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Highlight Review

Transition-metal-free Coupling Reactions of Aryl Halides

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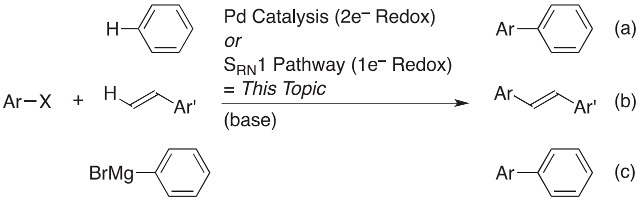
Abstract

Transition metal catalysis plays a leading role in C(sp^2)–C(sp^2) bond formation through substitution reactions. On the other hand, a similar type of substitution reaction has recently been achieved without the aid of transition-metal catalysts. In this review, recent transition-metal-free coupling reactions of aryl halides with arenes, alkenes, or aryl Grignard reagents are summarized in view of $S_{RN}1$ reaction.

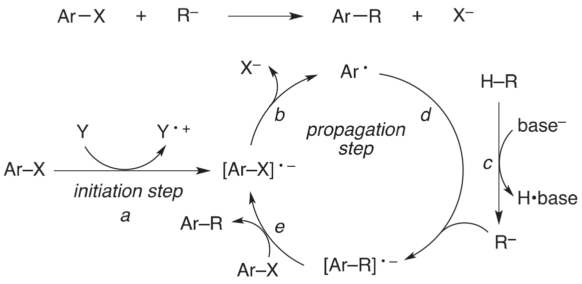
◆ Introduction

Aryl halides (Ar–X), readily available aryl electrophiles, do not undergo S_N2 nor S_N1 reaction. Instead, they are usually activated by reduction to participate in substitution reactions, even though the overall processes are not reduction or oxidation. Transition metal catalysis plays a dominant role to make use of Ar–X for substitution reactions in such a way.[1,2] In particular, palladium is versatile to catalyze the coupling reaction of Ar–X with nucleophiles such as arenes, alkenes, and aryl Grignard reagents (Scheme 1).[3] The generally accepted catalytic cycle consists of oxidative addition of Ar–X to a Pd(0) complex (i), reaction of the resulting Ar–Pd^{II}–X with a nucleophile (ii), and reductive elimination to give the coupling product with regeneration of the Pd(0) complex (iii). Ar–X is activated by two electron reduction in step i, whereas two electron oxidation takes place in step iii.

Single electron reduction also is effective for activation of aryl halides,[4] leading them to the substitution reaction ($S_{RN}1$ reaction) with anionic nucleophiles (R^-) (Scheme 2).[5] Radical anion $[Ar–X]^{\bullet -}$, produced by single electron transfer (SET) from single electron donor Y in the initiation step (*a*), is converted into an aryl radical ($Ar^\bullet$) upon elimination of X^- (*b*). Deprotonation from pronucleophile H–R gives R^- (*c*), which attacks $Ar^\bullet$ (*d*). SET from the resulting $[Ar–R]^{\bullet -}$ to Ar–X gives the coupling product (Ar–R) and regenerates $[Ar–X]^{\bullet -}$ (*e*). $S_{RN}1$ reaction includes reduction of Ar–X (steps *a* and *e*) and oxidation giving coupling products (step *e*), as same as the palladium-catalyzed reaction. A major difference between these is the number of electrons involved in the redox processes. $S_{RN}1$ reaction features high efficiency that such a small unit as a single electron works as a catalyst, avoiding the use of expensive transition-metal catalysts. Although $S_{RN}1$ reaction is expected to have ability to connect the aryl group of aryl halides to sp^2-carbons as same as transition metal catalysis,[6,7] the scope on anionic nucleophiles has been limited mainly to heteroatom anions and sp^3-carboanions such as enolates. No reports are available for use of arenes, alkenes, or aryl Grignard reagents as (pro)nucleophiles in $S_{RN}1$ reaction.



Scheme 1.



Scheme 2.

We have recently developed the transition-metal-free coupling reactions of aryl halides with arenes, alkenes, or aryl Grignard reagents (Scheme 1: a–c). All the reactions are considered to proceed within the boundary of $S_{RN}1$ mechanism. In this Highlight Review, we summarize our work on the transition-metal-free coupling reactions in addition to related reactions reported by others.

