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Organoaluminum-Mediated Direct Cross-Coupling Reactions**

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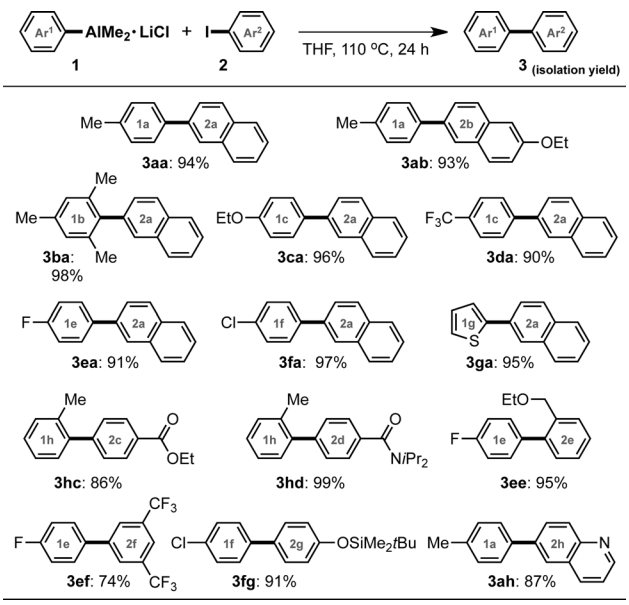
Abstract: *We present a direct cross-coupling reaction between arylaluminum compounds ($ArAlMe_2$·LiCl) and organic halides RX (R = aryl, alkenyl, alkynyl; X = I, Br, and Cl) without any external catalyst. The reaction takes place smoothly, simply upon heating, thereby enabling the efficient and chemo-/stereoselective formation of biaryl, alkene, and alkyne coupling products with broad functional group compatibility.*

Aluminum is the most abundant metal (and the third most abundant element) in the Earth's crust. It also provides the world's largest tonnage organometallic reagent, $AlMe_3$.[1a] Since the discovery of organoaluminum in 1859,[1b] various methods have been developed to create C–Al bonds.[1,2] For example, in 2010, the direct oxidative insertion of aluminium metal into a C–X (X = halogen) bond in the presence of LiCl was reported by Knochel and co-workers.[3] Organoaluminum reagents occupy a central position in synthetic organic and organometallic chemistry because of their low cost, ready availability, low toxicity, and exceptional Lewis acidity.[1–3]

However, the utilization of organoaluminum compounds in modern transition-metal-catalyzed cross-coupling reactions[1a] has been largely neglected in favor of organoboron (Suzuki–Miyaura reaction), organozinc (Negishi reaction), organomagnesium (Kumada–Tamao reaction), and organotin (Stille reaction) reagents,[4] despite the fact that Pd-catalyzed cross-coupling with organoaluminum reagents was first reported by Negishi et al. as early as in 1976.[5] The initial methods for cross-coupling with organoaluminum usually required a co-catalyst such as zinc or indium salts to accelerate the reaction.[2,6] However, in recent years, new coupling procedures that do not require those additives have also been developed: for example, 1) by appropriately tuning the coordination of aluminum (by using heteroleptic ligands,[7] triarylaluminum compounds such as Ar_3Al,[8,9] or a more reactive organoaluminate complex[10]), 2) by using another transition-metal catalyst such as Ni[11] or Fe,[9,12] and 3) notably, by using aryl- or benzylaluminum reagents freshly prepared in situ with proper Pd catalysts and ligands.[13] Now, we have discovered a direct cross-coupling reaction of organoaluminum that does not require any external catalyst. This reaction offers many advantages over transition-metal-catalyzed reactions, including 1) low halogen-metal exchange ability, so that side dehalogenation reactions are minimized, 2) applicability to a wide range of organic halides, including aryl/alkenyl/alkynyl iodide, bromide, and even chloride, and 3) excellent chemoselectivity for carbon–halogen and carbon–pseudohalogen coupling partners with broad functional group compatibility.

