CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.201100971

Catalytic Arylation of a C–H Bond in Pyridine and Related Six-Membered N-Heteroarenes Using Organozinc Reagents

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Abstract: Despite significant advances in the catalytic direct arylation of heteroarenes, the application of this reaction to pyridines has been met with limited success. An oxidative nucleophilic arylation strategy has been developed to overcome this problem. Pyridine, pyrazine, quinolone, and related electron-deficient N-heteroarenes can be arylated at the most electrophilic site using the developed nickel-catalyzed reaction. This protocol serves as a complementary method to catalytic direct arylation reactions.

Keywords: cross-coupling · heterocycles · homogeneous catalysis · nickel · zinc

Introduction

The catalytic direct arylation of heteroarenes has emerged as an atom-economical alternative to the traditional cross-coupling between organohalides and organometallic species for constructing heteroaryl–aryl linkages, which constitute an important class of substructures found in natural and non-natural products.[1] Important studies in this area during the last decade have delivered a number of catalytic protocols that allow direct arylation of two classes of heteroarenes: electron-rich species (Figure 1a) and those bearing a relatively acidic C–H bond (Figure 1b).[2] However, methods that are applicable to electron-deficient heteroarenes, such as pyridine, pyrazine, and pyrimidine (Figure 1c), which would produce heterobiaryls with widespread utility (Figure 2), have been slower to develop.[3] The difficulty associated with arylation of these heteroarenes stems primarily from the fact that the majority of direct arylation reactions depend upon electrophilic aromatic substitution (S_EAr) or concerted metalation/deprotonation (CMD) mechanisms.[4] These mechanisms are inherently unsuitable for electron-deficient and non-acidic heteroarenes. A partial solution to this issue has been provided by using pyridine *N*-oxide[5a,b] and related N-activated analogues,[5c,d] directing groups,[6] or intramolecular settings,[7] but a more straightforward and general method is desired.[8] At the time we began this study in 2008, no catalytic methods for the direct arylation of pyridines were available, with the notable exception of the work by Bergman and Ellman et al. using a rhodium catalyst.[9,10] In 2011, Chang and co-workers reported Rh^{II}/N-heterocyclic carbene catalyzed C4-arylation of quinolines.[11] Quite recently, palladium-catalyzed C3-arylation of pyridines was reported by Yu and co-workers.[12]

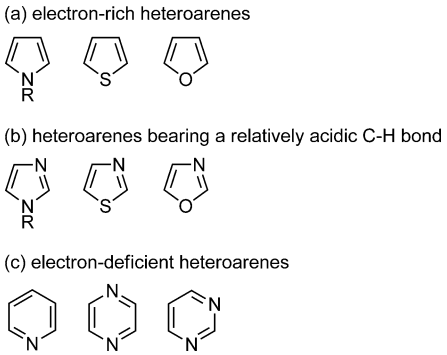

Figure 1. Classification of heteroarenes.

Our approach to solving the problem of pyridine arylation stems from the classical two-step procedure depicted in Scheme 1a. Aryl lithium and magnesium reagents are known to add across pyridines in a 1,2-fashion to form dihydropyridines **1**, which subsequently rearomatize to furnish 2-aryl pyridines upon oxidation.[13] The overall sequence falls in a general class of reaction known as oxidative nucleophilic substitution of hydrogen.[14] The 1,2-dearomatizing addition/oxidative rearomatization approach would serve as a versatile strategy for the arylation of electron-deficient heteroarenes, and complement to the S_EAr and CMD pathways, if the reaction could meet the following criteria: 1) use of less aggressive aryl nucleophiles, such as organozinc or -boron compounds, and 2) the unstable dihydropyri-

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201100971.

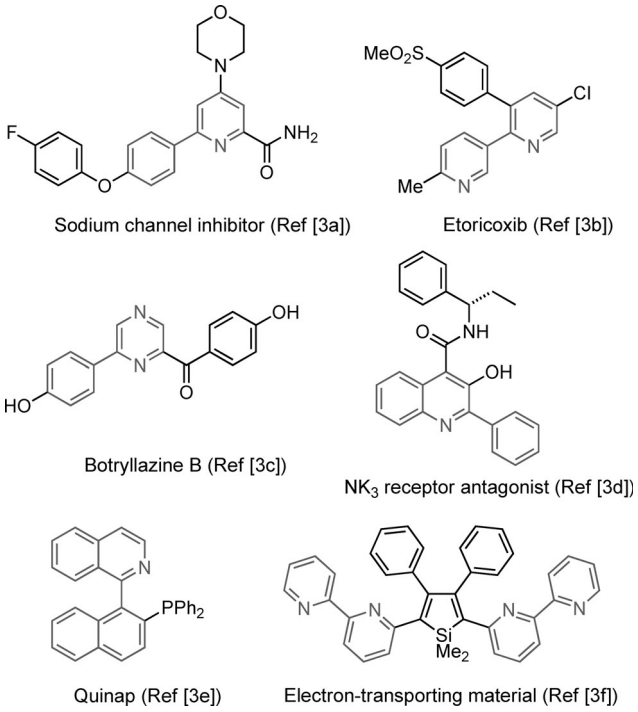
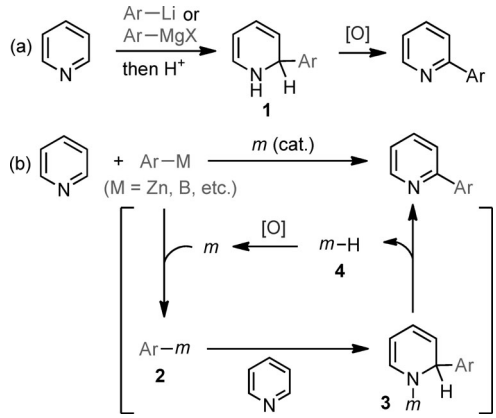


Figure 2. Examples of biaryls containing six-membered N-heteroarenes.



Scheme 1. Dearomatizing 1,2-addition/oxidative rearomatization strategy for arylation of pyridines.

