Cross-Coupling

International Edition: DOI: 10.1002/anie.201502379
German Edition: DOI: 10.1002/ange.201502379

Ligand-Free Copper-Catalyzed Negishi Coupling of Alkyl-, Aryl-, and Alkynylzinc Reagents with Heteroaryl Iodides**

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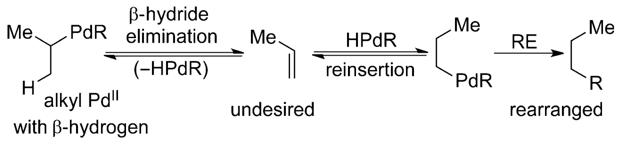
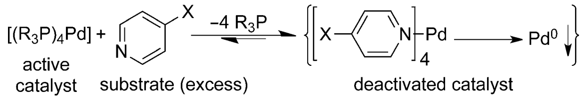
Abstract: *Reported herein is an unprecedented ligand-free copper-catalyzed cross-coupling of alkyl-, aryl-, and alkynylzinc reagents with heteroaryl iodides. The reaction proceeds at room temperature for the coupling of primary, secondary, and tertiary alkylzinc reagents with heteroaryl iodides without rearrangement. An elevated temperature (100°C) is required for aryl–heteroaryl and alkynyl–heteroaryl couplings.*

Negishi coupling represents one of the most versatile transformations utilized for constructing carbon–carbon (C–C) bonds in a variety of synthetic targets.[1] Over the course of the last three decades, tremendous progress has been made in the context of scope for this reaction and a wide variety of substrates can now be coupled effectively. Despite significant progress in the substrate scope, two classes of coupling partners, alkylzinc reagents and heteroaryl halides, still pose significant challenges.[2] Direct cross-coupling of alkylzinc reagents with heteroaryl halides only makes the transformation more challenging. As such, examples of couplings between alkylzinc reagents and heteroaryl halides to generate alkylated heteroarenes are limited.[3] Alkyl substrates containing β-hydrogen atoms generally derail the reaction pathway by β-hydride elimination after transmetalation and generate olefins as side products (Scheme 1).[4] In addition, secondary and tertiary alkylzinc reagents containing β-hydrogen atoms pose further challenges because of the rearrangement by a β-hydride elimination/migratory reinsertion process, thus affording a mixture of both the desired and rearranged products.[5] Heteroaryl halides are known to cause considerable problems by binding to the catalysts competitively over the ligands, thus eventually leading to catalyst inhibition and deactivation (Scheme 2).[6]

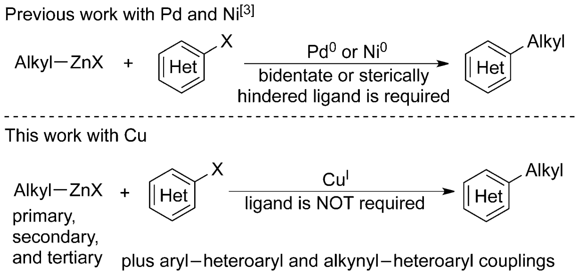


Scheme 1. Complications resulting from β-hydride elimination.



Scheme 2. Complications resulting from heteroaryl halides.

Inspired by the ubiquitous presence of alkylated and arylated heteroarenes in pharmaceuticals and drug candidates,[7] tremendous efforts have been dedicated to designing effective catalysts to overcome these limitations. In palladium- and nickel-based catalytic systems, the complication associated with alkylzinc reagents bearing β-hydrogen atoms is generally addressed by the application of bidentate and/or custom-designed, sterically hindered ligands (Scheme 3).[3g,8] This strategy renders reductive elimination faster than β-hydride elimination, thereby affording the desired products.[3g] Recently, seminal work by the groups of Lipshutz,[3l] Organ,[3g] Knochel,[3c,e] Biscoe,[3b] and Buchwald[3f] have further shown that these sterically hindered ligands also enable the efficient cross-coupling of alkylzinc reagents with heteroaryl halides using palladium and nickel catalysts to generate alkylated heteroarenes. Despite having this strategy already at our disposal, the availability of a simple reaction protocol which allows us to conduct similar transformations in the absence of custom-designed ligands would no doubt have a significant impact on the cost-effective and sustainable syntheses of pharmaceuticals and drug candidates. Herein, we report one such simple reaction protocol that enables us to



Scheme 3. Coupling of heteroaryl halides with alkylzinc reagents containing β-hydrogen atoms.

