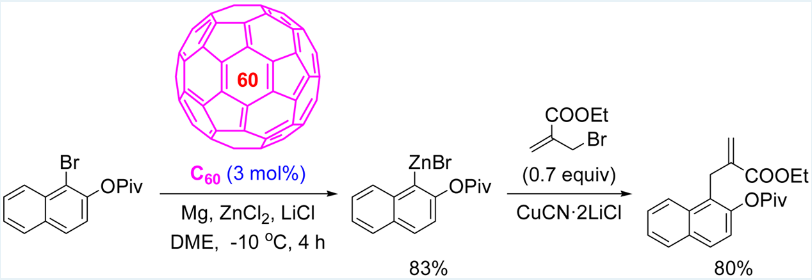
ACS Catalysis
Letter
pubs.acs.org/acscatalysis

C_{60}-Catalyzed Preparation of Aryl and Heteroaryl Magnesium and Zinc Reagents Using Mg/LiCl

Zhi-Liang Shen and Paul Knochel*

Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstrasse 5−13, Haus F, 81377 München, Germany

Supporting Information

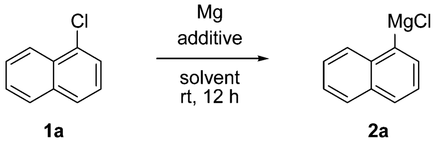


ABSTRACT: Addition of a catalytic amount of C_{60} fullerene (3 mol %) catalyzes the insertion of magnesium to polycyclic aromatic halides, allowing the preparation of the corresponding Grignard reagents in good yields. Furthermore, the use of a cocktail of metallic salts (Mg, $ZnCl_2$, LiCl) in the presence of C_{60} fullerene (3 mol %) allows preparation of some functionalized polyaromatic zinc reagents. The resulting organomagnesium and organozinc reagents efficiently underwent reactions with electrophiles, such as an aldehyde, an acid chloride, an allylic bromide, or an aryl iodide.

KEYWORDS: *C_{60} fullerene, organomagnesium, organozinc, lithium chloride, allylation, acylation, cross-coupling*

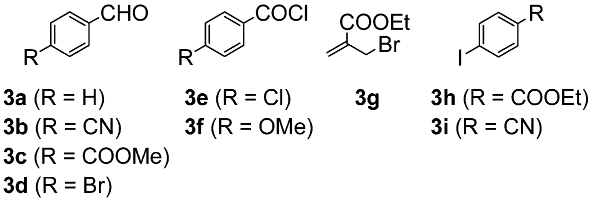
The preparation of organometallics by the direct insertion of a main-group metal, such as magnesium, into unsaturated organic halides is a very atom-economical method.[1] Because of the insolubility of metallic powders, such insertion reactions are heterogeneous and proceed readily only after the activation of the metal. The preparation of organomagnesium reagents largely depends on the activation of the magnesium surface.[2] Numerous methods for the activation of magnesium have been reported.[3] Several additives (such as catalytic amounts of $FeCl_2$,[4] DIBAL-H,[5] or transition metal−phosphine complexes[6]) have been found to facilitate the magnesium insertion to organic halides. The pioneering work of Rieke led to the discovery of much activated magnesium by the in situ reduction of $MgCl_2$ with lithium naphthalenide.[7] We have reported that the treatment of magnesium powder or turnings with lithium chloride lead to a similar activation.[8,9] LiCl plays the role of a Lewis acid and "surface cleaner". Its promoter activity can be enhanced by the presence of activated Lewis acids, such as $InCl_3$,[9−11] $PbCl_2$,[9,11,12] $TiCl_4$,[9] or $B(OR)_3$.[13] Aryl chlorides are usually cheaper and more readily available than the corresponding bromides or iodides; thus, there is still a lot of interest in converting aryl chlorides to Grignard reagents using mild conditions. Because the mechanism of the insertion involves electron transfer reaction steps,[14] we have envisioned that molecules that facilitate electron transfer reactions may be

Table 1. Screening of Different Additives and Solvents for Magnesium Insertion into 1-Chloronaphthalene (1a)



entry	additive	solvent	yield (%)[a]
1	LiCl	DME	0
2	C_{60}	DME	0
3	LiCl, C_{60}	DME	84
4	LiCl, C_{60}	THF	29
5	LiCl, C_{60}	Et_2O	0
6	LiCl, C_{60}	^{t}BuOMe	0
7	LiCl, C_{60}	tetrahydropyran	0

[a] Determined by iodolysis.



