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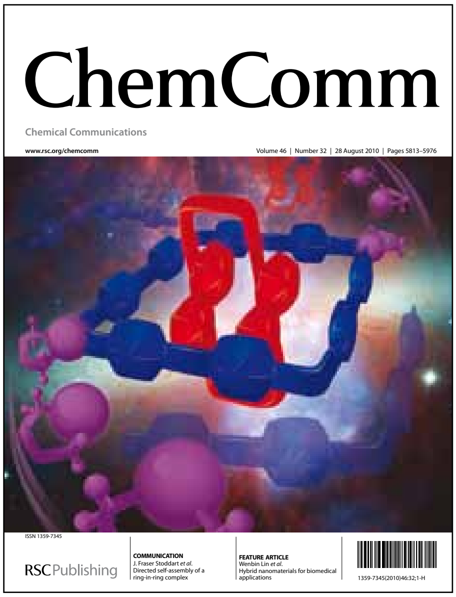

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Single Electron Transfer-Induced Grignard Cross-Coupling Involving Ion Radicals as Exclusive Intermediates

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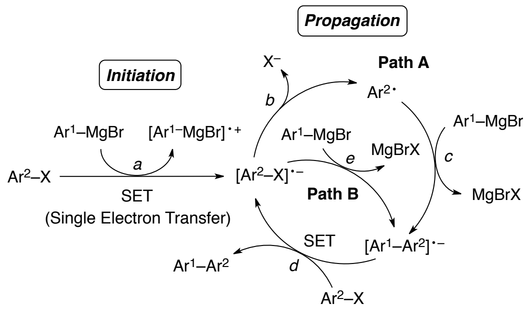
The mechanism of the previously developed cross-coupling reaction of aryl Grignard reagents with aryl halides was explored in more detail. Single electron transfer from an aryl Grignard reagent to an aryl halide initiates a radical chain by giving an anion radical of the aryl halide. The following propagation cycle consists entirely of anion radical intermediates.

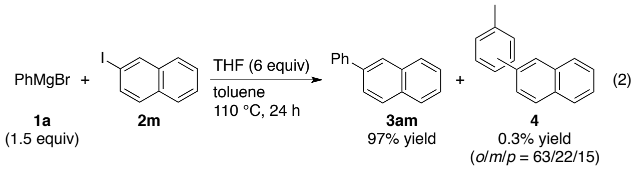
Cross-coupling of arylmetals with aryl halides is one of the most straightforward and reliable methods to obtain biaryls, where transition metal catalysts have inevitably been used.[1] On the other hand, we have recently reported the first transition metal-free coupling of arylmagnesium bromides ($\mathrm{Ar^1{-}MgBr}$) with aryl halides ($\mathrm{Ar^2{-}X}$) (eqn (1)), utilizing activation of $\mathrm{Ar^2{-}X}$ by single electron transfer (SET).[2] We proposed an $\mathrm{S_{RN}1}$ mechanism[3] shown as Path A in Scheme 1. Thus, SET from $\mathrm{Ar^1{-}MgBr}$ to $\mathrm{Ar^2{-}X}$ gives $[\mathrm{Ar^2{-}X}]^{\bullet-}$ (step *a*), which is converted to $\mathrm{Ar^{2\bullet}}$ upon elimination of $\mathrm{X^-}$ (step *b*). After nucleophilic attack of $\mathrm{Ar^1{-}MgBr}$ to $\mathrm{Ar^{2\bullet}}$ (step *c*), SET from the resulting $[\mathrm{Ar^1{-}Ar^2}]^{\bullet-}$ to $\mathrm{Ar^2{-}X}$ gives coupling product $\mathrm{Ar^1{-}Ar^2}$ and regenerates $[\mathrm{Ar^2{-}X}]^{\bullet-}$ to reenter the radical chain (step *d*).[4] We disclosed that addition of an anion radical of a biaryl as a single electron equivalent drastically accelerates the reaction, and that aryl halides show higher reactivities when they have lower reduction potentials. These results support that the reaction pathway includes SET as in steps *a* and *d*,[5] but elucidation of the rest steps (*b* and *c*) are left unexplored. Here we report what intermediates are involved in the Grignard cross-coupling, where $[\mathrm{Ar^2{-}X}]^{\bullet-}$ is transformed not through $\mathrm{Ar^{2\bullet}}$ but directly to $[\mathrm{Ar^1{-}Ar^2}]^{\bullet-}$ as Path B in Scheme 1.[6]