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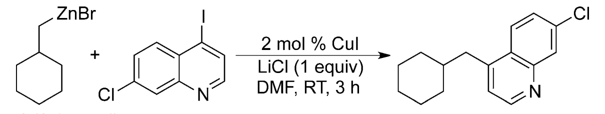
[**] We thank the University of New Mexico (UNM) for financial support, and upgrades to the NMR (NSF grants CHE08-40523 and CHE09-46690) and MS Facilities.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201502379.

execute, for the first time, a copper-catalyzed coupling of alkyl-, aryl-, and alkynylzinc reagents with heteroaryl iodides without requiring the addition of a ligand (Scheme 3).[9] The reaction proceeds efficiently at room temperature with primary, secondary, and tertiary alkylzinc reagents without β-hydride elimination and rearrangement. The reaction protocol can be extended to the coupling of aryl- and alkynylzinc reagents with heteroaryl iodides at an elevated temperature (100 °C).

Recently, we[10] and others[11] have demonstrated that copper catalysts could effect couplings of different organometallic reagents with aryl halides.[12] However, despite literature evidence for facile transmetalation of alkyl- and arylzinc reagents with copper salts,[13] as evidenced in allylic[14] and 1,2-addition[15] reactions, catalytic cross-coupling with organohalides has remained elusive.[16] In this regard, encouraged by the versatility and unique reactivity of copper catalysts towards heteroaryl iodides, a reaction which proceeds without requiring ligands,[10] we reasoned that successful execution of the coupling of alkylzinc reagents with heteroaryl iodides under ligand-free conditions could address the longstanding challenge entrenched in palladium and nickel catalysis where specially designed, sterically hindered ligands are required. Therefore, we initially attempted the coupling of cyclohexylmethylzinc bromide with 7-chloro-4-iodoquinoline. We were surprised to find that the reaction not only proceeded without a ligand but also was completed after 3 hours at room temperature in DMF, thus affording the alkylated heteroarene **3** in 64 % yield (Table 1, entry 1). Further analysis by seeding the reaction mixture with 1 equivalent of ZnI_2, a byproduct of the reaction, indicated that the cross-coupling was experiencing a mild product inhibition (entry 2), potentially a result of reverse transmetalation from [R-Cu] to ZnI_2 as the concentration of the latter increases during the reaction.[11c] Addition of LiCl, which is generally considered to generate more reactive organozinc species,[17] effectively eliminated the inhibition and furnished the coupled product in 98 % GC yield (entry 3).[18] Alternatively, addition of 2 equivalents of NaOAc, which would convert ZnI_2 into $Zn(OAc)_2$, also afforded the product in 96 % GC yield (entry 4).

Table 1: Standard and control reactions.[a]



1 (0.1 mmol) **2** (0.1 mmol) **3**

Entry	Modified reaction conditions	Yield [%][b]
1	without LiCl	64
2	1 equiv ZnI_2 without LiCl	10
3	standard conditions	98 (92)
4	2 equiv NaOAc instead of LiCl	96
5	without CuI	0
6	without CuI, 120 °C, 24 h	trace
7	CuO*t*Bu (sublimed) instead of CuI	97
8	1 mol % CuI	85
9	0.1 mol % CuI at 60 °C, 12 h	78
10	0.1 mol % [$Pd(dba)_2$] instead of CuI	trace
11	0.1 mol % [$(Ph_3P)_4Ni$] instead of CuI	trace
12	1,4-dioxane instead of DMF	trace
13	toluene instead of DMF	0
14	DMSO instead of DMF	96
15	DMA instead of DMF	95

[a] Reactions were run in 0.5 mL DMF. CuI (99.999 %) was used.
[b] Yields determined by GC using pyrene as a standard. Value within parentheses is yield of the product isolated from a 1.0 mmol scale reaction. Reactions with 2-bromopyridine, 2-chloropyridine, and 2-pyridyl triflate did not afford any product. dba = dibenzylideneacetone, DMA = dimethylacetamide, DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide.