3a (R = H)
3b (R = CN)
3c (R = COOMe)
3d (R = Br)
3e (R = Cl)
3f (R = OMe)
3g
3h (R = COOEt)
3i (R = CN)

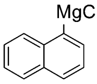
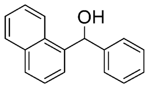
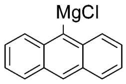
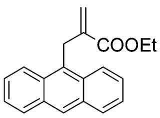
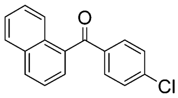
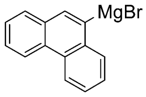
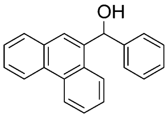
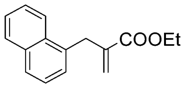
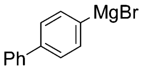
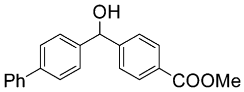
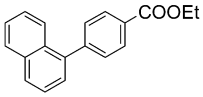
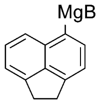
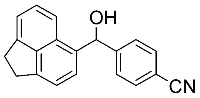
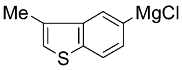
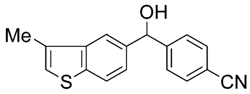
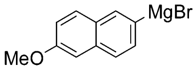
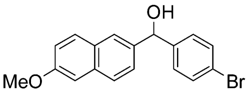
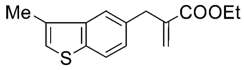
Figure 1. Electrophiles used for reactions with the formed organometallic reagents.

Received: February 9, 2015
Revised: March 9, 2015
Published: March 11, 2015

DOI: 10.1021/acscatal.5b00273
ACS Catal. 2015, 5, 2324−2328

Table 2. Preparation of Organomagnesium Reagents and Further Reactions with Electrophiles

$$\underset{\textbf{1a-g}}{\underset{(X = Cl, Br)}{Ar{-}X}} \xrightarrow[\text{DME, rt}]{\text{Mg,LiCl, 3 mol\% } C_{60}} \underset{\textbf{2a-g}}{Ar{-}MgX} \xrightarrow{E^+\ (\textbf{3a-h})} \underset{\textbf{4a-k}}{Ar{-}E}$$

entry	ArMgX (yield,[a] time)	E^+	product (yield)[b]	entry	ArMgX (yield,[a] time)	E^+	product (yield)[b]
1	 **2a** (84%,12 h)	**3a**	 **4a** (82%)	7	 **2c** (61%, 1 h)	**3g**	 **4g** (65%)[c]
2	**2a**	**3e**	 **4b** (77%)[c]	8	 **2d** (79%, 10 min)	**3a**	 **4h** (85%)
3	**2a**	**3g**	 **4c** (78%)[c]	9	 **2e** (70%, 2 h)	**3c**	 **4i** (75%)
4	**2a**	**3h**	 **4d** (91%)[d]	10	 **2f** (74%, 4 h)	**3b**	 **4j** (82%)
5	 **2b** (67%, 22 h)	**3b**	 **4e** (68%)	11	 **2g** (86%, 1 h)	**3d**	 **4k** (80%)
6	**2b**	**3g**	 **4f** (70%)[c]				

[a] Determined by iodolysis. [b] Yield of isolated, analytically pure product. [c] 20 mol % CuCN·2LiCl was used. [d] 4 mol % Pd(OAc)$_2$ and 8 mol % S-Phos were used, and the reactions were performed at 60 °C for 12 h.

