1972**, *94*, 4374–4376. (b) Corriu, R. J. P.; Masse, J. P. Activation of Grignard reagents by transition-metal complexes. A new and simple synthesis of *trans*-stilbenes and polyphenyls. *J. Chem. Soc., Chem. Commun.* **1972**, 144a.

(6) Wenkert, E.; Michelotti, E. L.; Swindell, C. S. Nickel-induced conversion of carbon–oxygen into carbon–carbon bonds. One-step transformations of enol ethers into olefins and aryl ethers into biaryls. *J. Am. Chem. Soc.* **1979**, *101*, 2246–2247.

(7) For selected reviews, see: (a) Li, B.-J.; Yu, D.-G.; Sun, C.-L.; Shi, Z.-J. Activation of “Inert” Alkenyl/Aryl C–O Bond and Its Application in Cross-Coupling Reactions. *Chem.—Eur. J.* **2011**, *17*, 1728–1759. (b) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. Nickel-Catalyzed Cross-Couplings Involving Carbon–Oxygen Bonds. *Chem. Rev.* **2011**, *111*, 1346–1416. (c) Tobisu, M.; Chatani, N. Catalytic Transformations Involving the Activation of sp² Carbon–Oxygen Bonds. *Top. Organomet. Chem.* **2013**, *44*, 35–53. (d) Yamaguchi, J.; Muto, K.; Itami, K. Recent Progress in Nickel-Catalyzed Biaryl Coupling. *Eur. J. Org. Chem.* **2013**, 19–30. (e) Cornella, J.; Zarate, C.; Martin, R. Metal-catalyzed activation of ethers via C–O bond cleavage: a new strategy for molecular diversity. *Chem. Soc. Rev.* **2014**, *43*, 8081–8097. For a comparison of the reactivities of various phenol derivatives under nickel catalysis, see: (f) Leowanawat, P.; Zhang, N.; Percec, V. Nickel Catalyzed Cross-Coupling of Aryl C–O Based Electrophiles with Aryl Neopentylglycolboronates. *J. Org. Chem.* **2012**, *77*, 1018–1025.

(8) Dankwardt, J. W. Nickel-Catalyzed Cross-Coupling of Aryl Grignard Reagents with Aromatic Alkyl Ethers: An Efficient Synthesis of Unsymmetrical Biaryls. *Angew. Chem., Int. Ed.* **2004**, *43*, 2428–2432.

(9) Xie, L.-G.; Wang, Z.-X. Cross-Coupling of Aryl/Alkenyl Ethers with Aryl Grignard Reagents through Nickel-Catalyzed C–O Activation. *Chem.—Eur. J.* **2011**, *17*, 4972–4975.

(10) Iglesias, M. J.; Prieto, A.; Nicasio, M. C. Kumada–Tamao–Corriu Coupling of Heteroaromatic Chlorides and Aryl Ethers Catalyzed by (IPr)Ni(allyl)Cl. *Org. Lett.* **2012**, *14*, 4318–4321.

(11) Miyaura, N. Metal-Catalyzed Reactions of Organoboronic Acids and Esters. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535–1553.

(12) (a) Tobisu, M.; Shimasaki, T.; Chatani, N. Nickel-Catalyzed Cross-Coupling of Aryl Methyl Ethers with Aryl Boronic Esters. *Angew. Chem., Int. Ed.* **2008**, *47*, 4866–4869. (b) Shimasaki, T.; Konno, Y.; Tobisu, M.; Chatani, N. Nickel-Catalyzed Cross-Coupling Reaction of Alkenyl Methyl Ethers with Aryl Boronic Esters. *Org. Lett.* **2009**, *11*, 4890–4892.

