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ARTICLE

Copper-Catalysed Cross-Coupling: An Untapped Potential

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Copper is emerging as a viable catalytic metal for cross-coupling reactions to construct carbon-carbon (C–C) bonds. Recent revelations that Cu-catalysts can execute with high efficacy the cross-couplings of a variety of organometallic reagents, including organomagnesium, organoboron, organosilicon, organoindium and organomanganese, with alkyl, aryl and heteroaryl halides clearly demonstrate the versatility of Cu-based catalytic systems in conducting these reactions. In addition, Cu-catalysts are exhibiting a unique reactivity pattern that allows ligandless cross-coupling for aryl-heteroaryl and heteroaryl-heteroaryl bond formation, a transformation that generally requires special custom-designed ligands with Pd-catalysts. This review summarises early discoveries and subsequent advancements made in the area of Cu-catalysed cross-couplings of organometallic reagents with organohalides to form C–C bonds.

Introduction

Cross-coupling reactions are powerful tools for carbon-carbon (C–C) bond formation[1,2] and have been widely utilized for the synthesis of a wide variety of molecules.[3] These transformations are typically catalysed by Pd complexes. Recently, tremendous efforts have been invested in developing Cu as an alternative to Pd for these processes.[4] Efforts to invent Cu-based catalytic protocols for cross-couplings are inspired by the concerns for their long-term sustainability due primarily to the high cost and low natural abundance of Pd. In general, the high costs of precious metals, including Pd, are the results of their scarcity in the Earth's crust. Therefore, the low availabilities of these metals remain the crux of concern, particularly in cases when the use of these noble metals is on the rise. An illustrative example can be drawn from the noble metal Pt, which has drawn broad interest for use in fuel cells in vehicles.[5] Gordon and co-workers predict, with the standard output of Pt-based fuel cells for a life of 10 years and with 50% recovery rate for recycling 90% of used Pt, that the remaining lithospheric Pt can sustain a fleet of 500 million fuel cell-operated vehicles only for 15 years.[6] As Pd exists in even lower quantities than Pt in the lithosphere,[7] our heavy dependence on

and ever-increasing demand of Pd as a catalyst to make drugs and commodity chemicals essential for life is alarming.[8] Evidence for soaring consumption of Pd can be gleaned from the ubiquitous and wide-spread applications of cross-coupling reactions in manufacturing materials, and in synthesising natural products and pharmaceuticals in recent years.[3] An example to this effect can be drawn from a recent review by Roughley and Jordan that stated that 62% of the total C–C bond forming processes utilised in the pursuit of drug candidates involved cross-couplings catalysed predominantly by Pd.[9] Therefore, it is reasonable to argue, based on the current rate of demand for Pd for various transformations, that the industrial application of cross-coupling reactions cannot remain sustainable in the future.

Interestingly, the use of Cu for cross-coupling reactions actually predates the discovery of Pd as a catalyst for these transformations.[10] Early investigations largely focused on the use of stoichiometric amounts of organocopper(I) species, such as Gilman reagents, with alkyl halides.[11] Catalytic use of Cu-salts, generally for the coupling of alkyl Grignard reagents with alkyl halides, remained unachieved as the reactions generally produced predominant amounts of decomposition products such

as alkanes by protodemetalation and olefins, in addition to small quantities of cross-coupled products.[12] These complications were generally ascribed to the instability of organocopper(I) species and the propensity of various Cu-species to undergo radical and disproportionation reactions.[13] Regardless of the existence of difficulties in developing Cu-catalysed cross-couplings, the utility of Cu-salts in forming C–C bonds has remained highly successful in processes such as conjugate addition, 1,2-addition, and allylic reactions of Grignard and organozinc[14] reagents.[15] These Cu-catalysed transformations have been shown to utilise not only the reactive and traditional organometallic reagents but also other stable organometallic compounds of silicon,[16] boron[17] and zirconium.[18] The ability of both reactive and stable organometallic reagents to undergo transmetalation with Cu-salts was a clear indication of optimism for developing Cu-catalysed cross-couplings for C–C bond formation. As such, a number of seminal reports began to appear before the turn of the 21st century describing the catalytic cross-couplings of the Grignard reagents and organotin compounds with alkyl and aryl halides. Therefore, this review will begin by summarizing this early work on cross-coupling of organometallic reagents with organohalides using Cu, and then move on to highlight and discuss recent developments with these and other new organometallic reagents. Due to short nature of this article, other Cu-catalysed C–C coupling processes,[19] such as oxidative Heck,[20] Sonogashira,[21] Glaser-Hay,[22] Castro-Stephen,[23] and Ullmann couplings[4e, f] will not be included despite their historical as well as synthetic significance.
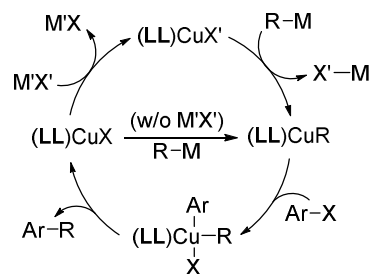
Catalytic Cycle

Detailed studies devoted to understanding the mechanism of Cu-catalysed cross-coupling with organometallic reagents are rare.[24] However, two basic catalytic cycles (Schemes 1 and 2) have been envisioned for this transformation based on sporadic mechanistic studies with alkyl and aryl electrophiles. Both catalytic cycles share transmetalation as the initial elementary step in which a nucleophilic moiety from an organometallic reagent exchanges with a halide on Cu^I and generates an organocopper(I) species as a reactive intermediate. In cases in which a base or a fluoride anion is required for reactivity, exchange of the halide on Cu^I-catalyst usually precedes transmetalation.[24-25] Early evidence for transmetalation was obtained from studies of the reactions of alkyl Grignard reagents with Cu^{II} salts in which Cu^{II} was reduced to Cu^I as an organocopper(I) species by two equivalents of the Grignard reagents.[12a-c] Occurrence of transmetalation to Cu-halides from other organometallic reagents such as organotin,[26] organozinc,[27] organosilicon,[16h-j] organoboron[24, 28] and organozirconium[18] are now known,[29] and many organocopper(I) complexes generated via this process have been structurally characterized by NMR spectroscopy and X-ray crystallography.[30] The organocopper(I) complexes thus generated[31] are known to react with alkyl and aryl electrophiles via different mechanisms. Reactions of organocopper(I) intermediates with alkyl halides and