Scheme 1. One-Pot Preparation of Organozinc Reagents with Improved Functional Group Tolerance and Their Subsequent Reactions with Electrophiles

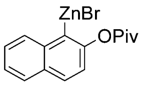
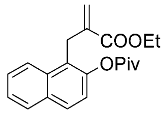
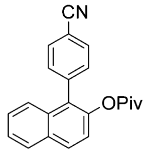
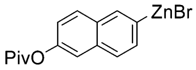
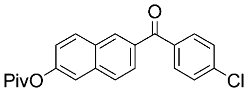
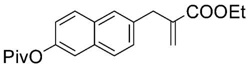
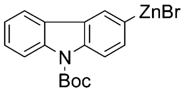
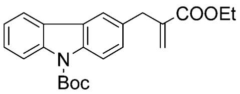
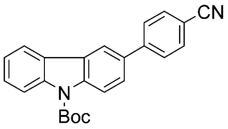
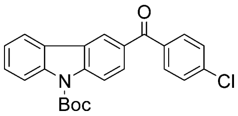
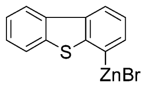
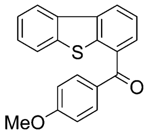
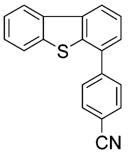
$$\underset{\textbf{5a-d}}{Ar{-}Br} \xrightarrow[\text{DME}]{\text{Mg, ZnCl}_2\text{, LiCl, 3 mol\% } C_{60}} \underset{\textbf{6a-d}}{Ar{-}ZnX} \xrightarrow{E^+\ (\textbf{3e-i})} \underset{\textbf{7a-i}}{Ar{-}E}$$

good catalysts for the magnesium insertion. After several unsuccessful attempts, we turned our attention to C_{60} fullerene because it is known that this highly unsaturated molecule readily accepts and transfers electrons.[15−17] Herein, we report that the addition of catalytic amounts of C_{60} catalyzes the magnesium insertion in the additional presence of LiCl, allowing the synthesis of aryl and heteroaryl magnesium or zinc reagents under mild conditions.

First, we tested the magnesium insertion to 1-chloronaphthalene (**1a**) using various ethereal solvents. Initially, the reaction of **1a** (1 equiv) with Mg turnings (3 equiv) in DME at 25 °C for 12 h was examined. The magnesium turnings were activated by the addition of 1,2-dibromoethane (5 mol %) and TMSCl (5 mol %). No reaction was observed with Mg turnings alone or in the presence of either LiCl (2 equiv) or C_{60} (3 mol %) (Table 1, entries 1−2). The addition of C_{60} (3 mol %) led to a complete conversion in the presence of LiCl, and the formation of the corresponding Grignard reagent (**2a**) was achieved in 84% yield as determined by iodolysis (Table 1, entry 3). It was important to use 99.9% pure C_{60} because we noticed that 98% pure C_{60} did not catalyze the magnesium insertion to an appreciable extent.[18] Under the same conditions, the insertion performed in other ethereal solvents led to either poor yields of Grignard reagent **2a** (THF, 29%, Table 1, entry 4) or no insertion reaction (Table 1, entries 5−7). Quenching with various electrophiles (Figure 1), such as a benzaldehyde (**3a**), an acid chloride (**3e**), an allylic bromide (**3g**),[19] or an aryl iodide (**3h**, after transmetalation with ZnCl$_2$; Negishi cross-coupling[20] using Pd(OAc)$_2$ and S-Phos[21]), produced the expected products (**4a−d**) in 77−91% yields (Table 2, entries 1−4).

With 99.9% pure C_{60}, it was possible to convert aryl chlorides (**1b−c**) into the corresponding Grignard reagents (**2b,c**; Table

Table 3. Preparation of Organozinc Reagents and Subsequent Reactions with Electrophiles

entry	ArZnX (yield,^{a} temp., time)	E$^+$	product (yield)^b
1	 **6a** (83%, -10 °C, 4 h)	**3g**	 **7a** (80%)^c
2	**6a**	**3i**	 **7b** (62%)^d
3	 **6b** (75%, -10 °C, 20 h)	**3e**	 **7c** (63%)^c
4	**6b**	**3g**	 **7d** (88%)^c
5	 **6c** (79%, rt, 1 h)	**3g**	 **7e** (78%)^c
6	**6c**	**3i**	 **7f** (69%)^d
7	**6c**	**3e**	 **7g** (71%)^c
8	 **6d** (84%, rt, 1 h)	**3f**	 **7h** (85%)^c
9	**6d**	**3i**	 **7i** (80%)^d

[a] Determined by iodolysis. [b] Yield of isolated, analytically pure product. [c] 20 mol % CuCN·2LiCl was used. [d] 4 mol % Pd(OAc)$_2$ and 8 mol % S-Phos were used, and the reactions were performed at 60 °C for 12 h.