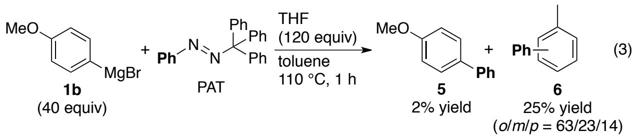
$$\underset{\mathbf{1}}{\mathrm{Ar^1{-}MgBr}} + \underset{\mathbf{2}}{\mathrm{Ar^2{-}X}} \xrightarrow[\text{toluene, 110 }^\circ\text{C}]{\text{THF (6 equiv)}} \underset{\mathbf{3}}{\mathrm{Ar^1{-}Ar^2}} \qquad (1)$$



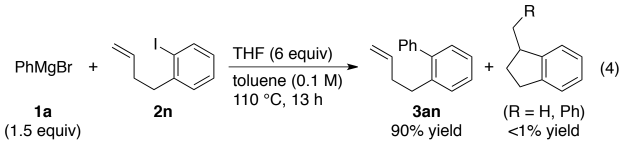
Scheme 1

The cross-coupling we developed gives biaryls in high yields.[2] For example, the reaction of PhMgBr (**1a**: 1.5 equiv) with 2-iodonaphthalene (**2m**) in toluene in the presence of THF (6 equiv) at 110 °C for 24 h gave 97% yield of 2-phenylnaphthalene (**3am**) (eqn (2)).[7] The yield was reasonably high but GC analysis of the reaction mixture showed existence of a trace amount (0.3%) of a regioisomeric mixture of 2-naphthyltoluenes (**4**: *o*/*m*/*p* = 63/22/15), which is likely to be produced through addition of the **2m**-derived naphthyl radical to toluene. The characteristic high ortho-selectivity strongly supports involvement of the radical addition to the benzene ring.[8] The generation of $\mathrm{Ar^{2\bullet}}$ from $\mathrm{Ar^2{-}X}$ in the reaction mixture is consistent with operation of $\mathrm{S_{RN}1}$ mechanism (Path A of Scheme 1), on condition that aryl radicals ($\mathrm{Ar^{2\bullet}}$) react preferentially with aryl Grignard reagents ($\mathrm{Ar^1{-}MgBr}$). This requirement seemed to be readily fulfilled, considering that the resulting anion radicals, $[\mathrm{Ar^1{-}Ar^2}]^{\bullet-}$, are much more stable than $[\mathrm{ArNH_2}]^{\bullet-}$, which is reported to be involved as intermediates in the $\mathrm{S_{RN}1}$ reaction.[9] However, the reaction of an aryl radical precursor with an aryl Grignard reagent gave a contradictory result. Thus, treatment of phenylazo(triphenyl)methane (PAT), which is known to generate $\mathrm{Ph^\bullet}$ upon heating,[10] with *p*-methoxyphenylmagnesium bromide (**1b**) in toluene gave 4-methoxybiphenyl (**5**) only in 2% yield, along with a regioisomeric mixture (*o*/*m*/*p* = 63/23/14) of methylbiphenyls (**6**) as a major product (25% yield) (eqn (3)).[11] The result shows that aryl radicals react much preferentially with a solvent amount of toluene over with aryl Grignard reagents,[12] and thus that $\mathrm{Ar^{2\bullet}}$ derived from $\mathrm{Ar^2{-}X}$ is unlikely to be involved in the cross-coupling reaction.

