Radical Reactions

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Cross-Coupling of Aryl Grignard Reagents with Aryl Iodides and Bromides through $S_{RN}1$ Pathway**

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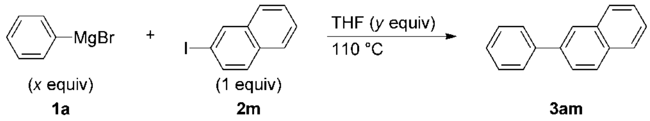
The transition-metal-catalyzed cross-coupling of aryl halides (Ar–X) with aryl metal reagents is one of the most reliable and widely applicable methods for biaryl synthesis. The catalytic cycle involves a two-electron reduction of Ar–X upon its oxidative addition to a low-valent transition metal.[1] Such a reduction is crucial for the employment of Ar–X as an electrophile in substitution reactions because Ar–X cannot undergo S_N1 or S_N2 reactions. A single-electron reduction also is effective for the activation of Ar–X, which is converted into $[Ar–X]^{\bullet-}$ then into $Ar^{\bullet}$ with elimination of X^-.[2,3] $Ar^{\bullet}$ is known to react with anionic nucleophiles (Nu^-), such as enolates and thiolates, to give $[Ar–Nu]^{\bullet-}$. A single-electron transfer (SET) from $[Ar–Nu]^{\bullet-}$ to Ar–X gives Ar–Nu and regenerates $[Ar–X]^{\bullet-}$, which reenters the chain reaction. In this pathway, called the $S_{RN}1$ pathway,[4] aryl metal compounds have never been utilized as anionic nucleophiles (Nu^-).[5,6] Herein, we report the coupling of aryl halides with aryl Grignard reagents that does not require the aid of transition metals and goes through an $S_{RN}1$ mechanism.[7,8]

Table 1: Coupling of phenylmagnesium bromide with 2-iodonaphthalene.[a]



Entry	Solvent in which **1a** was prepared	Reaction solvent	Amount (equiv)		*t* [h]	Conv. of **2m** [%][c]	Yield of **3am** [%][c]
			x	*y*[b]			
1[d,e]	THF	THF	2.0	–	24	29	2
2[e]	THF	toluene	2.0	0	24	19	17
3	THF	toluene	2.0	0	24	>99	93
4	Et_2O	toluene	2.0	0	24	4	1
5	Et_2O	toluene	2.0	6	24	>99	95
6	Et_2O	toluene	2.0	30	24	>99	93
7	THF	toluene	2.0	6	24	>99	98 (96)[f]
8	THF	toluene	1.2	6	24	87	86
9	THF	toluene	1.2	6	48	>99	97
10	THF	toluene	1.5	6	24	>99	95
11[g]	THF	toluene	1.5	6	24	>99	(97)[f]

[a] The reaction was carried out in a solvent (2.0 mL) under nitrogen using 2-iodonaphthalene (**2m**; 0.20 mmol) and phenylmagnesium bromide (**1a**), which was prepared in THF or Et_2O and then most of the solvent was removed in vacuo. [b] The amount of additionally added THF. [c] Determined by GC. [d] **1a** prepared in THF was used without solvent removal. [e] $T = 60$ °C. [f] The yield of the isolated product is given in parenthesis. [g] The reaction was conducted on a tenfold scale (2.0 mmol of **2m**). THF = tetrahydrofuran.

The reaction of phenylmagnesium bromide (**1a**; 2 equiv) with 2-iodonaphthalene (**2m**; 1 equiv) in THF at 60 °C for 24 h, after quenching with D_2O, gave 2-deuterionaphthalene (23 %, >95 % deuteration) and iodobenzene (16 %) in addition to a small amount (2 %) of 2-phenylnaphthalene (**3am**), with 29 % conversion of **2m** (Table 1, entry 1). This result shows that I/Mg exchange giving 2-naphthylmagnesium bromide and iodobenzene predominates, but the cross-coupling also takes place. The selectivity for the cross-coupling over the I/Mg exchange was drastically improved by changing the reaction solvent from THF to toluene, although a higher temperature (110 °C) was required (Table 1, entries 2 and 3). The Grignard reagent **1a** was prepared in THF and most of the solvent was removed in vacuo, and then it was used for the reaction with **2m** in toluene at 110 °C for 24 h to give **3am** in 93 % yield. In contrast, almost no coupling took place when **1a** prepared in Et_2O was used (Table 1, entry 4), thus implying that the presence of a small amount of THF has a positive effect. Addition of THF to the toluene solution of **1a**, which had been prepared in Et_2O, promoted the coupling; the yield of **3am** was high with 6 and 30 equivalents of THF (Table 1, entries 5 and 6).[9] THF is better than Et_2O as a solvent for Grignard reagent preparation because there is less formation of biaryl by-products in THF. The amount of THF remaining after evacuation is inconsistent;[10] therefore the addition of a sufficient amount (6 equiv; see Table 1, entry 5) of THF enhances the reproducibility of the reaction (Table 1, entry 7).[11] The coupling product was obtained in a high yield when a reduced amount (1.2 equiv) of Grignard reagent **1a** was used, although the reaction was slightly slower (Table 1, entries 8 and 9). A sufficient reaction rate is attained by using 1.5 equivalents of **1a** (Table 1, entry 10).[12] A high yield of the coupling product