pseudohalides have been shown to proceed via a traditional redox neutral S$_N$2 process and generate products with complete inversion of configuration (Scheme 1).[32] As well, radical clock experiments suggest that the reactions with organohalides and pseudohalides do not involve radical intermediates.[32a, 33] Reactions of organocopper(I) complexes with aryl halides have been proposed to proceed via oxidative addition and reductive elimination with the involvement of organocopper(III) intermediates (Scheme 2). Organocopper(III) species are generally invoked based on experiments using radical clocks and radical scavengers that discount the possibility of aryl radical intermediates,[25, 34] along with the existence and characterization of various Cu^{III}-complexes.[13d, 35] The sequential occurrence of the elementary steps in Scheme 2 has been demonstrated recently by our group based on *in situ* NMR studies of stoichiometric and catalytic reactions, and independent syntheses and characterization of reactive intermediates involved in the catalytic cycle.[24-25] Moreover, a recent study by DFT calculations on the Stille-type coupling of vinyltin reagents with vinyl iodide also supports the catalytic cycle in Scheme 2.[36]
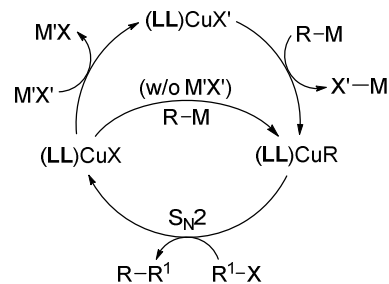
X = I, Br, Cl etc.; X' = F$^-$, MeO$^-$, etc.; R^1 = alkyl
R–M = aryl or alkyl organometallic reagents

Scheme 1 Proposed catalytic cycle I proceeding via an S$_N$2 pathway for coupling with alkyl electrophiles


X = I, Br; X' = F$^-$, MeO$^-$, etc.; R = aryl, alkyl
R–M = organometallic reagents

Scheme 2 Proposed catalytic cycle II proceeding via oxidative addition-reductive elimination sequence for coupling with aryl electrophiles

Recently, Cahiez and co-workers have proposed a unique catalytic cycle for the cross-coupling of Grignard reagents with alkynyl halides (Scheme 3).[37] A catalytically active organocopper(I) species [RCu] is proposed to be formed off-

cycle via the first transmetalation of Grignard reagents with CuX (X = halides), which further reacts with a second molecule of the Grignard reagent to generate a diorganocuprate complex [R_2CuMgX]. The diorganocuprate species is believed to undergo carbocupration with alkynyl halides via a five-coordinate, three-membered cyclic organocopper species to generate a β-halo-vinylcopper(I) complex. The β-halo-vinylcopper(I) species then undergoes β-halogen elimination to form the cross-coupled product and regenerate the catalyst.
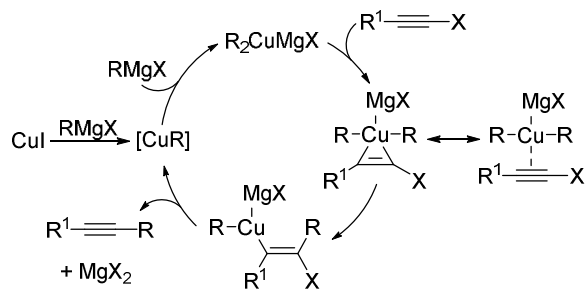
Scheme 3 Proposed catalytic cycle III proceeding via carbocupration for the coupling of Grignard reagents with alkynyl halides

Coupling with Grignard Reagents

Reaction of Grignard reagents with organohalides was reported seven decades ago by Kharash[38] with Co-salts and later by Tamura and Kochi using Cu-salts.[39] These early works and similar later reports have been extensively discussed elsewhere.[4b] In general, these initial reports showed that the reactions either required stoichiometric amounts of Cu-salts for high product yields,[40] or used catalytic quantities of Cu-salts but proceeded only with limited substrate scope in low yields.[41] In 1997, Burns and co-workers developed a highly active soluble Cu-catalyst by mixing equimolar amounts of CuBr•DMS, LiBr and LiSPh that allowed the cross-couplings of alkyl tosylates and mesylates to proceed efficiently with 1 equivalent of a variety of Grignard reagents.[42] The Cu-catalyst enabled the couplings of primary, secondary and tertiary alkyl, and aryl, vinyl and allyl Grignard reagents with primary alkyl iodides, bromides and tosylates (Scheme 4), as well as with secondary tosylates and mesylates (Scheme 5). Cahiez and co-workers later demonstrated a dramatic effect of NMP as an additive in THF with Li_2CuCl_4 or CuCl as a catalyst which enabled the use of secondary and tertiary alkyl Grignard reagents as coupling partners (Scheme 6).[43] Products were obtained in moderate to excellent yields. Recently, Liu and co-workers utilised CuI/TMEDA as an efficient catalyst in the presence of LiOMe as an additive that allowed cross-coupling to proceed between secondary alkyl Grignard reagents and secondary alkyl halides and tosylates (Scheme 7).[32b] These reactions have been shown to proceed via S_N2 pathways.[32]
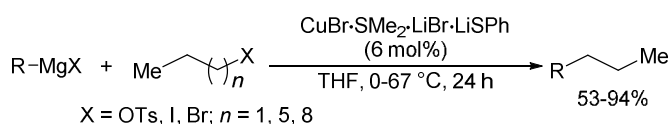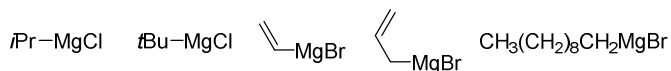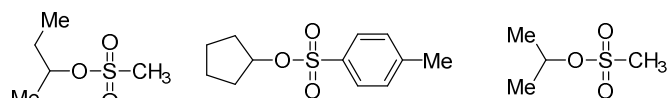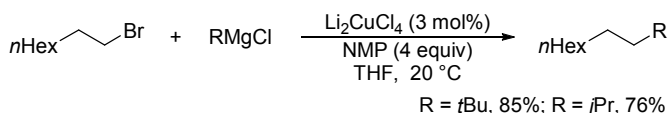

Scheme 4. Coupling of alkyl-, vinyl- and allyl Grignard reagents with primary alkyl iodides, bromides and tosylates
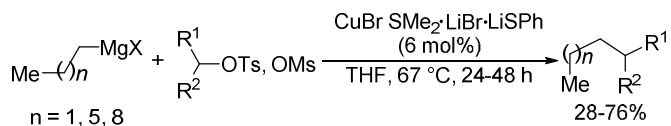
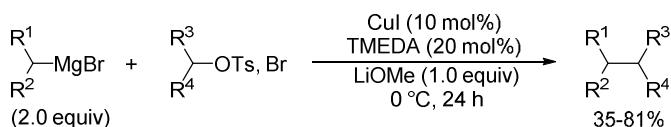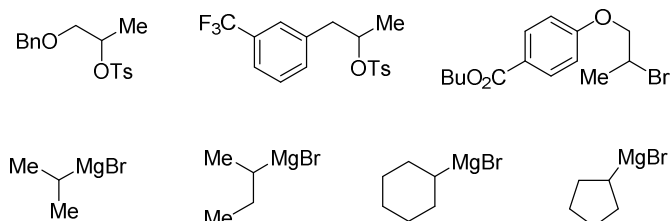**Scheme 5.** Coupling of primary alkyl Grignard reagents with secondary alkyl tosylates and mesylates