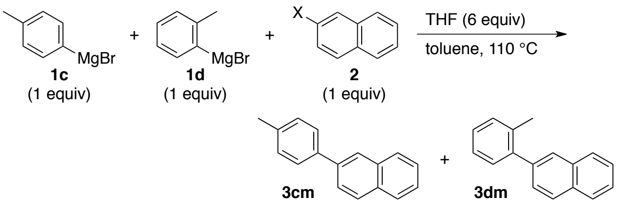




No involvement of aryl radical intermediates was further confirmed by a radical clock reaction using 2-(3-butenyl)phenyl iodide (**2n**), the corresponding aryl radical of which is known to readily cyclize (k_c = 5 x 10^8 s^{-1} at 50 °C).[13] The reaction of **2n** with **1a** gave no cyclization products but direct phenylation product **3an** (eqn (4)). Considering the observation that aryl radicals do not react smoothly with aryl Grignard reagents, no production of cyclization products supports no involvement of aryl radicals.[14]



Taking into account the previous conclusion that SET to Ar^2–X to give $[Ar^2–X]^{\bullet -}$ as steps *a* and *d* in Scheme 1 is operative, no participation of $Ar^{2\bullet}$ implies that $[Ar^2–X]^{\bullet -}$ reacts directly with Ar^1–MgBr as shown in step *e* in Scheme 1.[15] In that event, the kind of X possibly affects the reaction with aryl Grignard reagents. This holds true, thus in competition reactions between tolylmagnesium bromides **1c** and **1d**, both 2-naphthyl iodide (**2m**) and chloride (**2'm**) reacted preferentially with less hindered *p*-tolyl derivative **1c**, where the selectivity was considerably higher in the reaction of **2'm** (74:26) than **2m** (62:38) (Scheme 2).[16–18]

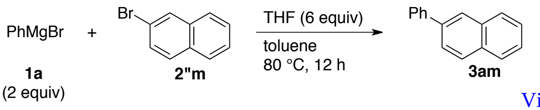


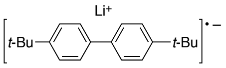
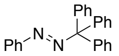
X in 2	time	conv. of 2	yield of 3	3cm:3dm
I (**2m**)	0.5 h	23%	22%	62:38
Cl (**2'm**)	24 h	12%	7%	74:26

Scheme 2

In the previous report,[2] we demonstrated the involvement of anion radical intermediates by the fact that addition of a similar anion radical accelerates the reaction (Scheme 3). Thus, the rate of the reaction of PhMgBr (**1a**) with unreactive 2-bromonaphthalene (**2"m**) was drastically increased by addition of lithium di-*tert*-butylbiphenylide (LDBB: 0.2 equiv). In contrast, addition of PAT (0.2 equiv) did not accelerate the reaction, where the generated phenyl radical was converted mainly to methylbiphenyls (**6**).[19] The result is rationally understood that acceleration is possible with addition of an anion radical intermediate but not with addition of an aryl radical, which is not an intermediate.

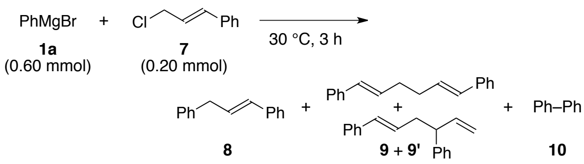
In this cross-coupling, an oxidative homocoupling product (Ar^1–Ar^1) of Ar^1–MgBr is always produced in a small but certain amount.[20] In the previous report, we took this result as a proof that SET from Ar^1–MgBr to Ar^2–X is operative in the initiation step (*a* in Scheme 1), considering that Ar^1–Ar^1 is produced through fragmentation of $[Ar^1–MgBr]^{\bullet +}$ followed by the reaction of the resulting $Ar^{1\bullet}$ with Ar^1–MgBr. However, an isomeric mixture of Ar^1–C_6H_4Me is produced only in a much less amount than Ar^1–Ar^1.[21] Taking it into account that aryl radicals react preferentially with a solvent amount of toluene over with aryl Grignard reagents (eqn (3)), this result shows that $Ar^{1\bullet}$ is generated only in a trace amount. Consequently, Ar^1–Ar^1 is likely to be produced by the reaction of $[Ar^1–MgBr]^{\bullet +}$ with Ar^1–MgBr in a similar manner that the reaction of $[Ar^2–X]^{\bullet -}$ with Ar^1–MgBr gives Ar^1–Ar^2.