(13) For Suzuki–Miyaura coupling of anisoles containing a directing group under ruthenium catalysis, see: (a) Kakiuchi, F.; Usui, M.; Ueno, S.; Chatani, N.; Murai, S. Ruthenium-Catalyzed Functionalization of Aryl Carbon–Oxygen Bonds in Aromatic Ethers with Organoboron Compounds. *J. Am. Chem. Soc.* **2004**, *126*, 2706–2707. (b) Ueno, S.; Mizushima, E.; Chatani, N.; Kakiuchi, F. Direct Observation of the Oxidative Addition of the Aryl Carbon–Oxygen Bond to a Ruthenium Complex and Consideration of the Relative Reactivity between Aryl Carbon–Oxygen and Aryl Carbon–Hydrogen Bonds. *J. Am. Chem. Soc.* **2006**, *128*, 16516–16517. (c) Zhao, Y.; Snieckus, V. Beyond Directed Ortho Metalation: Ru-Catalyzed C_{Ar}–O Activation/Cross-Coupling Reaction by Amide Chelation. *J. Am. Chem. Soc.* **2014**, *136*, 11224–11227.

(14) (a) Surry, D. S.; Buchwald, S. L. Biaryl Phosphane Ligands in Palladium-Catalyzed Amination. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338–6361. (b) Hartwig, J. F. Evolution of a Fourth Generation Catalyst for the Amination and Thioetherification of Aryl Halides. *Acc. Chem. Res.* **2008**, *41*, 1534–1544.

(15) (a) Tobisu, M.; Shimasaki, T.; Chatani, N. Ni⁰-Catalyzed Direct Amination of Anisoles Involving the Cleavage of Carbon–Oxygen Bonds. *Chem. Lett.* **2009**, *38*, 710–711. (b) Tobisu, M.; Yasutome, A.; Yamakawa, K.; Shimasaki, T.; Chatani, N. Ni(0)/NHC-catalyzed amination of N-heteroaryl methyl ethers through the cleavage of carbon–oxygen bonds. *Tetrahedron* **2012**, *68*, 5157–5161.

(16) Tobisu, M.; Yamakawa, K.; Shimasaki, T.; Chatani, N. Nickel-catalyzed reductive cleavage of aryl–oxygen bonds in alkoxy- and

pivaloxyarenes using hydrosilanes as a mild reducing agent. *Chem. Commun.* **2011**, 47, 2946–2948.

(17) (a) Álvarez-Bercedo, P.; Martín, R. Ni-Catalyzed Reduction of Inert C–O Bonds: A New Strategy for Using Aryl Ethers as Easily Removable Directing Groups. *J. Am. Chem. Soc.* **2010**, 132, 17352–17353. (b) Cornella, J.; Gómez-Bengoia, E.; Martín, R. Combined Experimental and Theoretical Study on the Reductive Cleavage of Inert C–O Bonds with Silanes: Ruling Out a Classical Ni(0)/Ni(II) Catalytic Couple and Evidence for Ni(I) Intermediates. *J. Am. Chem. Soc.* **2013**, 135, 1997–2009.

(18) Sergeev, A. G.; Hartwig, J. F. Selective, Nickel-Catalyzed Hydrogenolysis of Aryl Ethers. *Science* **2011**, 332, 439–443.

(19) For a related iron-catalyzed reaction using LiAlH_4 , see: Ren, Y.; Yan, M.; Wang, J.; Zhang, Z. C.; Yao, K. Selective Reductive Cleavage of Inert Aryl C–O Bonds by an Iron Catalyst. *Angew. Chem., Int. Ed.* **2013**, 52, 12674–12678.

(20) Wang, C.; Ozaki, T.; Takita, R.; Uchiyama, M. Aryl Ether as a Negishi Coupling Partner: An Approach for Constructing C–C Bonds under Mild Conditions. *Chem.—Eur. J.* **2012**, 18, 3482–3485.

(21) For selected examples of nickel-catalyzed reactions in which the formation of π -arene complexes was shown to play a key role, see: (a) Yoshikai, N.; Matsuda, H.; Nakamura, E. Ligand Exchange as the First Irreversible Step in the Nickel-Catalyzed Cross-Coupling Reaction of Grignard Reagents. *J. Am. Chem. Soc.* **2008**, 130, 15258–15259. (b) Bryan, Z. J.; McNeil, A. J. Evidence for a preferential intramolecular oxidative addition in Ni-catalyzed cross-coupling reactions and their impact on chain-growth polymerizations. *Chem. Sci.* **2013**, 4, 1620–1624. (c) Sontag, S. K.; Bilbrey, J. A.; Huddleston, N. E.; Sheppard, G. R.; Allen, W. D.; Locklin, J. π -Complexation in Nickel-Catalyzed Cross-Coupling Reactions. *J. Org. Chem.* **2014**, 79, 1836–1841.