Scheme 6. Coupling of secondary and tertiary alkyl Grignard reagents with primary alkyl bromides
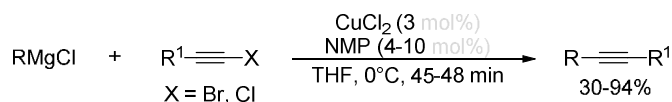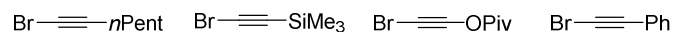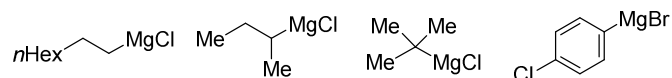

Scheme 7. Coupling of secondary alkyl Grignard reagents with secondary alkyl bromides and tosylates

Cahiez and co-workers further showed that catalytic amounts of NMP as an additive also facilitated the cross-coupling of primary, secondary and tertiary alkyl as well as aryl Grignard reagents with alkynyl halides, furnishing the products in moderate to excellent yields (Scheme 8).[37] Previous attempts to react these types of coupling partners resulted in poor product yields.[44] Beneficial effects of additives in Cu-catalysed cross-couplings were further shown by Kambe and co-workers, who demonstrated that the reaction of Grignard reagents with generally unreactive primary alkyl fluorides proceeded only in the presence of 1,3-butadiene as an additive (Scheme 9).[45] A
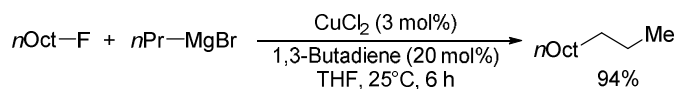
similar effect of 1-phenylpropyne was also disclosed in the reaction of Grignard reagents with primary alkyl chlorides (Scheme 10).[32a]
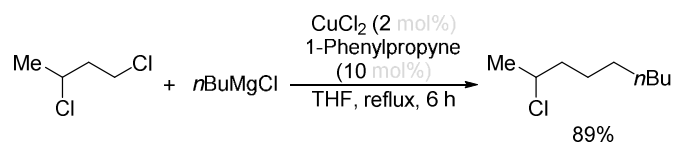

Scheme 8. Coupling of primary, secondary and tertiary alkyl as well as aryl Grignard reagents with alkynyl bromides and chlorides


Scheme 9. Coupling of Grignard reagents with primary alkyl fluorides


Scheme 10. Coupling of Grignard reagents with primary alkyl chlorides

Coupling with Organotin Reagents

In 1988, Lipshutz, Campbell, and co-workers demonstrated that vinylstannanes could undergo transmetalation with higher order cyanocuprates.[26] This seminal work opened the door for developing cross-coupling reactions of organotin reagents with Cu-salts as demonstrated independently by the research groups of Piers (Scheme 11),[46] Liebeskind (Scheme 12),[47] and Falck (Scheme 13).[14b] However, these transformations in which aryl-, vinyl- and alkyltin reagents were coupled with vinyl iodides and alkynyl bromides required stoichiometric amounts of CuX (I, Cl) and CuTC (TC = thiophene-2-carboxylate) as catalysts.
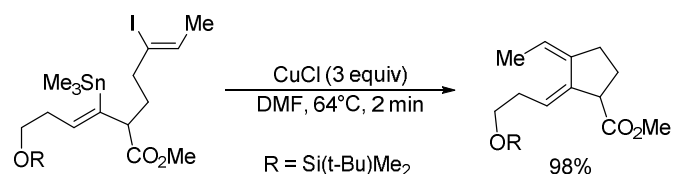
**Scheme 11.** Intramolecular coupling of vinyl iodides with vinyltin reagents using excess of CuCl
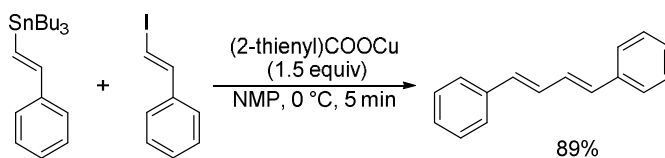
Scheme 12. Coupling of vinyltin reagents with vinyl iodides using excess of a Cu-catalyst
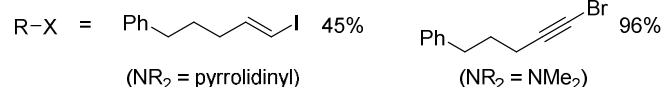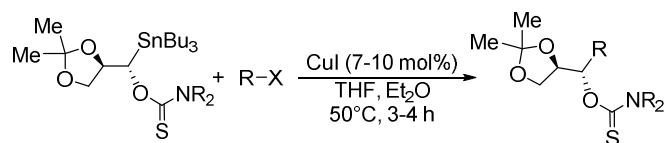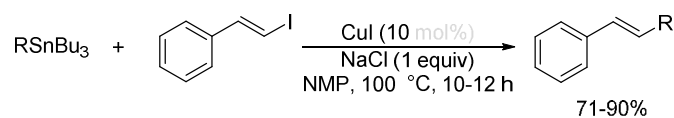

Scheme 13. Coupling of α-substituted alkyltin reagents with vinyl iodides and alkynyl bromides

In 1995, Falck and co-workers reported the Cu-catalysed cross-coupling of α-heteroatom-substituted alkyltributylstannanes with iodo- and bromobenzenes in THF (Scheme 14).[48] Despite the formation of the products in low yields, this report demonstrated for the first time the potential usefulness of Cu-salts as catalysts in Stille couplings. Kang and co-workers later disclosed that the cross-coupling could be performed with improved yields when the reaction was conducted in NMP at 90 °C in the presence of 1 equivalent of NaCl as an additive.[49] This reaction protocol allowed the cross-couplings of aryl-, heteroaryl-, vinyl- and alkynyltin reagents to proceed with different aryl- and vinyl iodides in good to excellent yields (Schemes 15-16). Moreover, the reaction protocol could be extended to diarylation of 1,4-diiodobenzene (Scheme 17). More recently, Li, Zhang, and co-workers utilised Cu₂O nanoparticles as catalysts in tetrabutylammonium bromide (TBAB), which enabled the reactions of aryl-, vinyl- and alkynyltin reagents to proceed with aryl iodides, bromides and chlorides in the presence of KF to afford the products in moderate to excellent yields (Scheme 18).[50]
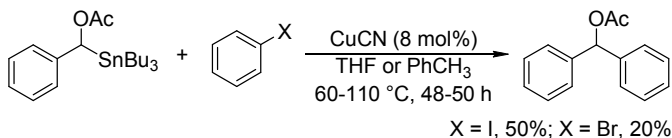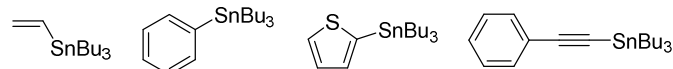