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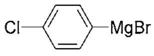
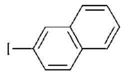
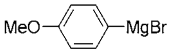
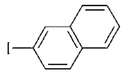
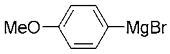
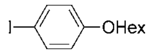
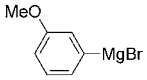
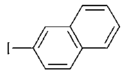
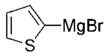
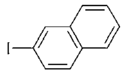
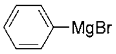
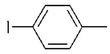
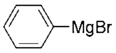
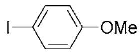
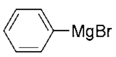
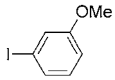
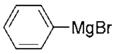
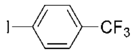
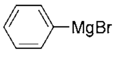
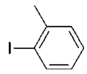
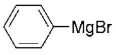
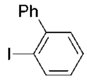
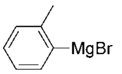
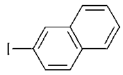
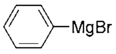
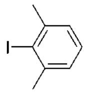
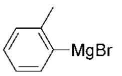
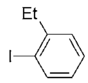
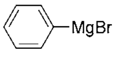
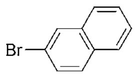
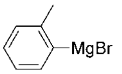
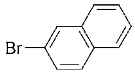
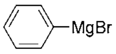
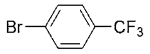
(**3am**) was obtained when the reaction scale was increased tenfold (2.0 mmol of **2m**; Table 1, entry 11).

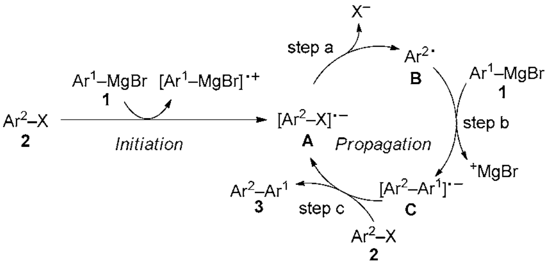
The cross-coupling reaction is applicable to a wide variety of aryl Grignard reagents and aryl halides (Table 2). Phenylmagnesium bromides having an electron-withdrawing or electron-donating group at the *para* or *meta* position underwent coupling with 2-iodonaphthalene (**2m**) or *p*-hexoxy(iodo)benzene (**2n**) in high yields (Table 2, entries 1–4). Unfortunately, p-CF$_3$C$_6$H$_4$MgBr was too unstable under the reaction conditions and gave $<10\%$ yield of the coupling product. A high yield was attained also in the reaction of a heteroaryl Grignard reagent (Table 2, entry 5). Tolyl and methoxyphenyl iodides underwent coupling with **1a** in high yields (Table 2, entries 6–8). For the reaction of *p*-iodo(trifluoromethyl)benzene (**2r**), the coupling product was obtained in only 55% yield because of halogen/magnesium exchange, which was probably induced by an electron-withdrawing substituent (Table 2, entry 9). The cross-coupling reaction is compatible with *ortho* substitution (Table 2, entries 10–14). Aryl bromides are less reactive than aryl iodides. Therefore, the reaction of 2-bromonaphthalene (**2′m**) with **1a** under the reaction conditions thus far employed gave only 72% yield of **3am** with 78% conversion. Addition of NaO*t*Bu[13] (1.0 equiv) in combination with an increased amount (2.0 equiv) of **1a** was found to be effective in improving the yield to 90% (Table 2, entry 15). The reaction of **2′m** with the *o*-tolyl Grignard reagent (**1f**) gave the corresponding coupling product in a high yield (Table 2, entry 16). The reaction of p-CF$_3$C$_6$H$_4$Br (**2′r**) gave **3ar** in a high yield (Table 2, entry 17), in contrast to the reaction with the corresponding iodide, where I/Mg exchange hampered the coupling (see Table 2, entry 9).