(22) Tobisu, M.; Xu, T.; Shimasaki, T.; Chatani, N. Nickel-Catalyzed Suzuki–Miyaura Reaction of Aryl Fluorides. *J. Am. Chem. Soc.* **2011**, 133, 19505–19511.

(23) Tobisu, M.; Nakamura, K.; Chatani, N. Nickel-Catalyzed Reductive and Borylative Cleavage of Aromatic Carbon–Nitrogen Bonds in *N*-Aryl Amides and Carbamates. *J. Am. Chem. Soc.* **2014**, 136, 5587–5590.

(24) (a) Muto, K.; Yamaguchi, J.; Itami, K. Nickel-Catalyzed C–H/C–O Coupling of Azoles with Phenol Derivatives. *J. Am. Chem. Soc.* **2012**, 134, 169–172. (b) Ehle, A. R.; Zhou, Q.; Watson, M. P. Nickel(0)-Catalyzed Heck Cross-Coupling via Activation of Aryl C–OPiv Bonds. *Org. Lett.* **2012**, 14, 1202–1205. (c) Correa, A.; León, T.; Martín, R. Ni-Catalyzed Carboxylation of $\text{C}(\text{sp}^2)$ - and $\text{C}(\text{sp}^3)$ -O Bonds with CO_2 . *J. Am. Chem. Soc.* **2014**, 136, 1062–1069. (d) Koch, E.; Takise, R.; Studer, A.; Yamaguchi, J.; Itami, K. Ni-Catalyzed α -arylation of esters and amides with phenol derivatives. *Chem. Commun.* **2015**, 51, 855–857.

(25) (a) Yu, D.-G.; Li, B.-J.; Zheng, S.-F.; Guan, B.-T.; Wang, B.-Q.; Shi, Z.-J. Direct Application of Phenolic Salts to Nickel-Catalyzed Cross-Coupling Reactions with Aryl Grignard Reagents. *Angew. Chem., Int. Ed.* **2010**, 49, 4566–4570. (b) Yu, D.-G.; Shi, Z.-J. Mutual Activation: Suzuki–Miyaura Coupling through Direct Cleavage of the sp^2 C–O Bond of Naphtholate. *Angew. Chem., Int. Ed.* **2011**, 50, 7097–7100.

(26) For example, see: Martín, R.; Buchwald, S. L. Palladium-Catalyzed Suzuki–Miyaura Cross-Coupling Reactions Employing Dialkylbiaryl Phosphine Ligands. *Acc. Chem. Res.* **2008**, 41, 1461–1473.

(27) (a) Correa, A.; Martín, R. Ni-Catalyzed Direct Reductive Amidation via C–O Bond Cleavage. *J. Am. Chem. Soc.* **2014**, 136, 7253–7256. (b) Takise, R.; Muto, K.; Yamaguchi, J.; Itami, K. Nickel-Catalyzed α -Arylation of Ketones with Phenol Derivatives. *Angew. Chem., Int. Ed.* **2014**, 53, 6791–6794. (c) Kuwano, R.; Shimizu, R. An Improvement of Nickel Catalyst for Cross-Coupling Reaction of Arylboronic Acids with Aryl Carbonates by Using a Ferrocenyl Bisphosphine Ligand. *Chem. Lett.* **2011**, 40, 913–915. Also see refs 24a–d.

(28) Tobisu, M.; Yasutome, A.; Kinuta, H.; Nakamura, K.; Chatani, N. 1,3-Dicyclohexylimidazol-2-ylidene as a Superior Ligand for the Nickel-Catalyzed Cross-Couplings of Aryl and Benzyl Methyl Ethers with Organoboron Reagents. *Org. Lett.* **2014**, 16, 5572–5575.