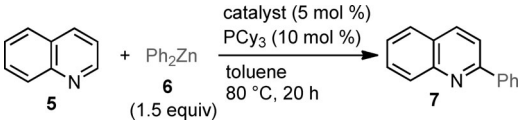
dine intermediate **1** should not need to be isolated, allowing for a one-pot protocol. We postulated a simple catalytic cycle that can accommodate the above requirements (Scheme 1b). A mild arylating agent (Ar−M) initially generates a more reactive aryl metal species **2** (Ar−*m*, where *m* is the catalytic metal center) by transmetalation. 1,2-Addition of **2** across pyridine then forms dihydropyridine intermediate **3**, which affords an aromatized product through β-hydrogen elimination. The addition of an external oxidant allows for catalyst turnover by oxidizing metal hydride **4**. In the preliminary studies, this working catalytic reaction can be realized by using organozinc reagents as aryl donor.[15] A notable feature of this methodology is that the organozinc reagent functions both as an aryl donor and oxidant, thus obviating the need for additional external oxidants. Herein, we describe this catalytic arylation of electron-deficient heteroarenes using organozinc reagents in detail, including preparative and mechanistic aspects.

Abstract in Japanese:
ニッケル触媒存在下、ピリジンやピラジン、ピリミジンなどの電子不足性含窒素ヘテロ芳香環とアリール亜鉛試薬との反応により、環の最も求電子的位置で選択的にC-Hアリール化が進行する。本反応は、ヘテロ芳香環の触媒的直接アリール化反応と相補的な手法として利用可能である。

Results and Discussion

Investigation based upon the working hypothesis outlined in Scheme 1 identified diaryl zinc reagents as viable aryl donor species.[16] For example, reaction of quinoline (**5**) with diphenylzinc (**6**) in the presence of $Pd(OAc)_2/PCy_3$ catalyst afforded 2-phenylquinoline (**7**) in 15% yield (entry 2 in Table 1). We initially expected that the addition of an oxidant may improve the yield of **7** by promoting the catalyst regeneration process, as is the case for C−H bond functionalization reactions using organometallic reagents.[17] However, addition of external oxidants gave no improvements. Further catalyst screening identified that Cu^{II} and Rh^{I} complexes exhibited promising levels of catalytic activity (Table 1, entries 3 and 4). Finally, it was found that quantitative formation of **7** was achieved with $[Ni(cod)_2]/PCy_3$ catalyst (Table 1, entry 5; cod = 1,5-cyclooctadiene).[18] The reaction mixture contained a precipitate of metallic zinc, indicating that zinc reagent **6** also acts as a stoichiometric oxidant (see below for the discussion of a plausible mechanism). The use of air-stable $[NiCl_2(PCy_3)_2]$ as a catalyst precursor

Table 1. Catalytic phenylation of quinoline (**5**) using diphenylzinc (**6**): Catalyst screening.[a]



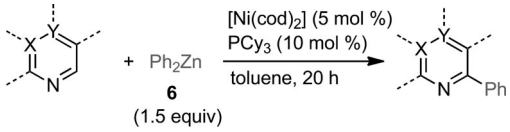
Entry	Catalyst	Yield of **7** [%][b]
1	none	0
2	$Pd(OAc)_2$	15
3	$Cu(OTf)_2$	16
4	$[\{RhCl(cod)\}_2]$	38
5	$[Ni(cod)_2]$	99
6[c]	$[NiCl_2(PCy_3)_2]$	33

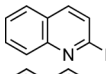
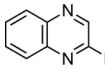
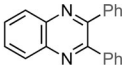
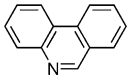
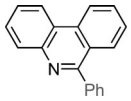
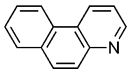
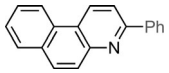
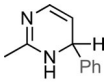
[a] Reaction conditions: **5** (0.25 mmol), **6** (0.38 mmol), catalyst (0.013 mmol), PCy_3 (0.025 mmol), and toluene (1.0 mL) in a screw-capped vial under N_2 at 80 °C for 20 h. [b] Yield of isolated product based on **5**. [c] Run in the absence of PCy_3.

resulted in a significant reduction in the yield of **7** (Table 1, entry 6).

Having an optimal catalyst in hand, we next explored the scope of this direct arylation reaction. Initially, simple six-membered N-heteroarenes and their benzo-fused analogues were examined to identify the scaffolds suitable for this catalytic direct arylation reaction (Table 2). Pyridine required harsher reaction conditions (130 °C, 3 equiv **6**) than those employed for quinoline (Table 2, entry 1 vs. entry 6). This trend in reactivity is similar to those observed for 1,2-dearomatizing addition of Grignard or organolithium reagents.[13a] Introducing another nitrogen atom into the pyridine ring led to an significant increase in the reactivity toward this nickel-catalyzed arylation. Pyrazine afforded a 2-phenylated product in 81% yield at 100 °C using 1.5 equiv **6** (Table 2, entry 2). Although pyrimidine itself did not react, 2-methylpyrimidine proved to be reactive. However, the product obtained after protic quenching was 1,6-dihydro-2-methyl-6-phenyl-pyrimidine (**8**), which is an addition product.[13e] Unlike other heteroarenes, in situ oxidative rearomatization did not proceed with pyrimidines, even at elevated temperature. The desired aromatized product was obtained quantitatively simply by treating the reaction mixture with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; Table 2, entry 3).[19] As observed for quinoline (Table 2, entry 4), six-membered heteroarenes bearing a fused benzene ring proved excellent substrates. Isoquinoline underwent arylation at the 1-position in a regioselective manner (Table 2, entry 5).[13b] Quinoxaline is more reactive than pyrazine to form mono- and diarylated products at 80 °C (Table 2, entry 6). A diarylated product was formed exclusively by using an excess amount of **6** (Table 2, entry 7). It should be noted that selective monoarylation is possible using a less reactive ArZnEt reagent (see below). Heteroarenes embedded in an extended π system, such as in phenanthridine, can be arylated under milder conditions (Table 2, entries 9 and 10). As revealed in Table 2, the reactivity and regioselectivity profiles are predictable on the basis of those observed in 1,2-dearomatizing addition using Grignard and organolithium reagents.[13] Consistent with our working hypothesis, electron-rich heteroarenes, such as indole and benzofuran, and those bearing an acidic C–H bond, including azoles and perfluorinated arenes, cannot be arylated under our catalytic conditions, although these are excellent substrates under the reported direct arylation reaction conditions (Figure 3).[2]