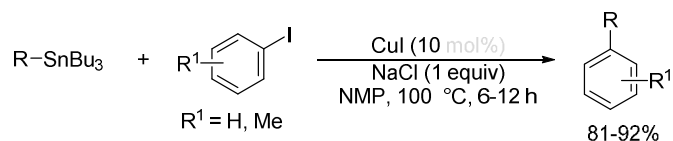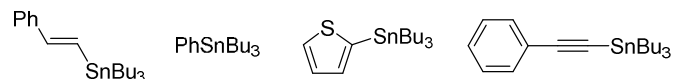**Scheme 14.** Coupling of a-heteroatom-substituted alkyltin reagents with aryl iodides and bromides

RSnBu₃ + [styryl iodide] → [styryl-R] 71-90%

CuI (10 mol%) / NaCl (1 equiv) / NMP, 100 °C, 10-12 h

Examples of organotin reagents

[vinyl–SnBu₃] [Ph–SnBu₃] [thienyl–SnBu₃] [Ph–alkynyl–SnBu₃]

Scheme 15. Coupling of organotin reagents with vinyl iodides

R−SnBu₃ + [R¹-aryl-I] → [aryl R/R¹] 81-92%

R¹ = H, Me

CuI (10 mol%) / NaCl (1 equiv) / NMP, 100 °C, 6-12 h

Examples of organotin reagents

[Ph-CH=CH-SnBu₃] [PhSnBu₃] [thienyl–SnBu₃] [Ph–alkynyl–SnBu₃]

Scheme 16. Coupling of organotin reagents with aryl iodides

[1,4-diiodobenzene] + [thienyl–SnBu₃] → [bis(thienyl)benzene] 86%

CuI (10 mol%) / NaCl (1 equiv) / NMP, 100 °C, 6 h
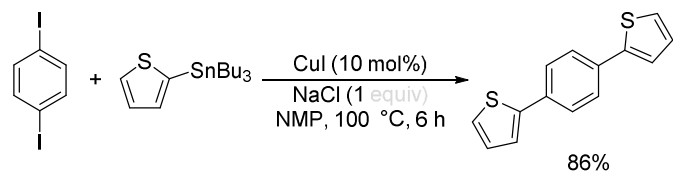
Scheme 17. Diarylation of 1,4-diiodobenzene with heteroaryltin reagents

[R-aryl-X] + R¹Sn(nBu)₃ → [R-aryl-R¹] 8-98%

Cu_2O (10 mol%) / P(o-tol)₃ (20 mol%) / KF·2H₂O, TBAB / 125-130°C, 11-72 h
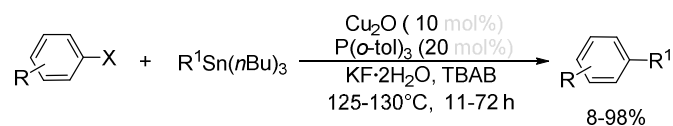
X = I, Br, Cl; R = H, Me, OMe, MeCO

Examples of aryl-, vinyl- and alkynyltin reagents

Ph−Sn(nBu)₃　　　[vinyl–Sn(nBu)₃]　　Ph──Sn(nBu)₃
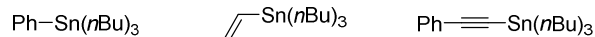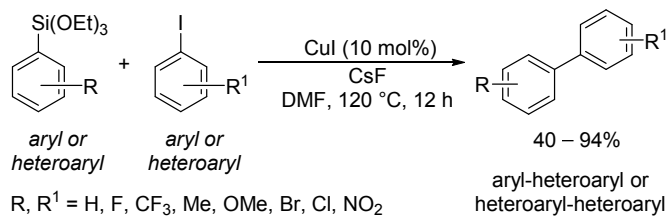
Scheme 18. Coupling of aryl-, vinyl- and alkynyltin reagents with aryl halides using Cu_2O nanoparticles

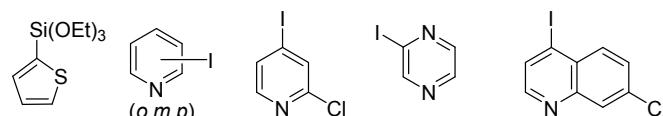## Coupling with Organosilicon Reagents

In 1997, Hosomi and co-workers demonstrated that arylsilicon reagents could be coupled with aryl iodides in the presence of CuI and $NaOC_6F_5$ (Scheme 19).[51] However, the reaction required a stoichiometric quantity of the Cu-salt and proceeded with very limited substrate scope. In 2013, our group reported the first Cu-catalysed cross-coupling of aryl- and heteroaryltriethoxysilanes with aryl and heteroaryl iodides that generated the coupled products in good to excellent yields.[34a] The reaction proceeded with 10 mol% CuI in the absence of ligands for aryl-heteroaryl and heteraryl-heteroaryl couplings when CsF was used as a fluoride source (Scheme 20).

[thiazolyl–SiMe₃] + [Ph-I] → [2-phenylthiazole] 93%

(2.0 equiv)

CuI (100 mol%) / C_6F_5ONa (1 equiv) / DMI, 130 °C, 12 h
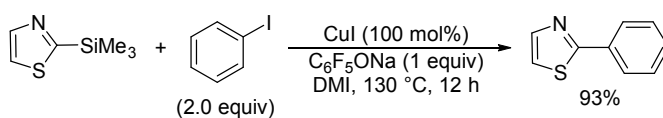
Scheme 19. Coupling of heteroarylsilicon reagents with aryl iodides using stoichiometric amouns of a Cu-catalyst

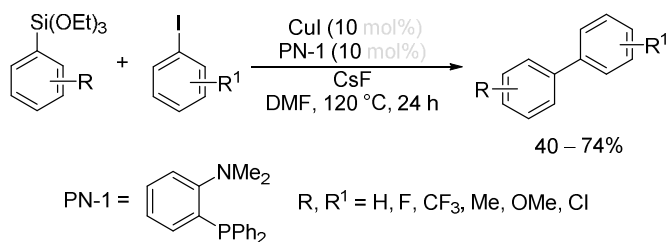[R-aryl-Si(OEt)₃] + [R¹-aryl-I] → [biaryl R/R¹] 40 – 94%

aryl or heteroaryl + aryl or heteroaryl

R, R¹ = H, F, CF₃, Me, OMe, Br, Cl, NO₂

CuI (10 mol%) / CsF / DMF, 120 °C, 12 h

aryl-heteroaryl or heteroaryl-heteroaryl

Examples of heterosilanes and heteroaryl iodides

[thienyl–Si(OEt)₃] [iodopyridine (o,m,p)] [iodo-chloropyridine] [iodopyrazine] [iodo-chloroquinoline]