Initially, we focused on the reaction between dimethyl-*p*-tolylaluminum (**1a**, easily prepared from *p*-tolyllithium and dimethylaluminum chloride)[14] and 2-iodonaphthalene (**2a**). After extensive studies,[15] we identified the optimum conditions for direct coupling to be heating at 110 °C in THF. We then examined the scope and limitations of the cross-coupling reaction between various aryl aluminum compounds **1** and aryl iodides **2** (Scheme 1). The steric and electronic properties of functional groups on the aromatic rings, such as ester (→**3hc**), amide (< Pr**3hd**), benzyl ether (→**3ee**), trifluoromethyl (→**3ef**), silyl ether (→**3fg**), and heterocycles (→**3ah**), had little influence on the reactivity, and the desired coupling



Scheme 1. Direct cross-coupling between arylaluminum **1** (2.5 equiv) and aryl iodide **2** (1.0 equiv).

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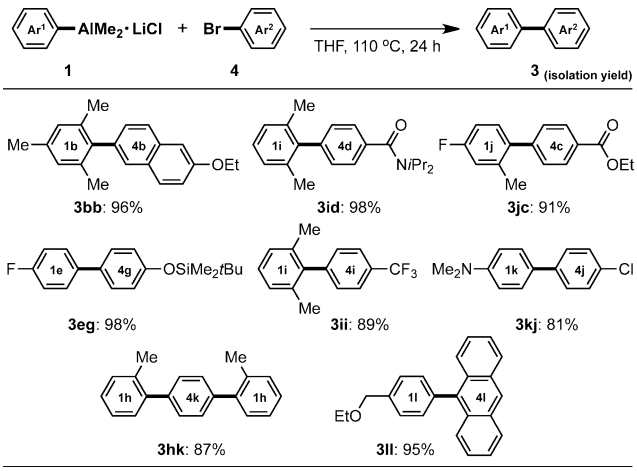
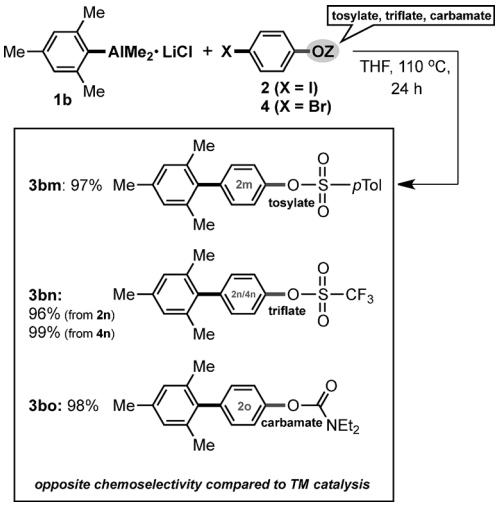
products were obtained in high yields without the formation of detectable amounts of dehalogenated side product.

Next, the reaction with aryl bromides **4** was investigated (Scheme 2). Under the same conditions, aryl bromides carrying various functional groups reacted with aluminum reagents **1** to form biaryl products **3** in high yields. Multiple coupling with dibromo substituents (**4k**) and reaction at sterically congested sites (**4l**) proceeded smoothly to give the desired terphenyl (**3hk**) and 9-phenylanthracene products in high yields. Therefore, this procedure is potentially applicable for the synthesis of functional molecules with extended π-conjugated systems.

To further investigate the chemoselectivity of this cross-coupling reaction, the reactions with aromatic iodides or bromides bearing tosylate, triflate, and carbamate groups were next examined (Scheme 3). It is well known that sulfonate usually shows reactivity similar to, or even higher



Scheme 2. Direct cross-coupling between arylaluminum **1** (2.5 equiv) and aryl bromides **4** (1.0 equiv). For **3eg**, the reaction was maintained for 48 h. For **3hk**, 3.5 equiv of **1h** was used.