additive (amount)	none	 LDBB (0.2 equiv)	 PAT (0.2 equiv)
conv. of 2"m	2%	98%	2%
yield of 3am	1%	80%	<1%

Scheme 3

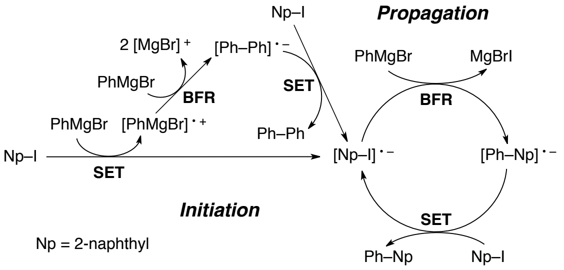
Aryl Grignard reagents are known to act as single electron donors toward certain electrophiles.[22] For example, SET from PhMgBr (**1a**) to cinnamyl chloride (**7**) to give $[\mathrm{PhMgBr}]^{\bullet +}$ and $[\mathbf{7}]^{\bullet -}$, respectively, is reported to take place during substitution reaction between **1a** and **7**.[22b] In this report, homocoupling products (**9** and **9'**) of **7** are regarded as end products of intermediate $[\mathbf{7}]^{\bullet -}$, but the course of cation radical $[\mathrm{PhMgBr}]^{\bullet +}$ is not disclosed. Then we conducted the reaction in our hands, paying attention to the course of $[\mathrm{PhMgBr}]^{\bullet +}$ (Scheme 4). The reaction of **1a** (0.60 mmol) with **7** (0.20 mmol) under the reported conditions gave Ph–Ph (**10**) in an amount (0.048 mmol) comparable to that (0.044 mmol) of **9**/**9'** in addition to substitution product **8**. The yields of **10** and **9**/**9'** were increased by use of the solvent system (toluene with 6 equiv of THF) used in the cross-coupling, giving no methylbiphenyls (**6**). No production of methylbiphenyls in use of toluene as a solvent shows that $Ph^{\bullet}$ is not present in the reaction mixture. Consequently, $[\mathrm{PhMgBr}]^{\bullet +}$, with no fragmentation to $Ph^{\bullet}$ and $[\mathrm{MgBr}]^{+}$, reacts with PhMgBr to give Ph–Ph *via* $[\mathrm{Ph–Ph}]^{\bullet -}$. It is most likely that Ph–Ph is produced in the same manner also in our cross-coupling and thus SET from aryl Grignard reagents to aryl halides is operative.



	8	9 + 9'	10
in THF	0.112 mmol	0.044 mmol (64:36)	0.048 mmol
in toluene with THF (6 equiv)	0.078 mmol	0.052 mmol (29:71)	0.076 mmol

Scheme 4

All these results are compiled into a mechanism shown in Scheme 5, exemplified by the reaction of PhMgBr (**1a**) with 2-iodonaphthalene (Np–I: **2m**). The whole scheme consists of three SETs toward Np–I giving $[\mathrm{Np–I}]^{\bullet -}$ and two C–C bond forming reactions (BFR) of PhMgBr with an ion radical. Two single electrons generated at the expense of two PhMgBr in the initiation step are handed over to Np–I to give [Np–I]$^{\bullet-}$, and then promote the propagation cycle.