Scheme 20. Coupling of aryl- and heteroarylsilicon reagents with aryl and heteroaryl iodides
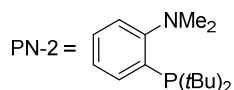
The "ligandless" condition could also be extended to aryl-aryl coupling, albeit generating the products in low yields. The product yields could be improved by 20 – 54% by utilising a combination of 2-(diphenylphosphino)-*N,N*-dimethylaniline (PN-1) and CuI as a catalyst (Scheme 21). Application of a similar but more sterically bulky and electron-rich ligand, 2-(di-*tert*-butylphosphino)-*N,N*-dimethylaniline (PN-2), also enabled the cross-coupling of aryltriethoxysilanes to proceed well with aryl bromides in the presence of stoichiometric amounts of CuI (Scheme 22).[52] A similar reaction was also recently reported by Riant and co-workers for the cross-coupling of vinyltriethoxysilanes with alkynyl bromides (Scheme 23).[53] The reaction was catalysed by a cationic copper complex, $Cu(MeCN)PF_6$, in the presence of tetrabutylammonium difluorotriphenylsilicate (TBAT), which enabled the use of both aromatic and aliphatic alkynyl bromides as coupling partners.

[R-aryl-Si(OEt)₃] + [R¹-aryl-I] → [biaryl R/R¹] 40 – 74%

CuI (10 mol%) / PN-1 (10 mol%) / CsF / DMF, 120 °C, 24 h

PN-1 = [2-(diphenylphosphino)-N,N-dimethylaniline, NMe₂ / PPh₂]
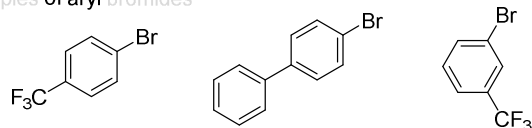
R, R¹ = H, F, CF₃, Me, OMe, Cl
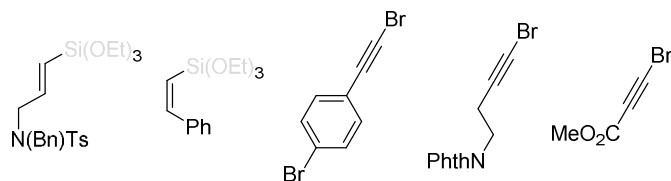
Scheme 21. Coupling of arylsilicon reagents with aryl iodides using (PN-1)CuI catalyst
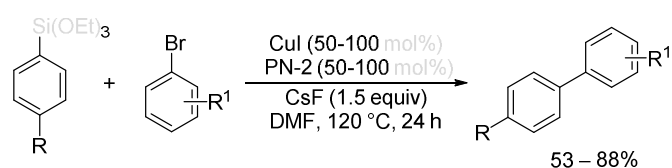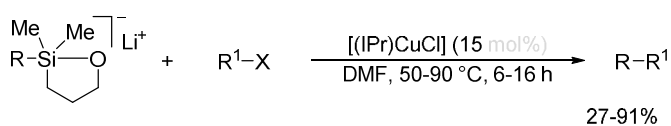
Scheme 22. Coupling of arylsilicon reagents with aryl bromides using stoichiometric quantities of CuI and PN-2
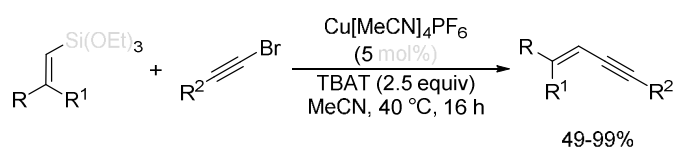
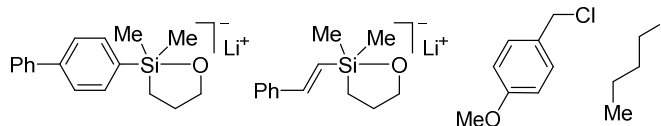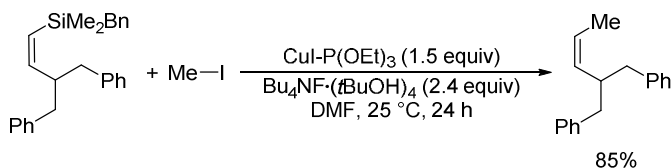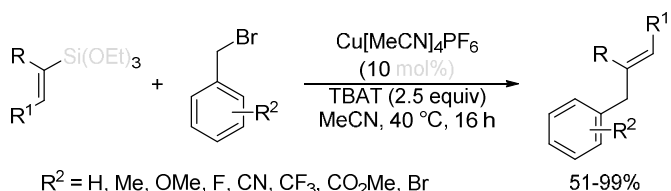**Scheme 23.** Coupling of vinylsilicon reagents with alkynyl bromides

Scheme 24. Coupling of aryl- and vinylsilicon reagents with alkyl and benzyl halides

Scheme 25. Coupling of vinylsilicon reagents with alkyl iodides using excess of CuI•P(OEt)$_3$ catalyst

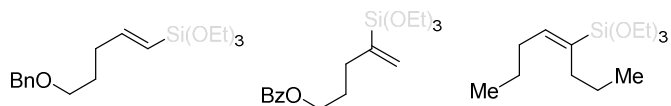**Scheme 26.** Coupling of vinylsilicon reagents with benzyl bromides

Takeda and co-workers demonstrated that aryl- and alkenylsilanes, activated by intramolecular coordination of an alkoxide group, could undergo alkylation with primary alkyl iodides and benzyl chlorides in the presence of an NHC-bound Cu^I, [(IPr)CuCl], as a catalyst (Scheme 24).[54] The authors later showed that the vinylsilicon reagents coupled with primary alkyl and benzyl halides without the need for coordination-assisted activation by alkoxide when the reaction was conducted in DMF in the presence of stoichiometric amounts of CuI•P(OEt)$_3$ as a catalyst and Bu$_4$NF•(tBuOH)$_4$ as a fluoride source (Scheme 25).[55] Similarly, Riant and co-workers also disclosed that their reaction protocol developed for coupling vinyltriethoxysilanes with alkynyl bromide (Scheme 23) could also utilise benzyl bromides as electrophiles (Scheme 26).[56] These couplings with primary alkyl and benzyl electrophiles are likely to proceed via a traditional S$_N$2-type mechanism analogous to the reactions of similar electrophiles with Grignard and organoboron reagents with Cu-catalysts discussed above.