The reaction did not furnish the coupled product in the absence of CuI, and provided only a trace amount of the product even after heating the reaction for 12 hours at 120 °C (Table 1, entries 5 and 6). Use of [CuO*t*Bu], purified by sublimation, as a catalyst also afforded the product in a similar yield (entry 7). While lowering the loading of CuI to 1 mol % at room temperature slightly decreased the yield (entry 8), the reaction could be conducted with as low as 0.1 mol % CuI at 60 °C with a turnover number (TON) of 780 and turnover frequency (TOF) of 65 h^{-1} (entry 9). The reaction produced the coupled products only in trace amounts when [$Pd(dba)_2$] and [$(Ph_3P)_4Ni$], known catalysts for the Negishi cross-coupling, were utilized instead of CuI under the current reaction conditions (entries 10 and 11), thus suggesting that the reaction is unlikely to be catalyzed by low levels of palladium and nickel contaminants. While the reactions in 1,4-dioxane and toluene did not produce the product, DMF can be replaced with similar solvents such as DMA and DMSO (entries 12–15).

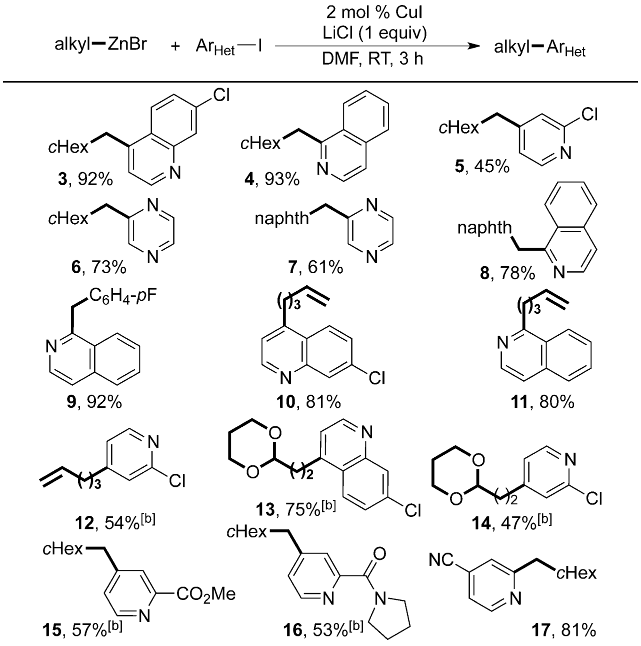
After optimizing the reaction conditions, we surveyed the substrate scope of the current cross-coupling. The reaction proceeds well for the coupling of different heteroaryl iodides with a variety of organozinc reagents to afford the desired products in excellent yields (Tables 2–5). Iodides of a number of nitrogen-containing heterocycles such as quinoline, isoquinoline, pyridine, and pyrazine can be utilized as coupling partners. The reaction demonstrates a high level of efficacy for the coupling of primary, secondary, and tertiary alkylzinc reagents containing β-hydrogen atoms.[19]

Primary alkylzinc reagents containing both aliphatic chains and aromatic rings can be utilized as coupling partners (Table 2). The coupling can be performed with heteroaryl iodides containing sensitive functional groups, such as Cl, ester, amide, and cyano, in good yields (**3**, **5**, **10**, **12**–**17**). Primary alkylzinc reagents bearing terminal olefins can be used as coupling partners (**10**–**12**). The reaction also tolerates oxygen-containing functional groups as demonstrated by the couplings of organozinc reagents derived from dioxanyl-protected aliphatic aldehydes, which furnished the products in good yields (**13** and **14**).

The coupling of secondary alkylzinc reagents proceeded smoothly with complete selectivity for the desired products (Table 3). In addition to simple open-chain and cyclic secondary alkylzinc reagents (products **18**–**24**), more sterically encumbered and strained 2-adamantyl- and cyclopropylzinc reagents can also be coupled to afford the products in high yields (**25**–**29**). The current reaction also proceeds with open-chain tertiary alkylzinc reagents and affords the desired products with complete selectivity (**30**–**33**). In addition, the tertiary adamantylzinc reagent can also be employed as a coupling partner with different heteroaryl iodides (**34** and **35**).