◆ *tert*-Butoxide-mediated Coupling with Arenes

During the course of our studies on the iron-catalyzed coupling reaction of aryl halides with arenes,[8] we found that iron is not essential for the coupling to take place. After investigation of better conditions for the coupling in the absence of any transition metals, the system shown in Scheme 3 was found to be effective.[9,10] Thus, the reaction of *p*-tolyl iodide with benzene (120 equiv) in the presence of NaO*t*-Bu (2 equiv) and 4,7-diphenyl-1,10-phenanthroline (Ph-phen: 0.1 equiv) at 155 °C[11] for 6 h gave 4-methylbiphenyl in 76% yield. Phenyl iodides having an electron-donating or -withdrawing group as well as heteroaryl iodides underwent the coupling in high yields. Aryl bromides were less reactive than the corresponding iodides, though introduction of conjugating substituents such as phenyl

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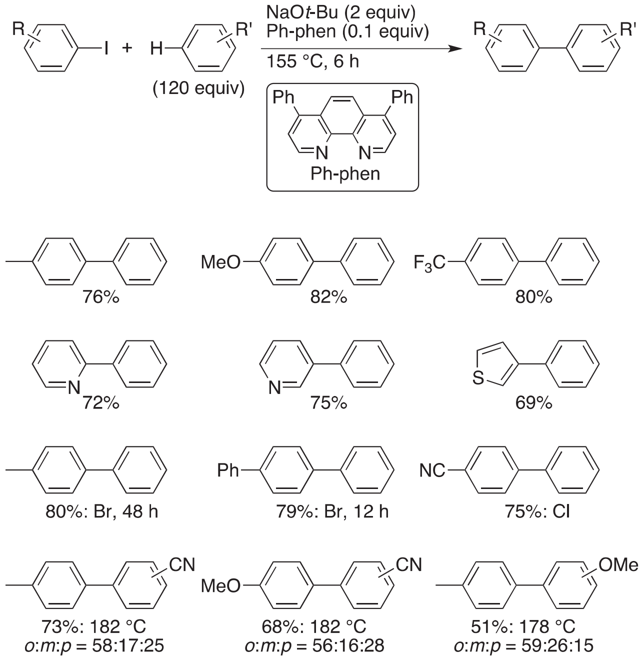
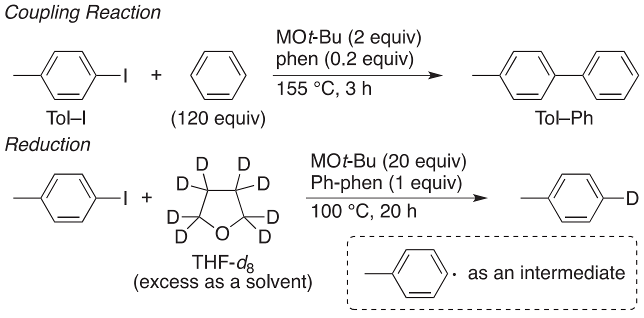
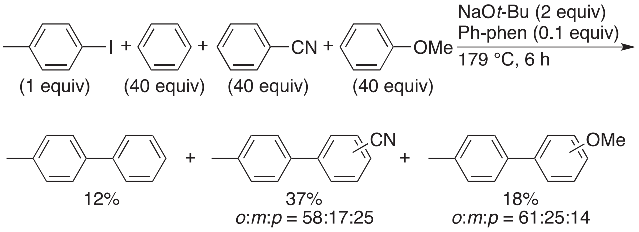


Scheme 3.