Table 2: Coupling of aryl Grignard reagents with aryl halides.[a]

$$\underset{\mathbf{1}}{\underset{(1.5\ \text{equiv})}{\text{Ar}^1\text{–MgBr}}} + \underset{\mathbf{2}}{\underset{(1\ \text{equiv})}{\text{X–Ar}^2}} \xrightarrow[\text{toluene, 110 °C, 24 h}]{\text{THF}} \underset{\mathbf{3}}{\text{Ar}^1\text{–Ar}^2}$$

Entry	1	2	Yield [%][b]
1	 **1b**	 **2m**	97
2	 **1c**	 **2m**	95[c]
3	 **1c**	 **2n**	91[d]
4	 **1d**	 **2m**	90
5[e]	 **1e**	 **2m**	96
6	 **1a**	 **2o**	97
7	 **1a**	 **2p**	96
8	 **1a**	 **2q**	93
9	 **1a**	 **2r**	55
10	 **1a**	 **2s**	91
11	 **1a**	 **2t**	93
12	 **1f**	 **2m**	96
13	 **1a**	 **2u**	91
14	 **1f**	 **2v**	89
15[f]	 **1a**	 **2′m**	90
16[f]	 **1f**	 **2′m**	96
17[f]	 **1a**	 **2′r**	92

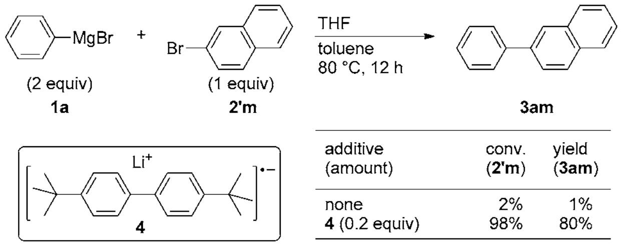
[a] The reaction was carried out in toluene (2.0 mL) at 110°C under nitrogen using THF (1.2 mmol), an aryl halide (**2**; 0.20 mmol), and an arylmagnesium bromide (**1**; 0.30 mmol), which was prepared in THF and then most of the solvent was removed in vacuo. [b] Yield of the isolated product. [c] 1-(4-Methoxyphenyl)naphthalene also was produced in 3% yield. [d] 3-Hexoxy-4′-methoxybiphenyl also was produced in 3% yield. [e] **1e** (0.40 mmol) was used. [f] NaO*t*Bu (0.20 mmol) and **1** (0.40 mmol) were used.



Scheme 1. A plausible reaction mechanism.

The fact that there is no production of the rearranged coupling products excludes the aryne mechanistic pathway.[7,14] Nucleophilic aromatic substitution is not operative either because electron-withdrawing substituents on aryl halides are not required.[7] On the assumption that the coupling reaction follows the $S_{RN}1$ pathway, the mechanism shown in Scheme 1 can be proposed. A single-electron transfer (SET) from Grignard reagent **1** to aryl halide **2** gives radical anion **A** (initiation step). After elimination of X$^-$ from **A** (step a), **1** attacks the resulting aryl radical **B** to give radical anion **C** (step b). An SET from **C** to **2** gives the coupling product **3** and regenerates **A** (step c). This mechanism includes "spontaneous initiation", in which the nucleophile (**1** in this case) in step b acts also as a single-electron donor in the initiation step. Even though 2-bromonaphthalene (**2′m**) is unreactive toward PhMgBr (**1a**) at 80°C, the coupling proceeded in the presence of lithium 4,4′-di-*tert*-