Table 2. Nickel-catalyzed phenylation of heteroarenes using **2**: Scope of heteroarenes.[a]



Entry	Heteroarene	T [°C]	Product	Yield [%][b]
1[c]		130		55
2		100		81
3		60		54[d]
4		80		99
5[e]		100		90
6		80	 + 	66 (1:1)[f]
7[c]		100		74 (0:1)[f]
8[e]		70		88
9		60		>99
10[c]		100		95
				
	8			

[a] Reaction conditions: heteroarene (0.25 mmol), **6** (0.38 mmol), $[Ni(cod)_2]$ (0.013 mmol), PCy_3 (0.025 mmol), and toluene (1.0 mL) in a screw-capped vial under N_2 for 20 h. [b] Yield of isolated product based on heteroarene. [c] Using 0.75 mmol **6**. [d] The initial product was dihydropyrimidine **8**. The yield was determined after oxidation of **8** with DDQ. [e] Using 0.50 mmol **6**. [f] The ratio in the parentheses is that for mono- to diarylated products.

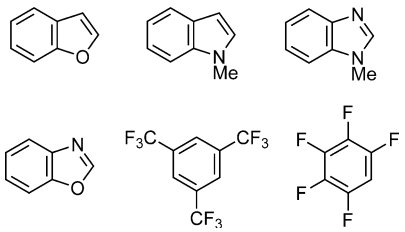
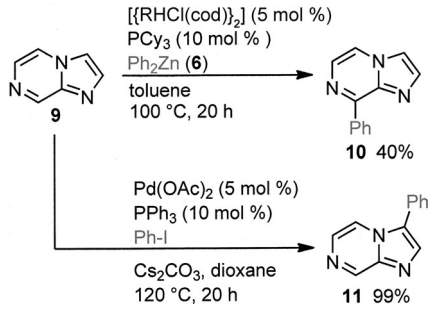


Figure 3. Inapplicable substrates.

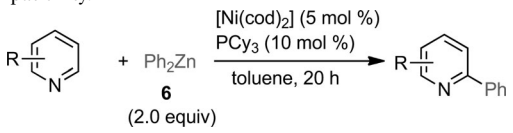
The regioselectivity observed with azine and azole fused systems further underscores the complementary nature of the present methodology to direct arylation methods. Oxidative nucleophilic arylation of an imidazo[1,2-a]pyrazine skeleton **9** proceeded regioselectively at the most electrophilic 8-position to form **10** (Scheme 2).[20] Interestingly, a rhodium catalyst, rather than $[Ni(cod)_2]/PCy_3$ proved suitable for the arylation of this specific substrate.[21] In contrast, electrophilic arylation using phenyl iodide under palladium catalysis delivered 3-phenylated product **11** in a regioselective manner.[22]

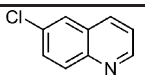
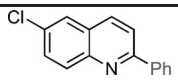
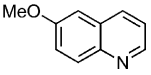
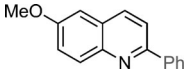
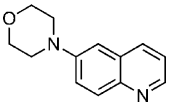
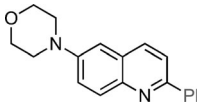
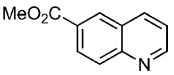
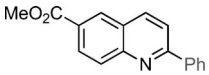
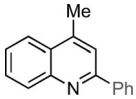
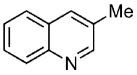
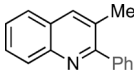
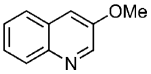
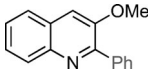
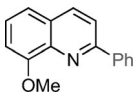
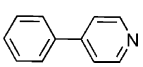
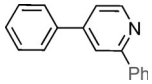
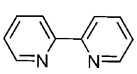
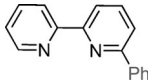
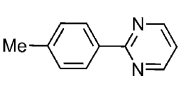
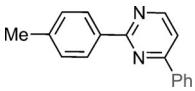
Several common functional groups are compatible with this nickel-catalyzed arylation reaction (Table 3). Chloro (Table 3, entry 1), methoxy (Table 3, entry 2), and amino (Table 3, entry 3) groups on the quinoline ring remained intact under these conditions. Esters can also survive, which is a notable advantage using organozinc reagents (Table 3,



Scheme 2. Regioselective C–H arylations of imidazo[1,2-a]pyrazine (**9**).

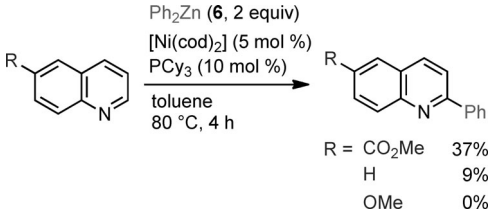
Table 3. Nickel-catalyzed phenylation of heteroarenes using **6**: Functional group compatibility.[a]



Entry	Heteroarene	*T* [°C]	Product	Yield [%][b]
1		130		94
2		160		94
3		160		70
4		80		61
5		130		99
6		160		90
7		160		99
8		160		88
9[c]		100		45
10[c]		130		71
11		60		78[d]

[a] Reaction conditions: heteroarene (0.25 mmol), **6** (0.50 mmol), $[Ni(cod)_2]$ (0.013 mmol), PCy_3 (0.025 mmol), and toluene (1.0 mL) in a screw-capped vial under N_2 for 20 h. [b] Yield of an isolated product based on heteroarene. [c] Using 0.75 mmol **6**. [d] The initial product was dihydropyrimidine **8**. The yield was determined after oxidation of **8** with DDQ.

entry 4). Although an electronically diverse array of quinolines efficiently afford 2-arylated products under optimized conditions, their reactivities are significantly different. Electron-deficient substrates are generally arylated more rapidly (Scheme 3).[23] This catalytic arylation is tolerant to steric



Scheme 3. Electronic effect of N-heteroarenes.

hindrance. 3-Substituted quinolines successfully underwent the arylation at the sterically congested C2-position to deliver 2,3-disubstituted quinolines (Table 3, entries 6 and 7). Moreover, introduction of a C8 substituent, which imposes a steric demand around a ring nitrogen atom, did not interfere the arylation (Table 3, entry 8). The present protocol can be used not only to construct heterobiaryls, but also to elaborate them (Table 3, entries 9–11). Of note is the high reactivity of 2,2′-bipyridine, which successfully afforded a monophenylated product in a selective manner, even in the presence of excess **6**.[13c] The reaction should be applicable to the synthesis of a range of C1-symmetric 2,2′-bipyridine ligands.