Coupling with Organoboron Reagents

In 2002, Rothenberg and co-workers reported the first example of Cu-catalysed Suzuki-Miyaura coupling. In this report, phenylboronic acid was cross-coupled with 4-iodotoluene using catalytic amounts of a Cu-nanocluster in DMF at 110 °C in the presence of K$_2$CO$_3$ (Scheme 27).[57] The reaction protocol was later extended to include a variety of arylboronic acids and aryl iodides as coupling partners.[58] A subsequent report revealed that replacement of DMF as a solvent with poly(ethylene)glycol (PEG)-400 allowed the use of commercially available Cu-powder as a catalyst under otherwise identical reaction conditions, although the latter protocol required Cu-powder in larger quantities than the Cu-nanocluster (Scheme 28).[59] It was further revealed that the reaction conditions could be applied to the couplings of aryl bromides and electron-deficient aryl chlorides in reasonable yields when a catalytic amount of I$_2$ was used as an additive (Scheme 29).
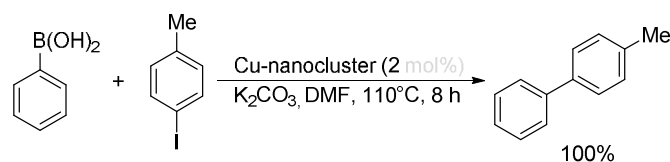
Scheme 27. Coupling of arylboronic acids with aryl iodides using Cu-nanocluster
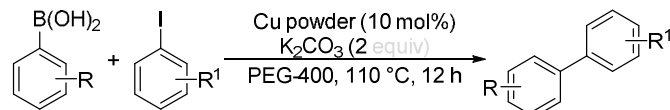
R = H, F, Cl, Me, OMe, CHO; R[1] = H, OMe, NO₂, Cl   77-99%

Scheme 28. Coupling of arylboronic acids with aryl iodides using Cu-powder

X = Br, Cl
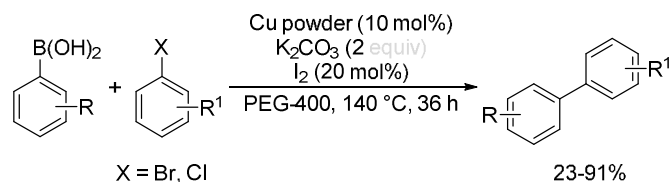
R = H, F, Cl, CHO; R[1] = H, OMe, NO₂, Cl, CF₃   23-91%

Scheme 29. Coupling of arylboronic acids with aryl bromides and chlorides using Cu-powder assisted by I₂

Despite Rothenberg's early evidence that Cu[0] could be used as a catalyst for the Suzuki-Miyaura coupling, later investigations showed that Cu[I]-salts were more effective. In this regard, Li and co-workers reported that CuI ligated by 1,4-diazabicyclo[2.2.2]octane (DABCO) was an efficient catalyst for coupling a variety of arylboronic acids with vinyl iodides and bromides when the reaction was conducted in DMF at 125-130 °C in the presence of Cs₂CO₃ and TBAB (Scheme 30).[60] The reaction protocol can also be extended to multiple arylations of di- and tri-iodobenzenes (Scheme 31). The authors further demonstrated that a similar reaction condition in which DMSO was used as a solvent in the absence of DABCO at 135-140 °C could be used for the coupling of both aryl- and heteroarylboronic acids with aryl- and vinyl iodides and bromides (Scheme 32).[61] Similarly, a combination of CuI and 8-hydroxyquinoline was also shown to be an active catalyst that facilitated cross-coupling between arylboronic acids and alkynyl bromides (Scheme 33).[62]
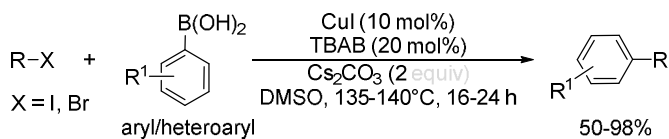
X = I, Br

R² = H, F, OMe

DMF, 125-130 °C, 18-24 h   50-95%
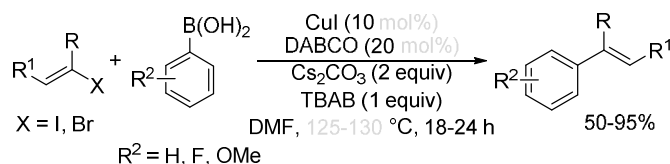
Examples of vinyl halides
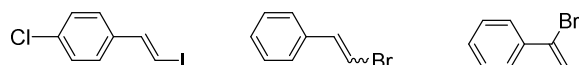
Scheme 30. Coupling of arylboronic acids with vinyl iodides and bromides

(5 equiv)   DMF, 125-130 °C, 24-48 h

diphenylation, 80%; triphenylation, 48%
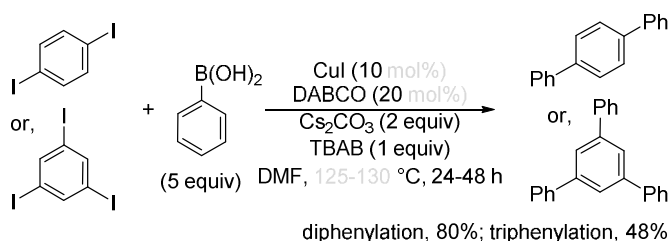
Scheme 31. Arylation of di- and tri-iodobenzenes with phenylboronic acid

R–X +

X = I, Br

aryl/heteroaryl   DMSO, 135-140°C, 16-24 h   50-98%

Examples of aryl and vinyl halides, and arylboronic acids
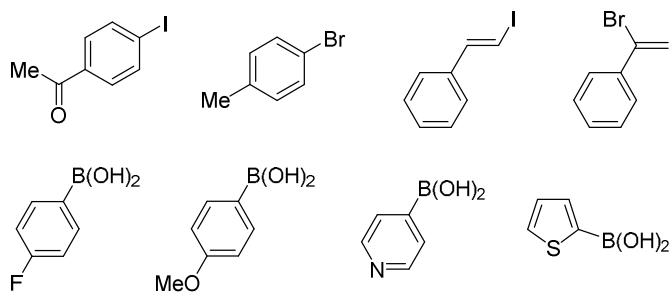
Scheme 32. Coupling of arylboronic acids with aryl and vinyl halides

CuI (10 mol%)
8-HQ (20 mol%)
Na₃PO₄ (2 equiv)
EtOH, 80 °C, 24 h   64-99%
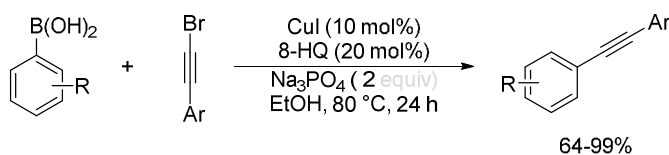
Examples of arylboronic acids and alkynyl bromides