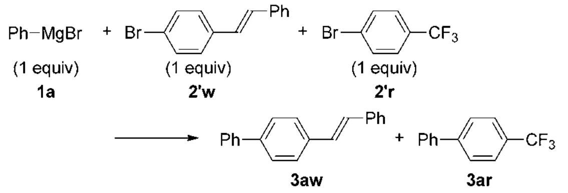
butylbiphenylide (**4**; 0.2 equiv)[15] to give 80% of **3am** after 12 h (Scheme 2).[16] Compound **4** is a biaryl radical anion that is analogous to intermediate **C**. Therefore, it is likely that **4** acts as a single electron donor in step c and accelerates the coupling by eliminating the reluctant initiation step.[17] In $S_{RN}1$ reactions that involve "spontaneous initiation" the initiation step has to be slower than the propagation steps, because a faster initiation step would result in increased consumption of the nucleophile, which is required for step b, and thus lower the efficiency of the reaction.[18,19] Upon SET to **2** in the initiation step **1** should be converted into $[Ar^1MgBr]^{\bullet +}$, which readily undergoes elimination of $[MgBr]^+$.[6] The resulting $Ar^{1\bullet}$ reacts by steps b and c to give $Ar^1{-}Ar^1$ and **A**. In the present coupling reaction, $Ar^1{-}Ar^1$ is always observed but in a small amount.[20]



additive (amount)	conv. (2'm)	yield (3am)
none	2%	1%
4 (0.2 equiv)	98%	80%

Scheme 2. The reaction in the presence of a radical anion of a biaryl.

A competition reaction between two aryl bromides gave further support to the involvement of SET to aryl halides (Scheme 3). In the reaction with **1a**, (*E*)-4-bromostilbene (**2′w**) showed higher reactivity than 4-bromo(trifluoromethyl)benzene (**2′r**) in spite of the lower electrophilicity of its carbon atom that is bonded to the bromide. The observation is consistent with the $S_{RN}1$ mechanism, in which aryl halides show higher reactivities when they have lower reduction potentials.[21] In contrast, **2′r** is much more reactive than **2′w** under palladium catalysis.



	3aw:3ar	
This method[a]	63:37	27% total yield (32% conv.)
Pd catalysis[b]	16:84	25% total yield (30% conv.)

Scheme 3. Competition reactions of aryl bromides. [a] THF (6 equiv), toluene, 110 °C, 3 h. [b] $[Pd(PPh_3)_4]$ (2 mol%), THF, 40 °C, 0.5 h.

In conclusion, we have disclosed the cross-coupling reaction of aryl Grignard reagents with aryl halides. Utilization of an SET mechanism for activation of aryl halides makes the cross-coupling possible without any transition-metal catalysts.

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Keywords: arenes · biaryls · C–C coupling · electron transfer · radical reactions

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[1] For reviews, see: a) S. P. Stanforth, *Tetrahedron* **1998**, *54*, 263–303; b) *Cross-Coupling Reactions: A Practical Guide* (Ed.: N. Miyaura), Springer, Berlin, **2002** (*Top. Curr. Chem.*, *Vol. 219*); c) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1469; d) *Metal-Catalyzed Cross-Coupling Reactions*, *Vol. 1–2*, 2nd ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; e) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651–2710.

[2] For reviews, see: a) J.-M. Savéant, *Tetrahedron* **1994**, *50*, 10117–10165; b) J. Grimshaw, *Electrochemical Reactions and Mechanism in Organic Chemistry*, Elsevier, Amsterdam, **2000**, chap. 4, pp. 89–157.

[3] Biaryl compounds are known to be produced from aryl radicals ($Ar^\bullet$) through homolytic aromatic substitution (HAS) consisting of the addition of $Ar^\bullet$ to an arene and elimination of $H^\bullet$ from the resulting cyclohexadienyl radical. For reviews, see: a) R. Bolton, G. H. Williams, *Chem. Soc. Rev.* **1986**, *15*, 261–289; b) J. Fossey, D. Lefort, J. Sorba, *Free Radicals in Organic Chemistry*, Wiley, Chichester, **1995**, chap. 14, pp. 166–180; c) A. Studer, M. Bossart in *Radicals in Organic Synthesis*, *Vol. 2* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, **2001**, chap. 1.4, pp. 62–80; d) W. R. Bowman, J. M. D. Storey, *Chem. Soc. Rev.* **2007**, *36*, 1803–1822. We have reported the arylation of arenes with aryl halides along an HAS pathway, which involves a single-electron reduction of aryl halides by a NaO*t*Bu/phenanthroline complex to give aryl radicals, see: e) E. Shirakawa, K. Itoh, T. Higashino, T. Hayashi, *J. Am. Chem. Soc.* **2010**, *132*, 15537–15539. Similar reactions using KO*t*Bu as a base have been independently studied, see: f) W. Liu, H. Cao, H. Zhang, H. Zhang, K. H. Chung, C. He, H. Wang, F. Y. Kwong, A. Lei, *J. Am. Chem. Soc.* **2010**, *132*, 16737–16740; g) C. L. Sun, H. Li, D.-G. Yu, M. Yu, X. Zhou, X.-Y. Lu, K. Huang, S.-F. Zheng, B.-J. Li, Z.-J. Shi, *Nat. Chem.* **2010**, *2*, 1044–1049. The mechanism of these reactions has been discussed, see: h) A. Studer, D. P. Curran, *Angew. Chem.* **2011**, *123*, 5122–5127; *Angew. Chem. Int. Ed.* **2011**, *50*, 5018–5022.