In the course of our investigation, we noticed that the efficiency of catalysis is highly dependent on the method used to prepare the organozinc reagent. We used commercially available solid Ph_2Zn (**6**), which successfully participated in the nickel-catalyzed arylation as described thus far. In contrast, no desired arylated product was obtained in the arylation of **5** when Ph_2Zn solution prepared by the reaction of $ZnCl_2$ with two equivalents of PhMgBr or PhLi was used. These results indicate that the presence of concomitant metal salts such as MgX_2 or LiX may have a detrimental effect on the nickel-catalyzed process.[24,25] Indeed, the yield of **7** was significantly improved (68%) by using salt-free Ph_2Zn solution prepared through the Charette and Côté's procedure ($2PhMgBr + Zn(OMe)_2$; filtration).[26] As an alternative metal-free protocol for the preparation of diorganozinc reagents, transmetalation from organoboron reagents was next examined.[27] Among those examined, zinc reagents prepared by the method of Fu and Smith, wherein aryl boronic acids were treated with Et_2Zn to generate ArZnEt,[27b] proved the most effective aryl donors for arylation of electron-deficient heteroarenes using the developed reaction. As shown in Table 4, a diverse range of aryl groups, which are derived from readily available aryl boronic acids, can be incorporated into a quinoline core. Functional groups including ethers (entries 3, 8, and 12), amines (entry 4), sulfides (entry 5), fluorides (entry 6), esters (entry 10) and chlorides (entry 12) are compatible with this arylation reaction. The

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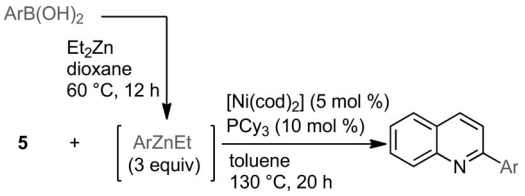
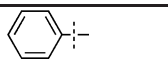
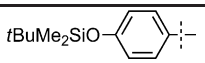
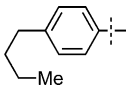
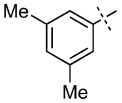
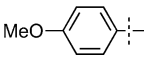
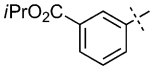
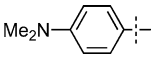
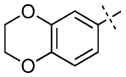
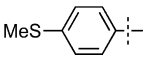
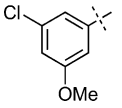
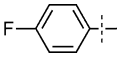
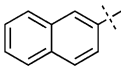
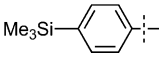
Table 4. Scope of organozinc reagents.[a]



Entry	Ar	Yield [%][b]	Entry	Ar	Yield [%][b]
1		75	8		86
2		97	9		71
3		97	10		31
4		93	11		90
5		56	12		51
6		56	13		65
7		63			

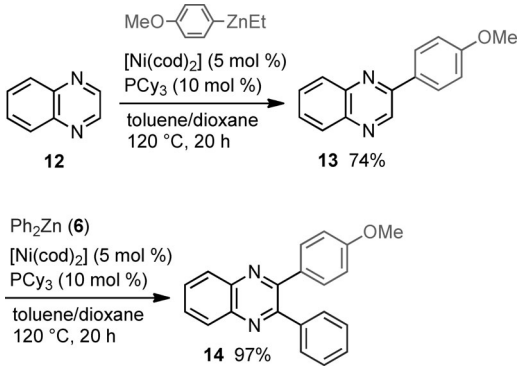
[a] Reaction conditions: $ArB(OH)_2$ (0.75 mmol) and $ZnEt_2$ (1.1 mmol) in dioxane (0.5 mL) at 60 °C for 12 h; **5** (0.25 mmol), $[Ni(cod)_2]$ (0.013 mmol), and PCy_3 (0.025 mmol) in toluene (1.0 mL) at 130 °C for 20 h. [b] Yields of isolated product based on **5**.

tolerance for a wide range of functionalities highlights the advantage of using organozinc reagents in view of the potential reactivity of C–O,[28] C–S,[29] C–F,[30] and C–Cl[31] bonds under Ni^0 catalysis when more nucleophilic Grignard reagents are employed. The electronic nature of the aryl group on the zinc reagent has a significant impact: arylation proceeds more efficiently with an electron-rich donor than with an electron-deficient donor, as anticipated in our initial reaction design.

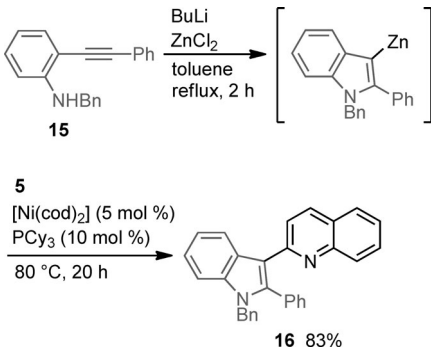
Use of ArZnEt reagents allows for sequential diarylation of heteroarenes containing two possible reaction centers. For example, two different aryl groups can be introduced onto a quinoxaline scaffold through two nickel-catalyzed arylations using different aryl zinc reagents (Scheme 4).[32]

More elaborate aryl zinc reagents can also be used in the developed reaction. Nakamura et al. reported that treatment of 2-alkynyl aniline derivatives, such as **15**, with *n*-butyllithium, followed by reaction with $ZnCl_2$, generates 2-indolylzinc reagents, which are amenable to various transformations, including Negishi-type cross-coupling.[33] The nickel-catalyzed reaction of the 2-indolylzinc generated from **15** with **5** successfully delivered a cross-coupled product **16**, further highlighting the synthetic utility of this methodology (Scheme 5).

Oxidative nucleophilic alkylation using the corresponding alkyl zinc reagents was examined briefly. Although Me_2Zn

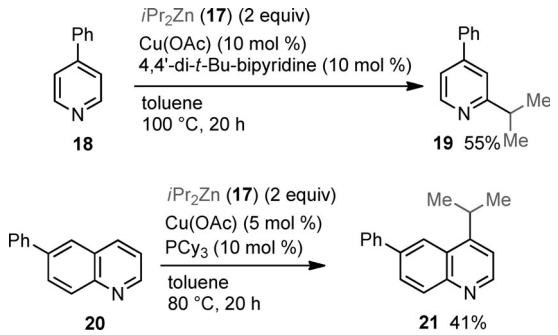


Scheme 4. Sequential direct arylations of a quinoxaline scaffold.