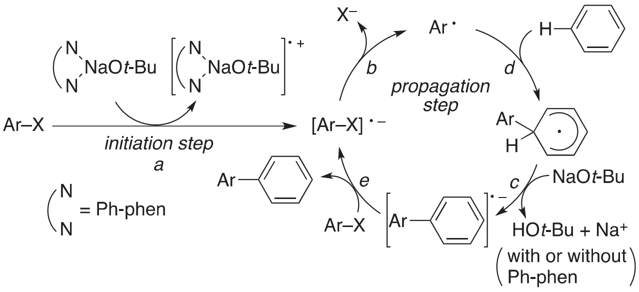


base	ligand	Coupling Reaction		Reduction	
MOt-Bu	phen or Ph-phen	conv. of Tol–I	yield of Tol–Ph	conv. of Tol–I	yield of Tol–D
NaO*t*-Bu	+	>99%	72%	>99%	79%
KO*t*-Bu	+	>99%	67%	>99%	72%
LiO*t*-Bu	+	23%	7%	<1%	<1%
NaO*t*-Bu	–	<1%	<1%	2%	2%

Scheme 4.



Scheme 5.



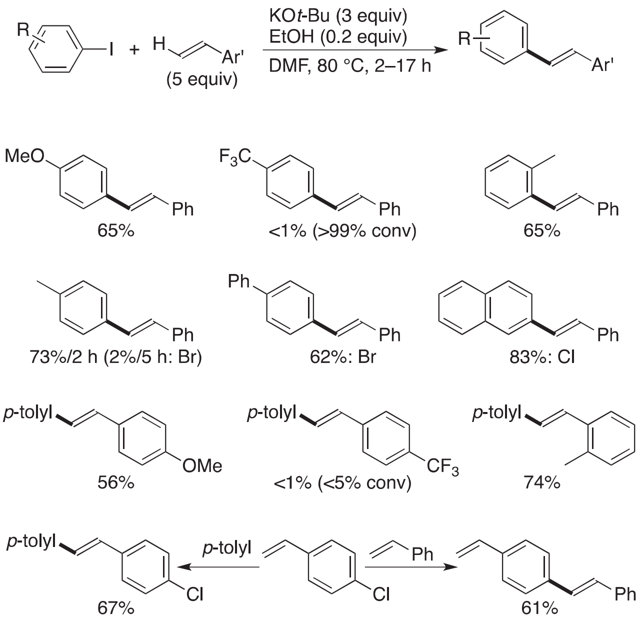
Scheme 6.

accelerated the reaction of bromides. Substitution by cyano, which is a highly electron-withdrawing conjugating group, makes even chlorides sufficiently reactive. Monosubstituted benzenes also underwent the coupling to give isomeric mixtures of a high ortho ratio.

Use of a strong base in combination with a phenanthroline ligand is crucial for the coupling. The reaction proceeded also by use of nonsubstituted 1,10-phenanthroline (phen), though an increased amount (0.2 equiv) was required (Scheme 4: Coupling Reaction). No coupling took place in the absence of phenanthroline ligands. More basic KO*t*-Bu showed ability comparable to NaO*t*-Bu, whereas the reaction was much more sluggish by use of less basic LiO*t*-Bu. Treatment of *p*-tolyl iodide (Tol–I) with NaO*t*-Bu and Ph-phen in THF-d_8 gave 4-deuteriotoluene (Tol–D), which is considered to be produced through SET from NaO*t*-Bu–Ph-phen to Tol–I, elimination of I^- from the resulting radical anion $[\text{Tol–I}]^{\bullet-}$ to give Tol$^\bullet$, and D$^\bullet$ abstraction from THF-d_8 (Scheme 4: Reduction). A drastic drop of the reactivity observed in the absence of Ph-phen shows that NaO*t*-Bu has single electron donor ability, which is enhanced by Ph-phen. A good correlation between the reduction and the coupling reaction was observed in the effect of bases and ligands. This observation implies that aryl radical generation, which requires a strong base and a phenanthroline ligand, is involved in the coupling reaction as a key step.

The result that the reaction of monosubstituted benzenes gave isomeric mixtures of a high ortho ratio (Scheme 3, bottom row) shows involvement of radical addition to benzene rings. This characteristic ortho-selectivity originates from the substituent effect that both electron-donating and -withdrawing groups on benzene accelerate addition of radicals to the benzene ring, in particular at its ortho positions. The involvement of the radical addition step was further confirmed by the competition reaction of arenes shown in Scheme 5. Both benzonitrile and anisole underwent coupling with *p*-tolyl iodide preferentially over benzene.