[4] For reviews of $S_{RN}1$ reactions, see: a) J. F. Bunnett, *Acc. Chem. Res.* **1978**, *11*, 413–420; b) R. A. Rossi, A. B. Pierini, A. B. Peñéñory, *Chem. Rev.* **2003**, *103*, 71–167.

[5] Resonance-stabilized sp^3 carboanions, which are produced by deprotonation of hydrocarbons such as indene and triphenylmethane, are reported to undergo an $S_{RN}1$ reaction with aryl halides. For examples, see: a) R. A. Rossi, J. F. Bunnett, *J. Org. Chem.* **1973**, *38*, 3020–3025; b) L. M. Tolbert, S. Siddiqui, *Tetrahedron* **1982**, *38*, 1079–1086; c) L. M. Tolbert, D. P. Martone, *J. Org. Chem.* **1983**, *48*, 1185–1190; d) M. P. Moon, A. P. Komin, J. F. Wolfe, *J. Org. Chem.* **1983**, *48*, 2392–2399; e) L. M. Tolbert, S. Siddiqui, *J. Org. Chem.* **1984**, *49*, 1744–1751.

[6] The reaction of Grignard reagents (R–MgX) with certain alkyl halides (R′–X; R′ = *tert*-alkyl, allyl) giving R–R′ is considered to proceed through SET from R–MgX to R′–X followed by coupling between the resulting radicals $R^\bullet$ and $R'^\bullet$. For examples, see: a) M. Ohno, K. Shimizu, K. Ishizaki, T. Sasaki, S. Eguchi, *J. Org. Chem.* **1988**, *53*, 729–733; b) K. Muraoka, M. Nojima, S. Kusabayashi, S. Nagase, *J. Chem. Soc. Perkin Trans. 2* **1986**, 761–767.

[7] Aryl Grignard reagents (Ar–MgX) are known to undergo nucleophilic aromatic substitution with aryl electrophiles (Ar′–X; X = F, OMe) that have Grignard reagent compatible

electron-withdrawing groups such as oxazolines or triethylmethoxycarbonyl, giving Ar−Ar′ through an addition/elimination mechanism. For a review, see: a) T. G. Gant, A. I. Meyers, *Tetrahedron* **1994**, *50*, 2297 – 2360; see also Ref. [1c]. Biaryl formation from aryl metal compounds and aryl halides via aryne intermediates is often considered to be a side reaction in the preparation of arynes but sometimes is utilized as a synthetic method. For such examples, see: b) R. Huisgen, H. Rist, *Justus Liebigs Ann. Chem.* **1955**, *594*, 137 – 158; c) H. Hart, K. Harada, C.-J. F. Du, *J. Org. Chem.* **1985**, *50*, 3104 – 3110. For a review that includes biaryl synthesis via aryne intermediates, see Ref. [1c].

[8] Transition-metal-free homocoupling of Grignard reagents, including aryl Grignard reagents, using diphenoquinone as an oxidant has been reported; A. Krasovskiy, A. Tishkov, V. del Amo, H. Mayr, P. Knochel, *Angew. Chem.* **2006**, *118*, 5132 – 5136; *Angew. Chem. Int. Ed.* **2006**, *45*, 5010 – 5014.

[9] Addition of dibutyl ether (6 equiv) instead of THF did not promote the coupling (1 % yield of **3am** with 4 % conversion of **2m**), thus suggesting that high coordinating ability of THF compared with the dialkyl ethers positively affects the reaction.

[10] The amount of THF remaining after in vacuo removal was estimated by GC analysis to be in the range of 2.3–6.8 equivalents to **1a** in several runs. GC analysis showed, in the average of three runs, that 84 % of the THF remained in the solution after heating a toluene solution (2.0 mL) of THF (97 μL, 1.2 mmol) at 110 °C.