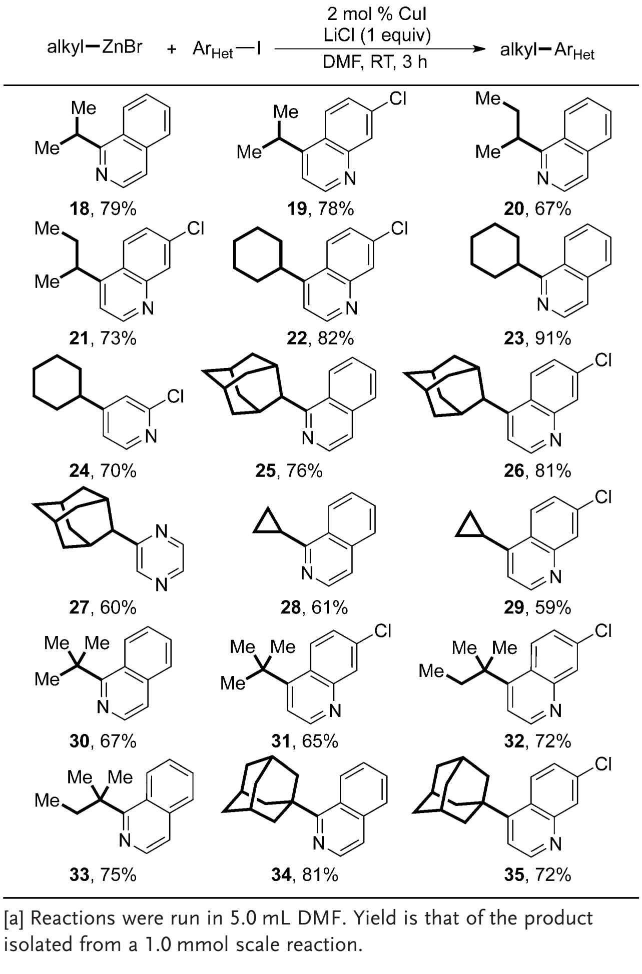
The current reaction protocol can also be extended to the coupling of arylzinc reagents with heteroaryl iodides (Table 4).[20] However, the reaction requires an elevated temperature (100 °C) to afford the products in the best yields. The reaction proceeds with a variety of heterocycles including the ones containing chloride substituent. Electron-neutral and electron-rich arylzinc reagents bearing substituents such as *ortho*-Me, OMe, and OTBS can be utilized as coupling partners. More pleasingly, the reaction also tolerates arylzinc reagents containing *ortho*-NR_2 substituents and affords the product in excellent yield (**50**). This latter aspect enabled us to use the current transformation to synthesize

Table 2: Coupling with primary alkylzinc reagents.[a]



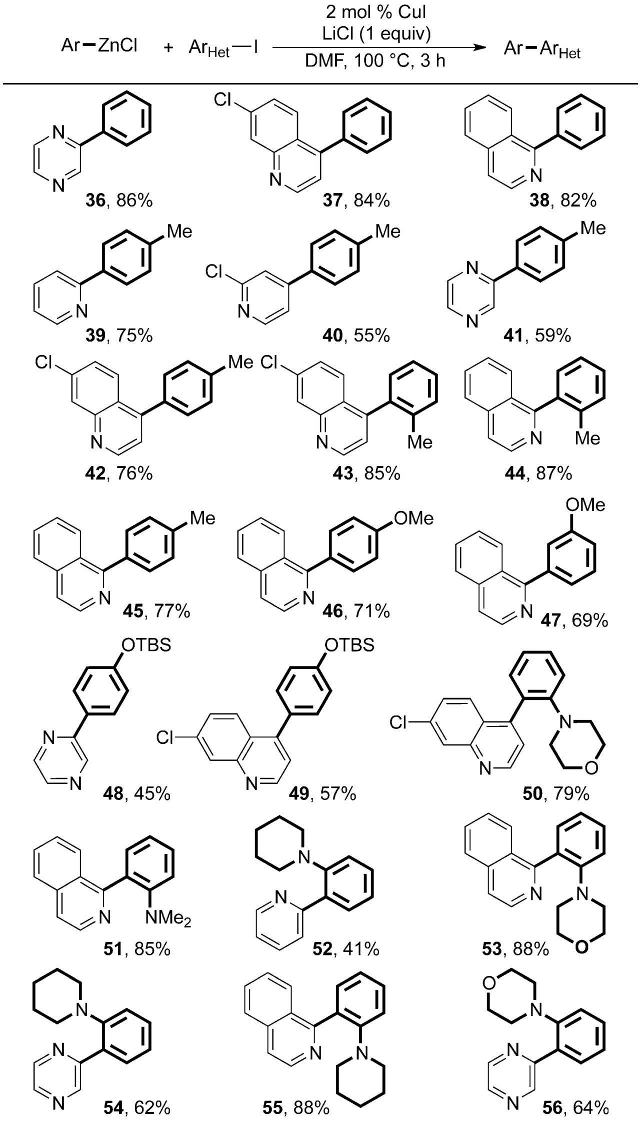
[a] Reactions were run in 5.0 mL DMF. Yield is that of the product isolated from a 1.0 mmol scale reaction. [b] 60 °C.