(29) Guan, B.-T.; Xiang, S.-K.; Wu, T.; Sun, Z.-P.; Wang, B.-Q.; Zhao, K.-Q.; Shi, Z.-J. Methylation of arenes via Ni-catalyzed aryl C–O/F activation. *Chem. Commun.* **2008**, 1437–1439.

(30) Leiendecker, M.; Hsiao, C.-C.; Guo, L.; Alandini, N.; Rueping, M. Metal-Catalyzed Dealkoxylyative $\text{C}_{\text{aryl}}\text{—C}_{\text{sp}^3}$ Cross-Coupling—Replacement of Aromatic Methoxy Groups of Aryl Ethers by Employing a Functionalized Nucleophile. *Angew. Chem., Int. Ed.* **2014**, 53, 12912–12915.

(31) Tobisu, M.; Takahira, T.; Ohtsuki, A.; Chatani, N. Nickel-Catalyzed Alkynylation of Anisoles via C–O Bond Cleavage. *Org. Lett.* **2015**, 17, 680–683.

(32) Chen, X. C.; Nishinaga, S.; Okuda, Y.; Zhao, J. J.; Xu, J.; Mori, H.; Nishihara, Y. A divergent synthesis of 3,10-dialkylpicenes. *Org. Chem. Front.* **2015**, 2, 536–541.

(33) Tobisu, M.; Hyodo, I.; Chatani, N. Nickel-Catalyzed Reaction of Arylzinc Reagents with *N*-Aromatic Heterocycles: A Straightforward Approach to C–H Bond Arylation of Electron-Deficient Heteroaromatic Compounds. *J. Am. Chem. Soc.* **2009**, 131, 12070–12071.

(34) For oxidative addition reactions using anisoles containing a directing group, see: Kelley, P.; Lin, S.; Edouard, G.; Day, M. W.; Agapie, T. Nickel-Mediated Hydrogenolysis of C–O Bonds of Aryl Ethers: What Is the Source of the Hydrogen? *J. Am. Chem. Soc.* **2012**, 134, 5480–5483. Also see ref 13b.

(35) Cornella, J.; Martín, R. Ni-Catalyzed Stereoselective Arylation of Inert C–O Bonds at Low Temperatures. *Org. Lett.* **2013**, 15, 6298–6301.

(36) For selected catalytic reactions involving nickel-mediated oxidative addition assisted by Lewis acids, see: (a) Yoshikai, N.; Matsuda, H.; Nakamura, E. Hydroxyphosphine Ligand for Nickel-Catalyzed Cross-Coupling through Nickel/Magnesium Bimetallic Cooperation. *J. Am. Chem. Soc.* **2009**, 131, 9590–9599. (b) Nakao, Y. Nickel/Lewis Acid-Catalyzed Carbocyanation of Unsaturated Compounds. *Bull. Chem. Soc. Jpn.* **2012**, 85, 731–745.

(37) For a leading review of catalysis by anionic ate complexes, see: Terao, J.; Kambe, N. Cross-Coupling Reaction of Alkyl Halides with Grignard Reagents Catalyzed by Ni, Pd, or Cu Complexes with π -Carbon Ligand(s). *Acc. Chem. Res.* **2008**, 41, 1545–1554.

(38) Kaschube, W.; Pörschke, K.-R.; Angermund, K.; Krüger, C.; Wilke, G. Zur Lewis-Acidität von Nickel(0), X. Diorganylmagnesium-Komplexe von Nickel(0): $(\text{TMEDA})\text{MgCH}_3(\mu\text{-CH}_3)\text{Ni}(\text{C}_2\text{H}_4)_2$. *Chem. Ber.* **1988**, 121, 1921–1929.

(39) Tobisu, M.; Morioka, T.; Ohtsuki, A.; Chatani, N. Nickel-Catalyzed Reductive Cleavage of Aryl Alkyl Ethers to Arenes in Absence of External Reductant. *Chem. Sci.* **2015**, 6, 3410–3414.

NOTE ADDED IN PROOF

Martin et al. recently reported Ni/PCy₃-catalyzed borylation of aryl ethers, one of the rare methods for heteroatom introduction to anisole derivatives (10.1021/jacs.5b03955).