[11] The reaction using toluene that was degassed by four freeze/thaw cycles just prior to use gave a comparable yield (98 %) of **3am**. It is unlikely that residual molecular oxygen promotes the reaction.

[12] Magnesium turnings (99.95 % purity trace metals basis, Aldrich Co., product number 403148) and toluene (> 99.5 % purity, dehydrated, Kanto Chemical Co. Ltd., Cat. No. 40500-85) purified by passing through an alumina/catalyst column system (GlassContour Co.) were used for Grignard reagent formation and the coupling reaction itself, respectively. ICP-AES analysis of the magnesium turnings showed that there was less than 5 ppm (within the detection limit) of Co, Ni, Cu, Ru, Rh, Pd, Ag, Ir, Pt, and Au and 13 ppm of Fe. To examine the effect of iron, the reaction in Table 1, entry 7 was conducted in the presence of $FeCl_3$ (5 mol %) to give 29 % of **3am** and 43 % of naphthalene, and 16 % of three regioisomers (60:23:17 ratio) of 2-naphthyltoluenes with full conversion of **2m** after 2 h. This result shows that iron drastically lowered the selectivity, thus it is unlikely that the trace amount of iron is involved in the present coupling reaction. ICP-MS analysis of the toluene showed that there was less than 1 ppb (within the detection limit) of Fe, Co, Ni, Cu, Ru, Rh, Pd, Ag, Ir, Pt, and Au.

[13] NaO*t*Bu purified by sublimation was used. ICP-AES and ICP-MS analysis showed that there was less than 0.05 ppm (within the detection limit) of Co, Ni, Rh, Pd, Ag, Ir, Pt, and Au and 0.50, 0.53, and 0.09 ppm of Fe, Cu, and Ru, respectively.

[14] Among the reactions in Tables 1 and 2, rearranged products were observed (3 %) only in the reaction of 4-methoxyphenylmagnesium bromide (**1c**; Table 2, entries 2 and 3), probably generated through an aryne intermediate formed owing to the high basicity of **1c**.

[15] P. K. Freeman, L. L. Hutchinson, *J. Org. Chem.* **1980**, *45*, 1924 – 1930.

[16] Reduction of **2′m** took place as a side reaction giving 2,2′-binaphthyl (11 %) and naphthalene (7 %).

[17] A radical anion of an arene, sodium naphthalenide, was used as an activator in the $S_{RN}1$ reaction of 2,2-dinitropropane with 2-lithio-2-nitropropane to give 2,3-dimethyl-2,3-dinitrobutane. G. A. Russell, R. K. Norris, E. J. Panek, *J. Am. Chem. Soc.* **1971**, *93*, 5839 – 5845.

[18] Related discussion on $S_{RN}1$ reactions that include "spontaneous initiation" is available in Section III-A in Ref. [4b].

[19] The reaction of **1a** with **2′m** in the presence of NaO*t*Bu (1.0 equiv), instead of **4**, under the same reaction conditions as Scheme 2 gave **3am** in 22 % yield (26 % conv. of **2′m**). This result implies that the effect of the addition of NaO*t*Bu (see Table 2, entries 15 – 17) is due mainly to promotion of the initiation step. PhMgO*t*Bu, generated from **1a** and NaO*t*Bu, possibly has a higher ability as a single-electron donor in the initiation step than **1a**. For the generation of PhMgO*t*Bu from **1a** and NaO*t*Bu, see: S. Gupta, S. Sharma, A. K. Narula, *J. Organomet. Chem.* **1993**, *452*, 1 – 4.

[20] For example, 0.010 mmol of Ph−Ph was produced by use of 0.20 mmol of **2m** in entry 10 of Table 1.

[21] The reactivity of aryl halides in the $S_{RN}1$ reaction with a pinacolone enolate are discussed in correlation with their reduction potentials: a) C. Galli, *Gazz. Chim. Ital.* **1988**, *118*, 365 – 368. Although the reduction potentials of aryl bromides **2′w** and **2′r** are not available, they should have close correlation with those of parent aromatic moieties. The reduction potential of (*E*)-stilbene and (trifluoromethyl)benzene are reported to be 2.14 (Ref. [21b]) and 2.54 (Ref. [21c]), respectively; b) D. Occhialini, J. S. Kristensen, K. Daasbjerg, H. Lund, *Acta Chem. Scand.* **1992**, *46*, 474 – 481; c) R. O. Loutfy, R. O. Loutfy, *Can. J. Chem.* **1976**, *54*, 1454 – 1463.