Scheme 5. Cyclization/direct arylation tandem reaction.

and Et_2Zn did not react with pyridine and quinoline, iPr_2Zn (**17**) proved to be a potential nucleophile (Scheme 6). For example, the reaction of 4-phenylpyridine (**18**) with **17** in the presence of Cu(OAc)/4,4′-di-*tert*-butylbipyridine catalyst

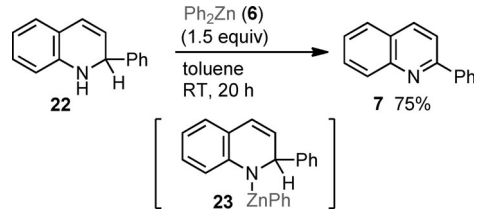


Scheme 6. Catalytic alkylation of pyridines and quinolines.

afforded 2-alkylated product **19**.[34] Interestingly, when an analogous alkylation reaction was applied to a quinoline ring system, an isopropyl group was selectively introduced at the 4-position, a completely different regioselectivity to that using Ph_2Zn (see entry 3 in Table 1).[34]

To probe the intermediacy of 1,2-dearomatized adduct (**3** in Scheme 1), the reaction of 2-phenyl-1,2-dihydroquinoline (**22**) was examined under several conditions. It was found that dehydrogenative aromatization of **22** occurs at ambient

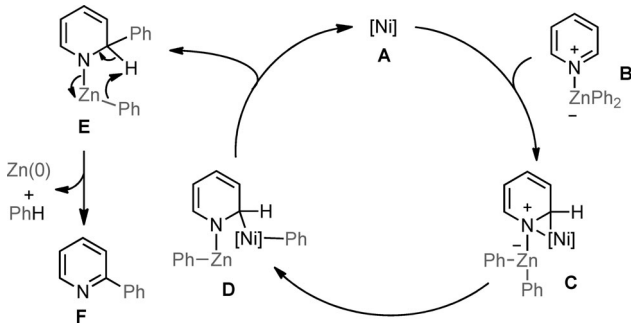
temperature upon treatment with **6**, even in the absence of a nickel catalyst (Scheme 7). Accordingly, after the formation of the postulated 1,2-dearomatized adduct, the hydrogen atom at the 2-position is eventually abstracted by an or-



Scheme 7. Rearomatization of dihydroquinoline **22** with Ph_2Zn (**6**).

ganozinc species like **23**, rather than through β-hydrogen elimination from a nickel-amide intermediate, as in **3** (m = Ni). Indeed, NMR spectroscopy studies of a nickel-catalyzed reaction of 2-deuteroquinoline with **6** indicates the formation of deuterobenzene.[35]

On the basis of the observations described above, a rational mechanistic framework for the nickel-catalyzed direct arylation of pyridine using **6** is outlined in Scheme 8. Ni^0 spe-



Scheme 8. Possible mechanism.

cies **A** initially reacts with diphenylzinc–pyridine adduct **B** to form azanickelacyclopropane **C**. An analogous intermediate was proposed in the nickel(0)-mediated addition of $AlMe_3$ across imines.[36] An intramolecular phenyl transfer (better described as intramolecular transmetalation between nickel(II) amide and diphenylzincate) affords a nickel species **D**,[37] which subsequently liberates a Ni^0 catalyst **A** along with zinc amide **E** by reductive elimination. In the case of pyrimidine substrates, intermediate **E** was intercepted by protonation to give 1,2-addition products (entry 3 in Scheme 2). For other heteroarenes, zinc amide species such as **E** underwent rapid oxidative rearomatization, leading to arylated products (Scheme 7). In this step, a phenyl group on the zinc center in **E** formally abstracts a hydrogen atom at the C2 position to form an aromatized heteroarene **F**, metallic zinc, and benzene,[38] which is in line with results obtained in labeling experiments.[35] The organozinc reagent plays three key roles in this mechanism: 1) as a Lewis acid to electrophilically activate pyridine substrates and strengthen their interaction with electron-rich nickel species, 2) as a mild aryl donor, and 3) as an oxidant to rearomatize the 1,2-addition product.

Conclusions

A catalytic variant of the classical two-step protocol for the C2-functionalization of pyridines using Grignard or organolithium reagents has been developed. The use of diorganozinc reagents renders the reaction one-step, catalytic, and functional-group-tolerant. $[Ni(cod)_2]/PCy_3$ proved the best catalyst, and zinc reagents prepared from aryl boronic acids bearing an array of functional groups were successfully employed. The methodology allows straightforward access to a range of arylated pyridines and related N-heteroarenes, which are poor substrates for the catalytic direct arylation reaction. The nucleophilic oxidative arylation reaction developed here provides a strategy for C–H functionalization of heteroarenes that is complementary to the well-established direct arylations by S_EAr and CMD pathways in terms of both applicable substrates and regioselectivity. Further development of alternative strategies for the functionalization of C–H bonds is in progress.

Experimental Section

General information

^1H NMR and ^{13}C NMR spectra were recorded on a JEOL JMN-270, JEOL ECS-400, or JEOL ECP-400 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sext = sextet, sept = septet, br = broad and m = multiplet), coupling constant (Hz), integration, and interpretation. Infrared spectra (IR) were obtained on a Horiba FT-720 spectrometer. Mass spectra were obtained on a Shimadzu GCMS-QP 5000 or GCMS-QP 2010 instrument with ionization voltages of 70 eV. Melting points were determined on a Yamato melting point apparatus and are uncorrected. Elemental analyses and high-resolution mass spectra (HRMS) were performed by the Elemental Analysis Section of Osaka University. Flash column chromatography was performed with SiO_2 (Silicycle Silica Flash F60 (230–400 mesh)). All catalytic reactions were carried out in 10 mL sample vials with a Teflon-sealed screw cap in a glovebox filled with N_2.