2, entries 5−7). Similarly, these two organomagnesium reagents were capable of undergoing either direct reactions with an aldehyde (**3b**) or CuCN·2LiCl-catalyzed allylation with ethyl 2-(bromomethyl)acrylate (**3g**),[22] affording the corresponding products (**4e−g**) in 65−70% yields. Interestingly, it was found that several aryl bromides (**1d−g**) smoothly underwent the magnesium insertion reactions to generate the corresponding Grignard reagents (**2d−g**) in 10 min to 4 h (Table 2, entries 8−11). In a same manner, reactions of the resulting organomagnesium reagents with aromatic aldehydes (with functional groups such as ester and nitrile) proceeded efficiently to produce the benzylic alcohols (**4h−k**) in 75−85% yields. It should be noted that polyaromatic halides are by far the best substrates, and attempts to activate simple aryl chlorides failed.

By simultaneously using Mg (3 equiv), ZnCl$_2$ (1 equiv), LiCl (2 equiv), and 3 mol % C$_{60}$, it was possible to convert functionalized organic bromides such as 1-bromonaphthalen-2-yl pivalate (**5a**) to the corresponding organozinc reagent **6a** in 83% yield at −10 °C within 4 h reaction time (Scheme 1 and Table 3, entry 1). It should be noted that under the same conditions, in the absence of C$_{60}$, only a poor conversion was obtained (<5%). The generated organozinc reagent **6a** efficiently underwent either copper-catalyzed allylation with allylic bromide **3g** or palladium-catalyzed cross-coupling with aryl iodide **3i**, leading to the respective products **7a−b** in 62−80% yields (entries 1−2). The same one-pot protocol was also successfully applied to aromatic bromides (**5b−d**), affording the desired organozinc reagents (**6b−d**) in 75−84% yields. Trapping of these organozinc species with electrophiles, such as an allyl bromide, an acid chloride, or an aryl iodide, led to the desired products (**7c−i**) in 63−88% yields (entries 3−9).

In summary, we have shown that the addition of a catalytic amount of C$_{60}$ fullerene catalyzes the insertion of magnesium turnings to polycyclic aromatic halides (X = Cl or Br), allowing the preparation of the corresponding Grignard reagent in good yields. The use of a cocktail of metallic salts (Mg, ZnCl$_2$, LiCl) in the presence of 3 mol % of C$_{60}$ fullerene (99.9% purity) also allows preparation of some functionalized polyaromatic zinc reagents. Extension to other metal insertions is currently underway in our laboratories.

■ EXPERIMENTAL SECTION

Typical Procedure for the Magnesium Insertion. LiCl (0.17 g, 4 mmol, 2 equiv) was added to a 20 mL Schlenk flask, equipped with a magnetic stirrer and a rubber septum, and dried at 380 °C by heat gun for 5 min under high vacuum. After cooling, the flask was flushed with nitrogen gas, and magnesium turnings (0.144 g, 6 mmol, 3 equiv) and anhydrous dimethoxyethane (DME, 6 mL) were introduced into the flask. The magnesium was sequentially activated by using 1,2-dibromoethane (5 mol %) and TMSCl (5 mol %). Then aryl halide (2 mmol, 1 equiv), internal standard (C$_{10}$H$_{22}$, 0.2 mL), and C$_{60}$ (0.044 g, 0.06 mmol, 3 mol %, 99.9% purity) were added to the flask, and the reaction mixture was stirred at room temperature for the time indicated in Table 2. The reaction progress was monitored by GC analysis of reaction aliquots quenched by sat. NH_4Cl solution until it showed >95% conversion of the starting material. The yield of the insertion reaction was determined by GC analysis of the reaction aliquot quenched with a solution of iodine in anhydrous THF. The supernatant solution was carefully transferred to another predried and nitrogen-flushed Schlenk flask by a syringe and used in subsequent reactions with electrophiles.