8-HQ =
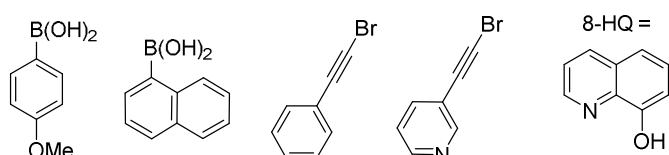
Scheme 33. Coupling of arylboronic acids with alkynyl bromides using 8-hydroxyquinoline with CuI as a catalyst

Since its discovery, Cu-catalysed Suzuki-Miyaura coupling with aryl halides had focused only on utilizing highly reactive arylboronic acids as coupling partners.[62] However, in 2014 our group reported a quite general and highly efficient cross-coupling of a variety of organoboron reagents, such as ArB(OR)₂, ArB(OH)₂, ArBF₃K, Ar₄B, Ar₄BCs and (ArBO)₃ (Ar = aryl), with aryl iodides.[24] The reactions for aryl-aryl coupling proceeded with 2 mol% CuI in the presence of PN-2 as a ligand and afforded the coupled products in good to excellent yields (Scheme 34). Analogous to the cross-coupling with arylsilicon reagents (Scheme 20), the reaction of both aryl- and heteroarylboronate esters with heteroaryl iodides proceeded in good to excellent yields without requiring the addition of the PN-2 ligand (Scheme 35). Brown and co-workers also reported

that a similar coupling of arylboronate esters with aryl iodides could be conducted using a combination of CuCl and Xantphos as a catalyst to afford biaryl products in good to excellent yields (Scheme 36).[34b, 63]

Scheme 34. Coupling of various arylboron reagents with aryl iodides using (PN-2)CuI catalyst

R, R[1] = H, F, CF$_3$, Me, OMe, Br, Cl

Examples of organoboron reagents

ArB(OH)$_2$　　Ar$_3$B　　Ar$_4$BCs　　ArBF$_3$K　　(ArBO)$_3$

Scheme 35. Ligand-free coupling of (hetero)arylboron reagents with (hetero)aryl iodides

R, R[1] = H, F, CF$_3$, Me, OMe; (OR)$_2$: neopentylglycol ester

Examples of heteroaryl boronate esters and heteroaryl iodides

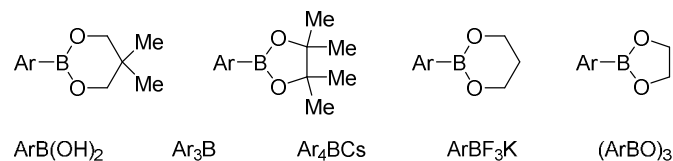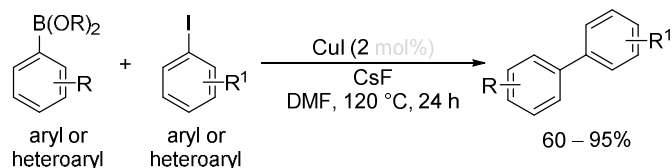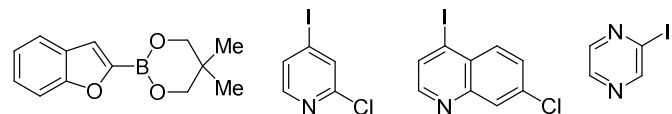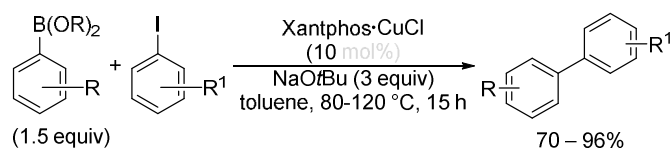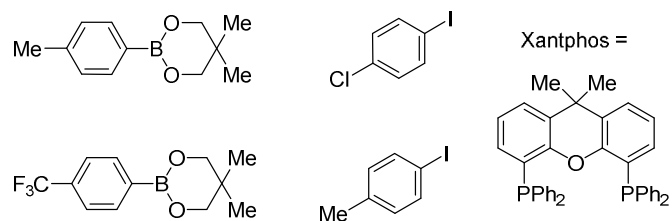**Scheme 36.** Coupling of arylboronate esters with aryl iodides using xantphos with CuCl as a catalyst

(1.5 equiv)　70 – 96%

Examples of organoboron reagents and aryl iodides

Xantphos =

Cross-couplings of alkyl- and arylboron reagents with primary alkyl halides and pseudohalides were reported recently by Liu and co-workers (Scheme 37).[33] Analogous to the coupling of Grignard reagents with alkyl electrophiles using Cu-salts, these reactions were shown to proceed via a traditional S$_N$2-type mechanism by catalytic generation of organocopper(I) species *in situ*. Moreover, Rao and Rao demonstrated that a similar reaction condition could be applied to the coupling of arylboronic acids with secondary benzylic thiomethyl ethers on special chromene scaffolds in which the thiomethyl moiety functioned as a leaving group (Scheme 38).[64]

R⌒X　+　R⌒BR[2]　→　R⌒R[1]

X = I, Br, Cl, OTs　　　　　　　　　　45-87%

Cul (10 mol%)
LiO*t*Bu (2 equiv)
DMF, 80 °C, 12-24 h
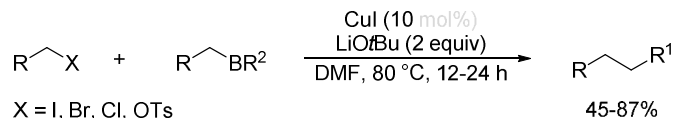
Examples of alkyl halides, alkyl tosylates and alkyl/arylboron reagents

n-C$_{10}$H$_{21}$-OTs　　C$_4$H$_9$Br-*n*　　C$_6$H$_{13}$-*n*
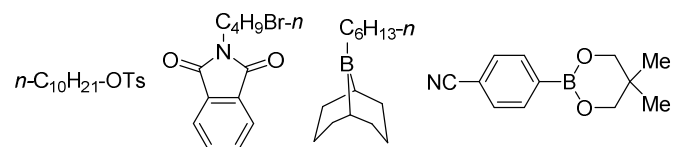
Scheme 37. Coupling of alkyl- and arylboron reagents with primary alkyl electrophiles

Cu(OAc)$_2$·H$_2$O
(10 mol%)
DMF, rt, 3 h

86%
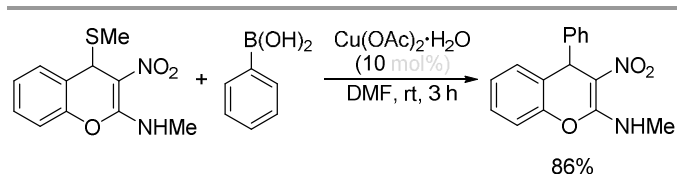
Scheme 38. Coupling of arylboronic acids with secondary benzylic thiomethyl ethers