Materials

1,4-Dioxane and toluene were used after distillation over sodium benzophenone and calcium hydride, respectively. $[Ni(cod)_2]$ was purchased from STREM chemicals, Inc. and used as received. Ph_2Zn (**6**) was purchased from Wako Chemicals and used as received. PCy_3 was purchased from Sigma–Aldrich and used as received. Pyridine was purchased from Wako chemicals and used after distillation. Quinoline (**5**) was purchased from Sigma–Aldrich and used after distillation. Isoquinoline, phenanthridine, 4-phenylpyridine, 4,4′-bipyridine, and pyrazine were purchased from TCI laboratory chemicals and used as received. Phenylboronic acid was purchased from TCI laboratory chemicals and used as received. 3,5-Dimethylphenylboronic acid, 2-naphthylboronic acid, 4-methoxyphenylboronic acid, 4-(*N*,*N*-dimethylamino) phenylboronic acid, and 3-chloro-4-methoxyphenylboronic acid were purchased from Sigma–Aldrich and used as received. Et_2Zn was purchased from Sigma–Aldrich and used as received. *N*-Benzyl-2-phenylethynyl aniline (**15**) was pre-

pared by alkynylation of 2-iodoaniline under Sonogashira conditions, followed by N-benzylation.[33] 2-Phenyl-1,2-dihydroquinoline (**22**) was prepared by the reaction of quinoline with phenyllithium.[39] 2-Deuteroquinoline was prepared by the deuteration of 2-quinolyllithium, prepared from the reaction of 2-bromoquinoline with *n*BuLi, using D_2O. 2-(4-Tolyl)pyrimidine and 6-phenylquinoline (**20**) were prepared through the procedure reported by Fu et al.[40]

*General procedure for nickel-catalyzed phenylation of heteroarenes using **6** (entry 4 in Table 2).*

An oven-dried 10 mL screw-capped vial was charged with $[Ni(cod)_2]$ (3.4 mg, 0.013 mmol), PCy_3 (7.0 mg, 0.025 mmol), **6** (84 mg, 0.38 mmol), **5** (32 mg, 0.25 mmol), and toluene (1.0 mL) in a glovebox. The cap was fastened and the mixture was stirred at 80 °C for 20 h. After the volatiles were removed in vacuo, chromatography on silica gel (hexane/EtOAc = 50:1 to 20:1) furnished 2-phenylquinoline (**7**, 50.8 mg, 99 %) as a white solid.

*2-Phenylquinoline (**7**)*

White solid; $R_f = 0.49$ (hexane/EtOAc = 5:1); m.p. = 86 °C; ^{1}H NMR ($CDCl_3$, 270 MHz): $\delta = 7.48$–7.58 (m, 4H), 7.74 (t, $J = 5.9$ Hz, 1H), 7.71–7.90 (m, 2H), 8.17–8.23 ppm (m, 4H); ^{13}C NMR ($CDCl_3$, 67.80 MHz): $\delta = 119.4$, 126.7, 127.6, 127.9, 128.0, 129.2, 129.8, 130.1, 130.2, 137.2, 140.1, 148.7, 157.8 ppm; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{11}N$: 205.0891; found: 205.0884.

2-Methyl-4-phenylpyrimidine

An oven-dried 10 mL screw-capped vial was charged with $[Ni(cod)_2]$ (3.4 mg, 0.0125 mmol), PCy_3 (7.0 mg, 0.025 mmol), **6** (83.5 mg, 0.38 mmol), 2-methylpyrimizine (23.5 mg, 0.25 mmol), and toluene (1.0 mL) in a glovebox. The cap was fastened, and the mixture was stirred for 20 h at 60 °C. The reaction mixture was quenched with MeOH (0.5 mL). The reaction mixture was then filtered through a Celite pad, and the pad was washed with Et_2O. After removing the volatiles in vacuo, 2-methyl-4-phenyl-3,4-dihydropyrimidine was obtained in quantitative yield. This addition product was then treated with HOAc (12 μL), DDQ (68.1 mg, 0.3 mmol), H_2O (0.5 mL), and THF (3 mL), and the mixture was stirred at room temperature in air for 20 h. The reaction mixture was quenched with NaOH (1 M, 0.3 mL, 0.3 mmol). The mixture was diluted with Et_2O (5 mL), dried over $MgSO_4$, and concentrated in vacuo. Chromatography on silica gel (hexane/EtOAc = 10:1) furnished 2-methyl-4-phenylpyrimidine (23.0 mg, 54 %).

White solid; $R_f = 0.11$ (hexane/EtOAc = 5:1); m.p. = 43 °C; ^{1}H NMR ($CDCl_3$, 399.78 MHz): $\delta = 2.81$ (s, 3H), 7.49–7.50 (m, 3H), 7.51 (s, 1H), 8.06–8.09 (m, 2H), 8.67 ppm (d, $J = 5.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz): $\delta = 26.3$, 113.9, 127.1, 128.9, 130.8, 136.9, 157.4, 164.1, 168.4 ppm; HRMS (ESI): *m*/*z* calcd for $C_{11}H_{10}N_2$: 170.0844; found: 170.0842.

*Regioselective C–H arylations of imidazo[1,2-a]pyrazine (Scheme 2).8-Phenylimidazo[1,2-a]pyrazine (**10**)*

An oven-dried 10 mL screw-capped vial was charged with $[\{RhCl(cod)\}_2]$ (6.2 mg, 0.013 mmol), PCy_3 (7.0 mg, 0.025 mmol), **6** (84 mg, 0.38 mmol), imodazo[1,2-a]pyrazine (**9**, 30 mg, 0.25 mmol), and toluene (1.0 mL) in a glovebox. The cap was fastened and the mixture was stirred at 100 °C for 20 h. After the volatiles were removed in vacuo, chromatography on silica gel (hexane/EtOAc = 5:1 to 1:1) furnished 8-phenylimidazo[1,2-a]pyrazine (**10**, 20 mg, 40 %) as a white solid. Analytically pure product was obtained by GPC.