Typical Procedure for the Magnesium Insertion in the Presence of $ZnCl_2$. LiCl (0.17 g, 4 mmol, 2 equiv) was added to a 20 mL Schlenk flask, equipped with a magnetic stirrer and a rubber septum, and dried at 380 °C by heat gun for 5 min under high vacuum. After cooling, the flask was flushed with nitrogen gas, and magnesium turnings (0.144 g, 6 mmol, 3 equiv) and anhydrous dimethoxyethane (DME, 6 mL) were introduced into the flask. The magnesium was sequentially activated by using 1,2-dibromoethane (5 mol %) and TMSCl (5 mol %), then aryl halide (2 mmol, 1 equiv), internal standard ($C_{10}H_{22}$, 0.2 mL), C_{60} (0.044 g, 0.06 mmol, 3 mol %), and $ZnCl_2$ (2 mmol, 2 mL, 1 M solution in THF) were sequentially added to the flask, and the reaction mixture was stirred at room temperature or −10 °C for the time indicated in Table 3. The reaction progress was monitored by GC analysis of reaction aliquots quenched by sat. NH_4Cl solution until it showed >95% conversion of the starting material. The yield of the insertion reaction was determined by GC analysis of reaction aliquots quenched with a solution of iodine in anhydrous THF using an internal standard. The supernatant solution was carefully transferred to another predried and nitrogen-flushed Schlenk flask by a syringe and used in subsequent reactions with electrophiles.

■ ASSOCIATED CONTENT

Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b00273.

Experimental details and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: paul.knochel@cup.uni-muenchen.de.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The research leading to these results has received funding from the European Research Council under the European Community's Seventh Framework Programme (FP7/2007−2013) ERC Grant Agreement No. 227763. We thank BASF SE (Ludwigshafen), W. C. Heraeus GmbH (Hanau), and Rockwood Lithium GmbH (Hoechst) for the gift of chemicals.

■ REFERENCES

(1) Trost, B. M. *Science* **1991**, *254*, 1471−1477.

(2) For reviews, see: (a) *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, 2005. (b) *Handbook of Grignard Reagents*; Silverman, G. S., Rakita, P. E., Eds.; Marcel Dekker: New York, 1996. (c) *The Chemistry of Organomagnesium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley-VCH: Weinheim, 2008. (d) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302−4320. (e) Nájera, C.; Sansano, J. M.; Yus, M. *Tetrahedron* **2003**, *59*, 9255−9303. (f) Chinchilla, R.; Najera, C.; Yus, M. *Tetrahedron* **2005**, *61*, 3139−3176. (g) Foubelo, F.; Yus, M. *Chem. Soc. Rev.* **2008**, *37*, 2620−2633. (h) Xi, Z. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1021−1032. (i) Xi, Z. *Acc. Chem. Res.* **2010**, *43*, 1342−1351.

(3) For examples, see: (a) Klabunde, K. J.; Efner, H. F.; Satek, L.; Donley, W. *J. Organomet. Chem.* **1974**, *71*, 309−313. (b) Oppolzer, W.; Schneider, P. *Tetrahedron Lett.* **1984**, *25*, 3305−3308.

(4) Bogdanović, B.; Schwickardi, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4610−4612.

(5) Tilstam, U.; Weinmann, H. *Org. Process Res. Dev.* **2002**, *6*, 906−910.

(6) (a) Jin, M. Y.; Yoshikai, N. *J. Org. Chem.* **2011**, *76*, 1972−1978. (b) Adak, L.; Yoshikai, N. *J. Org. Chem.* **2011**, *76*, 7563−7568.

(7) (a) Rieke, R. D. *Acc. Chem. Res.* **1977**, *10*, 301−306. (b) Rieke, R. D.; Hanson, M. V. *Tetrahedron* **1997**, *53*, 1925−1956. (c) Rieke, R. D. *Science* **1989**, *246*, 1260−1264. (d) Rieke, R. D.; Hudnall, P. M. *J. Am. Chem. Soc.* **1972**, *94*, 7178−7179. (e) Rieke, R. D.; Bales, S. E. *J. Am. Chem. Soc.* **1974**, *96*, 1775−1781.