From these results in addition to those obtained in the succeeding studies described in the following sections, a single electron is thought to catalyze the arylation of arenes as in the case with $S_{RN}1$ reaction.[12] A plausible catalytic cycle is shown in Scheme 6, where step labels (*a*–*e*) correspond to those of $S_{RN}1$ reaction shown in Scheme 2. The observations described in the last two paragraphs (Schemes 4 and 5) are highly consistent with the operation of steps *a*, *b*, and *d*. Thus, SET from NaO*t*-Bu–phenanthroline to Ar–X gives $[\text{Ar–X}]^{\bullet-}$ (*a*), which is converted to Ar$^\bullet$ upon elimination of X^- (*b*). After addition of Ar$^\bullet$ to benzene to give cyclohexadienyl radical $[\text{Ar–C}_6\text{H}_6]^{\bullet-}$ (*d*), radical anion $[\text{Ar–C}_6\text{H}_5]^{\bullet-}$ is generated by deprotonation (*c*). Finally, SET from $[\text{Ar–C}_6\text{H}_5]^{\bullet-}$ to Ar–X gives Ar–C_6H_5 and regenerates $[\text{Ar–X}]^{\bullet-}$ (*e*). Steps *c* and *e* also are likely to be operative, considering that strong base deprotonates the

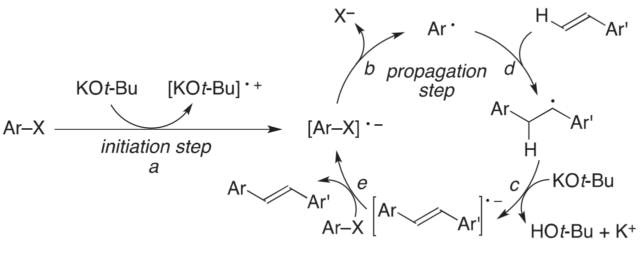


Scheme 7.

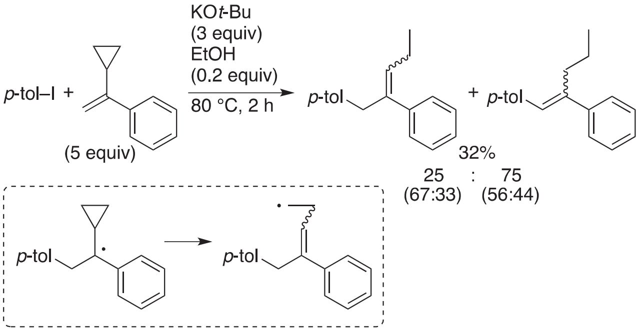
relatively acidic benzylic proton with the aid of aromatization as a driving force (step *c*) and that aryl iodides have lower reduction potentials than biaryls (step *e*). Compared with the original S$_{RN}$1 mechanism, the order of addition (step *d*) and deprotonation (step *c*) is reversed. Arenes usually cannot become pronucleophiles in S$_{RN}$1 reaction because deprotonation from not so acidic arenes is difficult. In the present system, deprotonation indispensable for S$_{RN}$1 reaction takes place not on the starting arenes but on more acidic intermediary cyclohexadienyl radicals. This must be a key point for the success in introduction of aryl nucleophiles into S$_{RN}$1 reaction.

◆ *tert*-Butoxide-mediated Mizoroki–Heck Type Reaction

The coupling reaction of aryl halides with arenes is considered to include addition of an aryl radical to a benzene ring followed by deprotonation and single electron oxidation. We anticipated that this mechanism is applicable also to alkenes. This turned out to be the case with styrene derivatives, though modification of the reaction system was required.[13] Thus, the reaction of *p*-methoxyphenyl iodide with styrene (5 equiv) in the presence of KO*t*-Bu (3 equiv) and EtOH (0.2 equiv) in *N*,*N*-dimethylformamide (DMF) at 80 °C for 2 h gave 4-methoxystilbene in 65% yield (Scheme 7). In contrast that both NaO*t*-Bu and KO*t*-Bu promoted the coupling with arenes, the Mizoroki–Heck type reaction proceeded only with more basic KO*t*-Bu. Acetonitrile, 1,4-dioxane, and toluene were totally ineffective as solvents. Slight decreases (ca. 10%) in yields were observed in the absence of EtOH, the role of which is not clear at present. Electron-deficient *p*-(trifluoromethyl)phenyl iodide did not undergo the coupling due to competitive reduction of the aryl iodide. Ortho-substitution did not largely affect the reaction. Although aryl bromides and chlorides were less reactive than iodides, substitution by a conjugating group drastically accelerated the coupling as in the case with the coupling with arenes. Introduction of an electron-donating group on styrene was tolerated, whereas electron-withdrawing substituents hampered the reaction. *p*-Chlorostyrene changed its role according to the reaction partners, reacting with *p*-tolyl iodide and styrene at its alkene and chloroarene moieties, respectively.