Table 3: Coupling with secondary and tertiary alkylzinc reagents.[a]



[a] Reactions were run in 5.0 mL DMF. Yield is that of the product isolated from a 1.0 mmol scale reaction.

Table 4: Coupling with arylzinc reagents.[a]

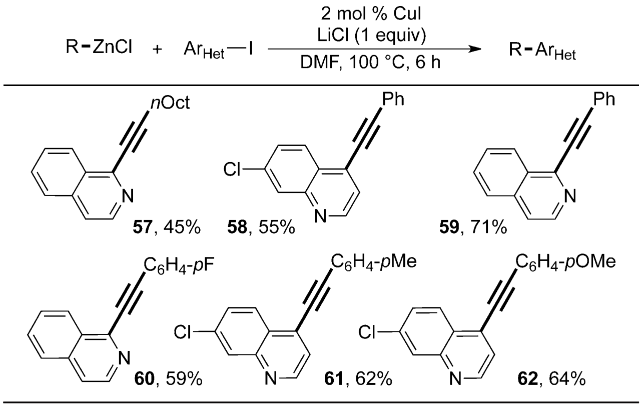


[a] Reactions were run in 5.0 mL DMF. Yield is that of the product isolated from a 1.0 mmol scale reaction. TBS = *tert*-butyldimethylsilyl.

a variety of bidentate pyridylamine ligands (**51**–**56**), thereby showcasing the practical implication of the current transformation for the synthesis of bidentate nitrogen-based ligands.

Moreover, the current conditions can be utilized for the cross-coupling of alkynylzinc reagents with heteroaryl iodides to afford the coupled heteroaryl-alkynyl products in good yields (Table 5). Alkynylzinc reagents containing both the aliphatic chains as well as aromatic rings can be utilized as coupling partners.[21]

Table 5: Coupling with alkynylzinc reagents.[a]



[a] Reactions were run in 5.0 mL DMF. Yield is that of the product isolated from a 1.0 mmol scale reaction.

In summary, we have developed an unprecedented reaction protocol for copper-catalyzed cross-coupling of alkyl-, aryl-, and alkynylzinc reagents with heteroaryl iodides without requiring the addition of ancillary ligands. The reaction affords desired cross-coupled products with primary, secondary, and tertiary alkylzinc reagents without β-hydride elimination and rearrangement. Sterically hindered alkylzinc reagents, *ortho*-amine-substituted arylzinc reagents, as well as sensitive functional groups, such as TBS-protected phenols and dioxanyl-protected aliphatic aldehydes are well tolerated.

Keywords: copper · cross-coupling · heterocycles · synthetic methods · zinc

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 8236–8240
Angew. Chem. **2015**, *127*, 8354–8358

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[21] Based on previous copper-catalyzed couplings (see Ref. [10]), the current reaction can be assumed to proceed by transmetalation followed by reaction with ArI. Since RZnX are known to undergo transmetalation with copper(I) salts below room temperature (see Ref. [13]), we believe that the reaction with ArI could be rate-limiting. In addition, alkylcopper(I) species are more electron-rich than aryl- and alkynylcopper(I) species and are more likely to react with ArI at lower temperatures than aryl- and alkynylcopper(I) species formed after transmetalation with alkyl-, aryl-, and alkynylzinc reagents.

Received: March 13, 2015
Revised: April 28, 2015