(8) For representative LiCl-mediated metal insertions into organic halides, see: (a) Piller, F. M.; Metzger, A.; Schade, M. A.; Haag, B. A.; Gavryushin, A.; Knochel, P. *Chem.—Eur. J.* **2009**, *15*, 7192−7202. (b) Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 6802−6806. (c) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6040−6044. (d) Boudet, N.; Sase, S.; Sinha, P.; Liu, C.-Y.; Krasovskiy, A.; Knochel, P. *J. Am. Chem. Soc.* **2007**, *129*, 12358−12359. (e) Chen, Y.-H.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 7648−7651. (f) Chen, Y.-H.; Sun, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 2236−2239.

(9) Blümke, T. D.; Chen, Y.-H.; Peng, Z.; Knochel, P. *Nat. Chem.* **2010**, *2*, 313−318.

(10) (a) Takai, K.; Ikawa, Y. *Org. Lett.* **2002**, *4*, 1727−1729. (b) Peng, Z.; Blümke, T. D.; Mayer, P.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 8516−8519. (c) Blümke, T. D.; Klatt, T.; Koszinowski, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9926−9930. (d) Groll, K.; Blümke, T. D.; Unsinn, A.; Haas, D.; Knochel, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 11157−11161. (e) Blümke, T. D.; Groll, K.; Karaghiosoff, K.; Knochel, P. *Org. Lett.* **2011**, *13*, 6440−6443. (f) Shen, Z.-L.; Peng, Z.; Yang, C.-M.; Helberg, J.; Mayer, P.; Marek, I.; Knochel, P. *Org. Lett.* **2014**, *16*, 956−959.

(11) Peng, Z.; Knochel, P. *Org. Lett.* **2011**, *13*, 3198−3201.

(12) (a) Takai, K.; Ueda, T.; Hayashi, T.; Moriwake, T. *Tetrahedron Lett.* **1996**, *37*, 7049−7052. (b) Takai, K.; Ueda, T.; Ikeda, N.; Ishiyama, T.; Matsushita, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 347−353.

(13) Haag, B. A.; Sämann, C.; Jana, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7290−7294.

(14) For a review regarding the use of electron as catalyst, see: Studer, A.; Curran, D. P. *Nat. Chem.* **2014**, *6*, 765−773.

(15) *Fullerenes: Chemistry and Reactions*; Hirsch, A., Brettreich, M., Eds.; Wiley-VCH: Weinheim, 2005.

(16) For the only two applications of fullerene as reaction catalyst in organic synthesis, see: (a) Li, B.; Xu, Z. *J. Am. Chem. Soc.* **2009**, *131*, 16380−16382. (b) Shi, Y.; Gan, L.; Wei, X.; Jin, S.; Zhang, S.; Meng, F.; Wang, Z.; Yan, C. *Org. Lett.* **2000**, *2*, 667−669.

(17) On the basis of the high reduction potential of magnesium ($E^0 = -2.37$ V), the transfer of an electron from the magnesium surface to the absorbed C_{60} fullerene should readily proceed. For the reduction potential of magnesium and C_{60} fullerene, see: (a) Reed, C. A.; Bolskar, R. D. *Chem. Rev.* **2000**, *100*, 1075−1120. (b) *CRC Handbook of Chemistry and Physics*, 87th ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, 2006.

(18) Both 99.9% and 98% pure C_{60} powders were purchased from Aldrich company (Product Nos. 572500 and 483036). It should be noted that the use of only 1 mol % of C_{60} (99.9%) did not lead to a metal activation; the minimum amount of C_{60} was ∼3 mol%. We suggest that C_{60} facilitates the electron transfer from the magnesium surface to the organic halide. In addition, attempts to extend this activation to zinc dust failed.

(19) For the preparation of ethyl 2-(bromomethyl)acrylate, see: Villieras, J.; Rambaud, M. *Org. Synth.* **1988**, *66*, 220−224.

(20) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340−348.

(21) (a) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871−1876. (b) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685−4696. (c) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461−1473. (d) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338−6361. (e) Surry, S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27−50.

(22) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390−2392.

■ NOTE ADDED AFTER ASAP PUBLICATION

This paper was published ASAP March 13, 2015. Production errors were corrected in two table references and in the Supporting Information, and the corrected version was reposted March 13, 2015.