Scheme 8.

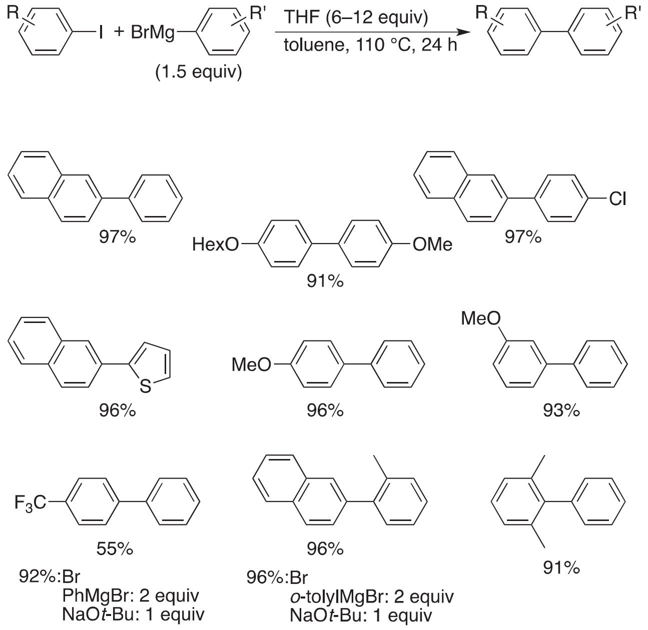


Scheme 9.

The reaction is considered to proceed in a similar manner to the coupling with arenes (Scheme 8). SET from KO*t*-Bu to Ar–X gives radical anion [Ar–X]$^{\bullet -}$, where DMF is likely to enhance the single electron donor ability of KO*t*-Bu (*a*). After elimination of X$^-$ (*b*), the resulting Ar$^\bullet$ adds to styrene to give a benzylic radical (*d*), which is converted to radical anion [ArCH=CHAr′]$^{\bullet -}$ through deprotonation by KO*t*-Bu (*c*). Finally, SET from [ArCH=CHAr′]$^{\bullet -}$ to Ar–X gives ArCH=CHAr′ and regenerates [Ar–X]$^{\bullet -}$ (*e*). Several experimental results support this mechanism. Biphenyl-4-yl iodide was reduced to biphenyl by treatment with KO*t*-Bu in DMF, showing that SET from KO*t*-Bu to Ar–X is operative. The reaction of α-cyclopropylstyrene gives ring-opening products albeit in low yields (Scheme 9).[14] This is rationally explained by involvement of step *d* giving a benzylic radical, which undergoes ring opening. The reactivity order of aryl halides is reasonable if we consider as follows: 1) Readily reducible aryl iodides are fully consumed irrespective of their substituents in the reaction with styrene, though over-reduction takes place with those having an electron-withdrawing group. 2) When the arene moiety is highly conjugated, aryl bromides and even chlorides are sufficiently reactive. 3) Even aryl iodides fail to react when the coupling partner is an electron-deficient styrene, which accepts an electron from KO*t*-Bu more easily than the aryl iodide.