White solid; $R_f = 0.57$ (EtOAc); m.p. = 85 °C; ^{1}H NMR ($CDCl_3$, 399.78 MHz): $\delta = 7.49$–7.58 (m, 3H), 7.72 (d, $J = 0.1$ Hz, 1H), 7.86 (d, $J = 0.8$, 1H), 7.97 (d, $J = 4.4$, 1H), 8.0 (d, $J = 4.4$ Hz, 1H), 8.63–8.66 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 100.53 MHz): $\delta = 113.8$, 117.9, 128.4, 129.1, 129.5, 130.3, 134.9, 136.0, 139.5, 150.4 ppm; HRMS (ESI): *m*/*z* calcd for $C_{12}H_9N_3$: 195.0796; found: 195.0799. The structure was confirmed by the comparison of these spectra with those reported in the previous report.[20]

*3-Phenylimidazo[1,2-a]pyrazine (**11**)*

The procedure for the arylation of imidazo[1,2-a]pyrimidine was followed.[41] An oven-dried 10 mL screw-capped vial was charged with $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), PPh_3 (6.6 mg, 0.025 mmol), iodobenzene (102.0 mg, 0.50 mmol), Cs_2CO_3 (163 mg, 0.5 mmol), imodazo[1,2-a]pyrazine (**9**, 30 mg, 0.25 mmol), and dioxane (2.0 mL) in a glovebox. The cap was fastened, and the mixture was stirred at 120 °C for 20 h. After the volatiles were removed in vacuo, chromatography on silica gel (hexane/EtOAc = 1:1 to 0:1) furnished 3-phenylimidazo[1,2-a]pyrazine (**11**, 48.3 mg, 99 %) as a white solid.

White solid; $R_f = 0.17$ (hexane/EtOAc = 5:1); m.p. = 94 °C; ^{1}H NMR ($CDCl_3$, 399.78 MHz): $\delta = 7.47$–7.51 (m, 1H), 7.55–7.60 (m, 4H), 7.89 (s, 1H), 7.91 (d, $J = 4.4$ Hz, 1H), 8.27 (dd, $J = 1.6$, 4.4 Hz, 1H), 9.16 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz): $\delta = 116.2$, 126.9, 127.8, 127.9, 129.0, 129.4, 129.9, 134.5, 141.3, 144.5 ppm; HRMS (ESI): *m*/*z* calcd for $C_{12}H_9N_3$: 195.0796; found: 195.0803.

*General procedure for nickel-catalyzed arylation of **5** using aryl zinc reagents generated from aryl boronic acid and diethylzinc (entry 1 in Table 4).*

An oven-dried 10 mL screw-capped vial was charged with Et_2Zn (130 mg, 1.1 mmol) and 1,4-dioxane (0.5 mL) in a glovebox, followed by the addition of phenylboronic acid (91 mg, 0.75 mmol; most of the aryl boronic acid examined dissolved exothermically with ethane generation). The cap was fastened and the mixture was stirred at 60 °C for 12 h. After the mixture cooled to room temperature, $[Ni(cod)_2]$ (3.4 mg, 0.013 mmol), PCy_3 (7.0 mg, 0.025 mmol), quinoline (**5**, 32 mg, 25 mmol), and toluene (1.0 mL) were added in a glovebox. The mixture was stirred at 130 °C for 20 h. After the volatiles were removed in vacuo, chromatography on silica gel (hexane/EtOAc = 50:1 to 20:1) furnished 2-phenylquinoline (**7**, 38.5 mg, 75 %) as a white solid.

*A procedure for Scheme 52-(1-Benzyl-2-phenyl-1H-indol-3-yl)quinoline (**16**)*

An oven-dried 10 mL pressure-screw-capped vial was charged with *N*-benzyl-2-phenylethynylaniline (180.3 mg, 0.63 mmol) and toluene (0.75 mL). Then, *n*BuLi (1.6 M in hexane, 0.39 mL, 0.63 mmol) was added slowly at room temperature and heated at reflux for 2 h to afford 2-phenyl-3-zincioindole.[33] $[Ni(cod)_2]$ (3.5 mg, 0.0129 mmol), PCy_3 (8.0 mg, 0.029 mmol), quinoline (32.7 mg, 0.25 mmol), and toluene (0.5 mL) were added to this reaction mixture in a glovebox. The reaction mixture was subjected to column chromatography on silica gel to give the *N*-benzyl-2-phenyl-3-(2-quinolyl) indole as a colorless solid (84.9 mg, 83 %).

White solid; $R_f = 0.43$ (hexane/EtOAc = 5:1); m.p. = 186 °C; ^{1}H NMR ($CDCl_3$, 270.05 MHz): $\delta = 5.34$ (s, 2H), 6.94–7.01 (m, 3H), 7.21–7.49 (m, 12H), 7.68–7.73 (m, 2H), 7.80 (d, $J = 8.6$ Hz, 1H), 8.51 (d, $J = 8.6$ Hz, 1H), 8.62 ppm (d, $J = 7.3$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 150.84 MHz): $\delta =$ 47.5, 110.4, 115.2, 121.5, 121.8, 122.4, 123.0, 125.5, 126.0, 126.1, 127.2, 127.3, 127.4, 128.6, 128.8, 128.9, 129.1, 131.0, 131.7, 135.0, 137.2, 137.6, 140.6, 148.3, 155.5 ppm; HRMS (ESI): *m*/*z* calcd for $C_{30}H_{22}N_2$: 410.1783; found: 410.1781.

*Catalytic Alkylation of N-Heteroarenes Using iPr_2Zn (**17**) (Scheme 6).2-Isopropyl-4-phenylpyridine (**19**) [883566–21–0]*

An oven-dried 10 mL screw-capped vial was charged with Cu(OAc) (3.0 mg, 0.025 mmol), 4,4′-di-*tert*-butylbipyridine (6.7 mg, 0.025 mmol), diisopropylzinc solution (1 M in toluene, 0.5 mL, 0.50 mmol), 4-phenylpyridine (**18**, 39 mg, 0.25 mmol), and toluene (0.5 mL) in a glovebox. The cap was fastened, and the mixture was stirred at 120 °C for 20 h. After the volatiles were removed in vacuo, chromatography on silica gel (hexane/EtOAc = 50:1 to 30:1) furnished 2-isopropyl-4-phenylpyridine (**19**, 27 mg, 55 %) as a greenish oil. Analytically pure product was obtained by GPC.