Scheme 5

In conclusion, we have revealed that the transition metal-free coupling of Ar^1–MgBr with Ar^2–X is initiated by SET from Ar^1–MgBr to Ar^2–X and propagated by a scheme consisting of the reaction of the resulting [Ar^2–X]$^{\bullet-}$ with Ar^1–MgBr and SET from [Ar^1–Ar^2]$^{\bullet-}$ to Ar^2–X. No involvement of Ar$^{2\bullet}$, which would induce side reactions such as hydrogen abstraction from solvents and addition to benzene rings, is likely to contribute to high selectivity and thus high yields of the cross-coupling.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedure and spectral data. See DOI: 10.1039/b000000x

1 For reviews, see: J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359–1469; *Metal-Catalyzed Cross-Coupling Reactions, Vol. 1–2, 2nd ed.* ed. A. de Meijere, F. Diederich, Wiley-VCH, Weinheim, 2004.

2 E. Shirakawa, Y. Hayashi, K. Itoh, R. Watabe, N. Uchiyama, W. Konagaya, S. Masui, T. Hayashi, *Angew. Chem., Int. Ed.*, 2012, **51**, 218–221.

3 For reviews of S$_{RN}$1 reactions, see: J. F. Bunnett, *Acc. Chem. Res.*, 1978, **11**, 413–420; R. A. Rossi, A. B. Pierini, A. B. Peñéñory, *Chem. Rev.*, 2003, **103**, 71–167.

4 Various anionic nucleophiles such as enolates and thiolates act as reaction partners of Ar$^{2\bullet}$ in S$_{RN}$1 reaction but arylmetals had never been used. See ref. 3. The reaction of Grignard reagents (R–MgX) including arylmagnesium bromides with *tert*-alkyl halides (R'–X) to give R–R' is reported to involve SET from R–MgX to R'–X. However, the coupling is considered to proceed not through S$_{RN}$1 mechanism but through radical coupling between the resulting R$^\bullet$ and R'$^\bullet$. M. Ohno, K. Shimizu, K. Ishizaki, T. Sasaki, S. Eguchi, *J. Org. Chem.*, 1988, **53**, 729–733.

5 The possibilities that the cross-coupling reaction proceeds through transition metal catalysis, aryne intermediates, or nucleophilic aromatic substitution are excluded from the considerations described in the previous report (ref. 2).

6 This kind of mechanism, which includes the reaction of anion radicals of aryl halides with anionic nucleophiles, has sometimes been called as S$_{RN}$2 mechanism in comparison with S$_{RN}$1 mechanism, which includes aryl radical intermediates. There have been debates as to which one is operative. For an example of the debates, see: D. B. Denney, D. Z. Denney, *Tetrahedron*, 1991, **47**, 6577–6600; J. F. Bunnett, *Tetrahedron*, 1993, **49**, 4477–4484; R. A. Rossi, S. M. Palacios, *Tetrahedron*, 1993, **49**, 4485–4494.

7 We used the same magnesium turnings and toluene as those used in the previous report. For their ICP analysis, see ref. 2.

8 Addition of aryl radicals to benzene rings is known to lead to biaryls through homolytic aromatic substitution (HAS), where both electron-donating and -withdrawing substituents on the benzene ring accelerate the addition, especially to their ortho-positions. For recent reviews on HAS, see: A. Studer, M. Bossart, in *Radicals in Organic Synthesis*, *Vol. 2,* ed. P. Renaud, M. P. Sibi, Wiley-VCH, Weinheim, 2001, chap. 1.4, pp. 62–80; W. R. Bowman, J. M. D. Storey, *Chem. Soc. Rev.*, 2007, **36**, 1803–1822.

9 J. K. Kim, J. F. Bunnett, *J. Am. Chem. Soc.*, 1970, **92**, 7463–7464; J. K. Kim, J. F. Bunnett, *J. Am. Chem. Soc.*, 1970, **92**, 7464–7466. See also ref. 3.

10 PAT is known to undergo decomposition into Ph$^\bullet$, N$_2$, and Ph$_3$C$^\bullet$ in toluene at 60 °C. (*a*) G. A. Russell, R. F. Bridger, *Tetrahedron Lett.*, 1963, **4**, 737–740; (*b*) T. Suehiro, A. Suzuki, Y. Tsuchida, J. Yamazaki, *Bull. Chem. Soc. Jpn.*, 1977, **50**, 3324–3328.