Coupling with Organoindium Reagents

Our group has recently shown for the first time that triorganoindium reagents are excellent coupling partners for Cu-catalysed cross-coupling with aryl halides in DMF in the presence of PN-2 ligand and NaOMe.[25] Triorganoindium reagents generally transfer all three organic nucleophilic moieties into products via consecutive transmetalations and, therefore, the transformation requires only one-third equivalents of the organometallic reagents. Reaction proceeds with both aryl- and alkylindium reagents (Schemes 39-40). The reaction utilizes various aryl iodides as electrophiles and tolerates a wide range of functional groups and steric hindrance. In addition, electron-deficient and heteroaryl bromides can also be used as electrophiles (Scheme 41). Consistent with the reactivity patterns observed for organoboron and organosilicon reagents, the current reaction conditions allowed the reactions of heteroaryl iodides to proceed with organoindium reagents in the absence of the PN-2 ligand (Scheme 42).
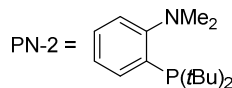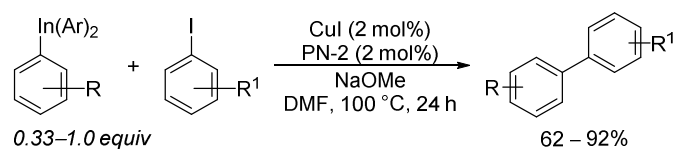
Scheme 39. Coupling of triarylindium reagents with aryl iodides via three consecutive transmetalations
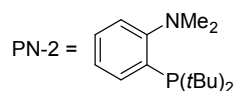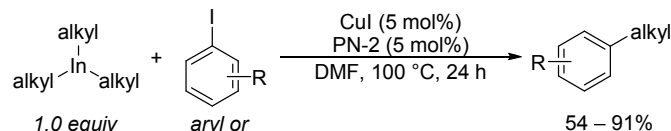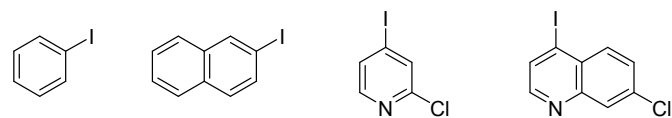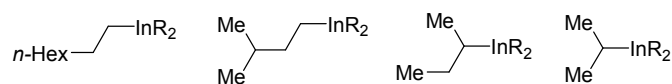
Scheme 40. Coupling of primary and secondary trialkylindium reagents with aryl and heteroaryl iodides
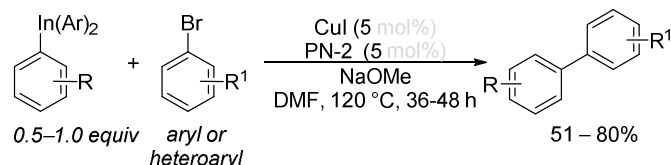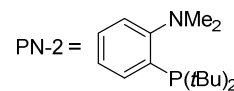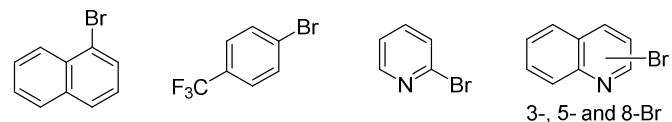
Scheme 41. Coupling of triarylindium reagents with aryl and heteroaryl bromides
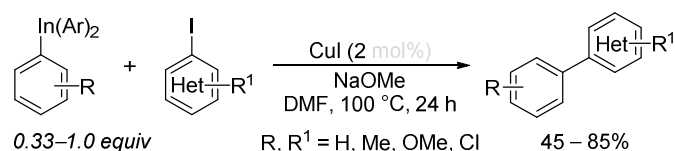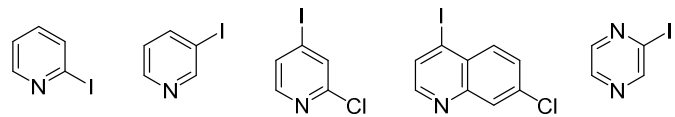
Scheme 42. Ligand-free coupling of triarylindium reagents with heteroaryl iodides

Coupling with Organomanganese Reagents

In 1993, Cahiez and Marquais reported the first example of Cu-catalysed cross-coupling of organomanganese chloride with alkyl halides and phenylsulfonates.[65] Similar to the coupling of Grignard reagents with alkyl halides (Scheme 6), the addition of NMP as a co-solvent dramatically improved the reaction, affording the cross-coupled products in good to excellent yields. The reaction could utilize primary, secondary and tertiary alkyl as well as vinyl-, allyl- and arylmanganese reagents to couple with primary alkyl iodides, bromides, and phenylsulfonates, and tolerated functional groups such as esters and ketones (Scheme 43). The reaction was later extended to the coupling of alkyl bromides containing free carboxyl and hydroxyl groups, as well as vinyl iodides.[66]

Scheme 43. Coupling of secondary and tertiary alkyl Grignard reagents with primary alkyl bromides

Conclusion and Perspectives

Cu-catalysts are emerging as viable alternatives to Pd-based systems for cross-coupling reactions. The motivation for this new focus rests on the concept of developing cross-coupling transformations into a sustainable chemical process with particular emphasis placed upon replacing rare, expensive, and toxic Pd with earth abundant, inexpensive, and non-toxic TM. In this respect, Cu can in particular be regarded as the TM of choice that fulfils these requirements. Recent revelations of the high efficacy of Cu-catalysts in executing cross-couplings of a variety of organometallic reagents, such as organomagnesium, organoboron, organosilicon, organoindium and

organomanganese, with alkyl, aryl and heteroaryl halides clearly demonstrate the potential application of Cu as an alternative to Pd. In addition, Cu-catalysts are displaying a reactivity pattern that is different and unique from Pd-catalysts as demonstrated, for example, in the "ligandless" Cu-catalysed aryl-heteroaryl and heteroaryl-heteroaryl coupling, an otherwise difficult transformation when utilizing Pd-catalysts. However, Cu-based catalytic systems are still far from being general, especially when inexpensive but less reactive aryl chlorides and tosylates are utilized as coupling partners. Therefore, despite recent encouraging developments, enormous efforts still need to be made in order to match Cu-based catalytic systems with the Pd-based systems that have been rigorously optimized over the course of three decades.

Acknowledgements

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Graphical Table of Content (TOC)

$R-MgX$, $RSnR'_3$, $R-MnX$

$R-M$ + R^1-X $\xrightarrow{Cu}$ $R-R^1$

alkyl—alkyl   alkyl—vinyl   alkyl—alkynyl
alkyl—aryl   aryl—vinyl   aryl—alkynyl
aryl—aryl   vinyl—vinyl   vinyl—alkynyl

$R-SiR'_3$, $R-BR'_2$, $R-InR_2$

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