◆ *Cross-coupling Reaction with Aryl Grignard Reagents*

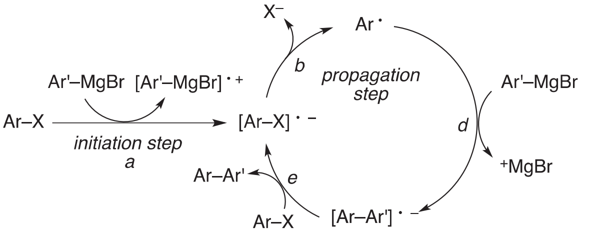
As shown thus far, the coupling of aryl halides with arenes or styrenes proceeds through an irregular S$_{RN}$1 mechanism. The



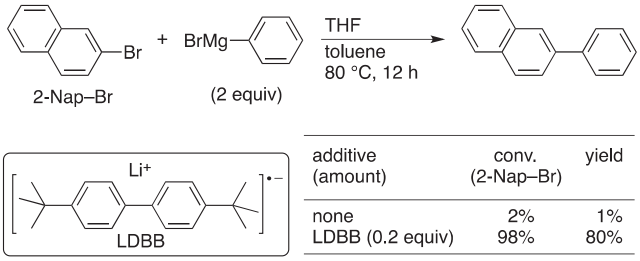
Scheme 10.

reversed order of deprotonation (step *c*) and addition (step *d*) compared with the original $S_{RN}1$ reaction makes it possible to use sp^2-carbon nucleophiles in $S_{RN}1$ reaction. We expected that the coupling reaction of aryl halides with sp^2-carbon nucleophiles through the original $S_{RN}1$ mechanism also is possible. After several investigations, use of toluene as a solvent in the presence of a small amount of THF was found to be effective for promotion of the coupling reaction (Scheme 10).[15] Thus, the reaction of 2-iodonaphthalene (1 equiv) with phenylmagnesium bromide (1.5 equiv) in the presence of THF (6–12 equiv) in toluene at 110 °C for 24 h gave 2-phenylnaphthalene in 97% yield. In contrast, halogen–magnesium exchange was predominated by use of THF as the sole solvent. High yields of coupling products were obtained in the reaction of electron-donating or -withdrawing group-substituted phenyl Grignard reagents and a heteroarylmagnesium bromide. Iodoanisoles underwent efficient coupling, whereas the reaction of phenyl iodide having a trifluoromethyl group resulted in a low yield due to competitive halogen–magnesium exchange reaction. For such electron-withdrawing group-substituted aryl halides, use of bromides was effective to suppress the halogen–magnesium exchange, where addition of NaO*t*-Bu (1 equiv) accelerated the reaction. Introduction of substituents at ortho-positions did not largely affect the coupling.

Assuming that the coupling reaction follows an $S_{RN}1$ pathway, the mechanism shown in Scheme 11 can be drawn. SET from Ar′–MgBr to Ar–X gives $[\text{Ar–X}]^{\bullet-}$ (*a*), which is converted to $\text{Ar}^{\bullet}$ upon elimination of X^- (*b*). Attack of Ar′–MgBr to $\text{Ar}^{\bullet}$ followed by SET from the resulting $[\text{Ar–Ar}']^{\bullet-}$ to Ar–X gives coupling product Ar–Ar′ and regenerates $[\text{Ar–X}]^{\bullet-}$ (*d* and *e*). Several experimental results that are consistent with this mechanism exist. Addition of lithium 4,4′-di-*tert*-butylbiphenylide (LDBB: 0.2 equiv) drastically accelerated the reaction of 2-bromonaphthalene with phenylmagnesium bromide (Scheme 12). LDBB, which is a much more effective single electron donor than PhMgBr, is likely to work efficiently in the otherwise reluctant initiation step. A competition reaction between aryl bromides also is informative (Scheme 13). 4-Bromostilbene showed higher reactivity than 4-bromo(trifluoromethyl)benzene, where the former has a lower reduction potential and the latter has higher electrophilicity at the carbon atom attached to Br. The result is in good agreement with an $S_{RN}1$ mechanism, where the reactivities of aryl halides are higher when their reduction potentials are lower. In contrast, more electron-deficient 4-bromo(trifluoromethyl)benzene was preferred under palladium catalysis.

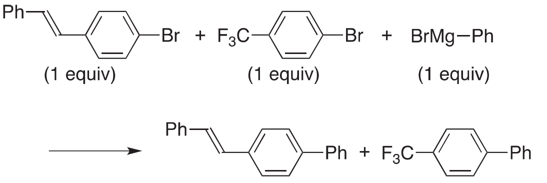


Scheme 11.



additive (amount)	conv. (2-Nap–Br)	yield
none	2%	1%
LDBB (0.2 equiv)	98%	80%

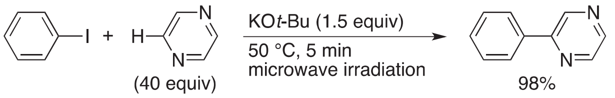
Scheme 12.