Greenish oil; $R_f = 0.26$ (hexane/EtOAc = 5:1); ^{1}H NMR ($CDCl_3$, 399.78 MHz): $\delta = 1.36$ (d, $J = 6.8$ Hz, 6H), 3.14 (sept, $J = 6.8$ Hz, 1H), 7.32–7.33 (m, 1H), 7.38 (s, 1H), 7.41–7.51 (m, 3H), 7.63–7.65 (m, 2H), 8.59 ppm (d, $J = 5.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz): $\delta = 22.6$,

36.4, 118.7, 119.2, 127.1, 128.8, 129.0, 138.7, 148.9, 149.4, 167.8 ppm; HRMS (ESI): *m/z* calcd for $C_{14}H_{15}N$: 197.1204; found: 197.1207.

*4-Isopropyl-6-phenylquinoline (**21**)*

An oven-dried 10 mL screw-capped vial was charged with Cu(OAc) (1.5 mg, 0.013 mmol), PCy_3 (7.0 mg, 0.025 mmol), diisopropylzinc solution (1 M in toluene, 0.5 mL, 0.50 mmol), 6-phenylquinoline (**20**, 51 mg, 0.25 mmol), and toluene (0.5 mL) in a glovebox. The cap was fastened and the mixture was stirred at 80 °C for 20 h. After volatiles were removed in vacuo, chromatography on silica gel (hexane/EtOAc = 10:1 to 5:1) furnished 4-isopropyl-6-phenylquinoline (**21**, 25 mg, 41 %) as a clear oil. Analytically pure product was obtained by GPC.

Greenish-yellow oil; R_f = 0.14 (hexane/EtOAc = 5:1); ^{1}H NMR ($CDCl_3$, 399.78 MHz): δ = 1.44 (d, J = 7.2 Hz, 6H), 3.83 (sept, J = 7.2 Hz, 1H), 7.33 (d, J = 4.4 Hz, 1H), 7.40–7.43 (m, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.72 (d, J = 7.2 Hz, 2H), 7.95 (dd, J = 2.0, 8.8 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.26 (d, J = 2.0 Hz, 1H), 8.85 ppm (d, J = 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.53 MHz): δ = 22.9, 28.3, 117.3, 121.1, 127.0, 127.6, 127.6, 128.6, 128.9, 130.7, 139.0, 140.9, 147.6, 150.3, 154.5 ppm; IR (neat): $\tilde{\nu}$ = 3060 (m), 3028 (m), 2966 (s), 2931 (m), 2871 (m), 1926 (w), 1587 (s), 1492 (s), 1460 (m), 1388 (m), 1362 (s), 1279 (w), 1241 (m), 1215 (w), 1155 (m), 1105 (w), 1076 (w), 1051 (w), 1011 (w), 968 (w), 922 (w), 885 (m), 856 (s), 831 (m), 762 (s), 698 (s), 600 cm^{-1} (w); MS (70 eV): *m/z* (%): 248 (20), 247 (M^+, 100), 246 (10), 233 (18), 232 (95), 230 (19), 217 (11), 115 (11), 88 (10); HRMS (ESI): *m/z* calcd for $C_{18}H_{17}N$: 247.1361; found: 247.1366.

*The reaction of 2-phenyl-1,2-dihydroquinoline (**13**) with Ph_2Zn (Scheme 7).*

An oven-dried 10 mL pressure-screw-capped vial was charged with Ph_2Zn (83.6 mg, 0.38 mmol), 2-phenyl-1,2-dihydroquinoline[39] (**13**, 51.5 mg, 0.25 mmol), and toluene (1.0 mL) in a glovebox. The cap was fastened and the mixture was stirred for 20 h at room temperature. The reaction mixture was subjected to column chromatography on silica gel to afford 2-phenylquinoline (38.5 mg, 75 %). This result shows that the oxidation process of 1,2-dihydroquinoline proceeds in the absence of a nickel catalyst at room temperature.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis" from the Ministry of Education, Culture, Sports, Science and Technology, Japan. I.H. thanks to JSPS for a Research Fellowship for Young Scientists and the Global COE Program of Osaka University. We also thank the Instrumental Analysis Center, Faculty of Engineering, Osaka University, for assistance with the MS, HRMS, and elemental analyses.

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[34] a) In the case of $i Pr_2Zn$ (**17**) as a nucleophile, nickel and other metal catalysts were ineffective. See the Supporting Information for details. b) The mechanism with copper-based catalyst is likely to be different from that with a nickel catalyst. An alkyl copper(I) species is a potential intermediate. See the Supporting Information.

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[37] a) An alternative pathway to intermediate **D** involves an anionic phenylnickelate species, which may be formed by the reaction of Ni^0 with Ph_2Zn. For a proposal of a similar nickelate intermediate, see: J. Terao, S. Nii, F. A. Chowdhury, A. Nakamura, N. Kambe, *Adv. Synth. Catal.* **2004**, *346*, 905; b) When Cu^I or Rh^I catalyst was used, the phenylmetal complex is likely to serve as an active species to form an intermeditate analogous to **D**. See the Supporting Information for a possible catalytic cycle for Cu^I and Rh^I catalysis.

[38] a) Intermolecular hydrogen abstraction of **E** by an external Ph_2Zn is unlikely since the arylation proceeds in 62% yield when only 1 equiv Ph_2Zn is used; b) When *N*-benzylideneaniline, in place of quinoline, was used in a nickel-catalyzed reaction with Ph_2Zn, a mixture of an addition product (54%) and an oxidative arylation product (39%) was obtained. These results indicate that aromatization is the primary driving force for the reaction of **E** to **F**.

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Received: November 30, 2011
Revised: February 8, 2012
Published online: ■■ ■■, 0000

FULL PAPERS

Catalytic Arylation

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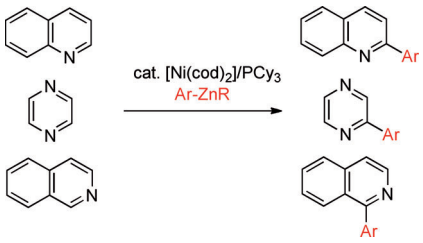
Catalytic Arylation of a C–H Bond in Pyridine and Related Six-Membered N-Heteroarenes Using Organozinc Reagents



Less is more: Pyridine, pyrazine, quinoline and related electron-deficient N-heteroarenes can be arylated at the most electrophilic site using organozinc reagents through nickel catalysis. This protocol serves as a complementary method to catalytic direct arylation reactions.