11 Thermolysis of PAT in the absence of an aryl Grignard reagent (in toluene with 120 equiv of THF, 110 °C, 1 h) gave 31% yield (*o*/*m*/*p* = 59:24:17) of **6**. A similar result is reported in ref. 10*b*.

12 Toluene:**1b** is 47:1 in eqn (3), whereas toluene:**1** is 63:1 under the standard cross-coupling conditions, e.g., in eqn (2).

13 A. N. Abeywickrema, A. L. J. Beckwith, *J. Chem. Soc., Chem. Commun.*, 1986, 464–465; H. Yasuda, Y. Uenoyama, O. Nobuta, S. Kobayashi, I. Ryu, *Tetrahedron Lett.*, 2008, **49**, 367–370. We conducted reduction of **2n** in toluene (0.2 M, 110 °C, 1 h) with Bu$_3$SnH (1.3 equiv) in the presence of AIBN (0.1 equiv) to give 70% yield of cyclization products (1-methylindane and 1,2,3,4-tetrahydronaphthalene, 93:7) with 7% yield of the simple reduction product (4-phenyl-1-butene).

14 Generation of cyclization products in a similar radical clock reaction was used as a support for exclusion of S$_{RN}$2 mechanism. A. L. J. Beckwith, S. M. Palacios, *J. Phys. Org. Chem.*, 1991, **4**, 404–412.

15 The lifetime of [Ar^2–X]$^{\bullet-}$ is reported to be too short to react with some substrates due to fast fragmentation of [Ar^2–X]$^{\bullet-}$ into Ar$^{2\bullet}$ and X$^-$. However, only the data in the reaction in polar solvents such as *N*-methylpyrrolidone and *N,N*-dimethylformamide are available. For recent examples, see: C. Costentin, M. Robert, J.-M. Savéant, *J. Am. Chem. Soc.*, 2004, **126**, 16051–16057; N. Takeda, P. V. Poliakov, A. R. Cook, J. R. Miller, *J. Am. Chem. Soc.*, 2004, **126**, 4301–4309.

16 Transformation of [Ar^2–X]$^{\bullet-}$ into [Ar^1–Ar^2]$^{\bullet-}$ possibly takes more than one step. In any case, the reaction of Ar^1–MgBr with [Ar^2–X]$^{\bullet-}$, not with Ar$^{2\bullet}$, should take place, though, at present, we do not have any convincing experimental data and/or theoretical explanation as to how this process proceeds. We consider it to be an important future subject to elucidate the mechanism of this process.

17 Low reactivity of 2-naphthyl chloride (**2'm**) compared with the iodide (**2m**) is ascribed mainly to its low electron acceptor character in steps *a* and *d* in Scheme 1.

18 The absence of the leaving group effect on the selectivity in similar competition reactions is used as a proof for S$_{RN}$1 mechanism. C. Galli, J. F. Bunnett, *J. Am. Chem. Soc.*, 1981, **103**, 7140–7147.

19 Methylbiphenyls (**6**) were produced in a yield (30% based on PAT) similar to that (31%) in the reaction in the absence of **1a** and **2"m**. See footnote 11.

20 For example, in the reaction of **1a** (0.30 mmol) with **2m** (0.20 mmol) shown in eqn (2), the amount of biphenyl was determined to be 0.010 mmol by GC analysis.

21 In the reaction of **1a** with **2m** shown in footnote 20, methylbiphenyls were produced in 0.0003 mmol (0.1% GC yield based on **1a**, *o*/*m*/*p* = 63/23/14), where ratio of Ar^1–C$_6$H$_4$Me:Ar^1–Ar^1 is 1:33.

22 For SET from aryl Grignard reagents to benzophenones, see: (*a*) K. Maruyama, *Bull. Chem. Soc. Jpn.*, 1964, **37**, 897–898. To *tert*-alkyl halides: ref. 4. To cinnamyl chlorides: (*b*) K. Muraoka, M. Nojima, S. Kusabayashi, S. Nagase, *J. Chem. Soc., Perkin Trans. 2,* 1986, 761–767.