This Method[a] 63:37 27% total yield (32% conv)
Pd Catalysis[b] 16:84 25% total yield (30% conv)

[a] THF (6 equiv), in toluene, 110 °C, 3 h.
[b] $[\text{Pd}(\text{PPh}_3)_4]$ (2 mol %), in THF, 40 °C, 0.5 h.

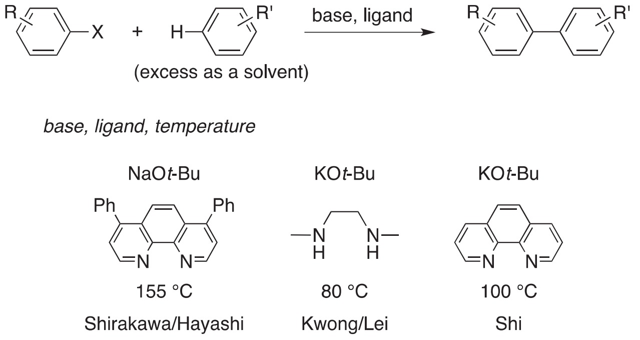
Scheme 13.



Scheme 14.

♦ Related Reactions and Conclusion

In 2008, Itami and co-workers reported the transition-metal-free coupling of aryl halides with *N*-heteroarenes (Scheme 14).[10] Although the scope is strictly limited to electron-deficient



Scheme 15.

6-membered *N*-heteroarenes such as pyrazine and microwave irradiation is required for high yields, the work is significant as the first example of C(sp^2)–C(sp^2) coupling taking place without the aid of transition metals. In 2010, we and two other groups independently reported the coupling of aryl halides with benzene derivatives (Scheme 15). Our results are described in the second section of this review. In contrast to our use of NaO*t*-Bu as a base, KO*t*-Bu was used by both Kwong/Lei[16] and Shi groups.[17] Ph-phen is the ligand in our and Shi's system, whereas *N*,*N'*-dimethylethylenediamine was chosen by Kwong/Lei.

Related reports on the coupling of aryl halides with arenes followed the above three reports. All the systems employ KO*t*-Bu as a base. 1-Aminoquinoline-2-carboxylic acid is shown to be effective as a ligand.[18] A stable 11π-electron zwitterionic radical was used as an activator.[19] Two reports are available for intramolecular aryl–aryl coupling to give tricyclic compounds.[20] A combination of KO*t*-Bu and a 1,10-phenanthroline derivative is used for inter- and intramolecular coupling of aryl halides with 1,1-diarylalkenes.[21]

This Highlight Review describes our recent results on the coupling reactions of aryl halides with arenes, styrenes, or aryl Grignard reagents. S$_{RN}$1 pathway offers a new way of C(sp^2)–C(sp^2) bond formation, which has been difficult to achieve without the aid of transition-metal catalysis. Use of strong bases such as *tert*-butoxides and aryl Grignard reagents is crucial. The bases are thought to have two important roles. First, they act as single electron donors toward aryl halides and convert them into aryl radicals. The second role is introduction of anionic species leading to the radical anions of coupling products. In the coupling reaction with arenes or styrenes, the radical anions are generated through deprotonation from radicals by the bases, whereas attack of aryl Grignard reagents to aryl radicals gives the radical anions in the cross-coupling reaction. As with palladium-catalyzed coupling reactions, aryl halides are activated by reduction. Although the reaction modes of the intermediates are different between these two reactions, both aryl radicals and arylpalladium(II) complexes prefer sp^2-carbon-containing compounds as reaction partners. This is why the same compounds have been obtained (Scheme 1: a–c) and other C(sp^2)–C(sp^2) coupling products are expected to be obtained by S$_{RN}$1 reaction. A sign of prosperity of this methodology is found in the fact that more than ten related papers have appeared within a year.

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