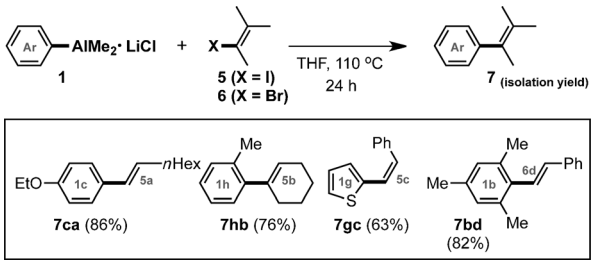
Scheme 3. Direct cross-coupling between arylaluminum **1** (2.5 equiv) and aryl iodide **2** or bromides **4** (1.0 equiv). The reaction exhibits different chemoselectivity from transition-metal-catalyzed reactions.

than, that of halides in transition-metal-catalyzed cross-couplings reactions. Recently, aryl carboxylates (ester, carbamate, etc.) have also been reported to be good coupling partners in the presence of transition-metal catalysts.[16] The functional-group specificity of our coupling was very high, with tosylate, carbamate, and especially the highly reactive triflate not reacting at all. In competitive reactions, cross-coupling at iodide (surprisingly, also at bromide versus OTf) proceeded in excellent yield with more than 99% selectivity. This is in sharp contrast with transition-metal-catalyzed procedures, and opens up new possibilities for the diversified synthesis of multifunctionalized aromatic compounds with high chemoselectivity.

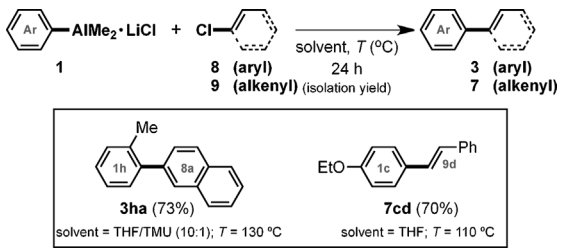
This reaction also proceeded with alkenyl iodides **5** and bromides **6** (Scheme 4). In all cases, the stereochemistry of the starting materials was retained in the products. Therefore, this coupling reaction is expected to be a powerful tool for the region-/stereocontrolled synthesis of multisubstituted olefins. This finding also strongly suggests that no free radical process is involved in the present reaction.

Another highly attractive feature of this reaction is its applicability to organic chlorides. According to previous reports, aryl and vinyl chlorides are much less reactive toward both Grignard[17] and organozinc[18] reagents. However, the reaction of aryl or vinyl chloride (**8** or **9**) with aluminum reagent **1** enabled formation of coupling products **3** or **11**, respectively, albeit in moderate yield (Scheme 5).

Transition-metal-catalyst-free coupling of alkynyl halides with organometallic compounds has not been previously reported. Here, we found that the direct cross-coupling of alkynyl iodides or bromides with aluminum reagent **1** afforded the aryl–alkynyl cross-coupling product in low yield as a mixture with free alkyne and the aryl–aryl homocoupling

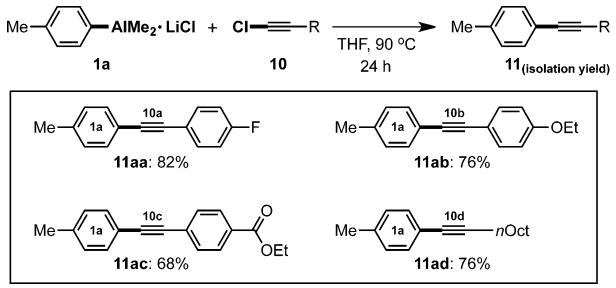


Scheme 4. Direct cross-coupling between arylaluminum **1** (2.5 equiv) and alkenyl iodides **5** or bromides **6** (1.0 equiv). No C=C bond isomers were observed by both GC and NMR spectroscopic analysis of the crude products.



Scheme 5. Direct cross-coupling of arylaluminum **1** (2.5 equiv) with aryl or alkenyl chloride **8** or **9** (1.0 equiv).

products, presumably as a result of halogen–aluminum exchange. However, alkynyl chlorides **10** were found to be good substrates for the present reaction, affording the desired aryl–alkynyl cross-coupled **11** as the sole product in moderate to good yields without exchange-associated side reactions (Scheme 6). These results demonstrate the broad scope, high selectivity, and diverse applicability of this transition-metal-catalyst-free cross-coupling reaction.



Scheme 6. Direct cross-coupling of arylaluminum **1** (2.5 equiv) with alkynyl chloride **10** (1.0 equiv).

To examine whether any transition metals were present, ICP-MS analysis was performed on the solvents, aluminum reagents, and aryl halides. No transition metals were detected at the level of 1 ppb (the detection limit). Although this result may not entirely rule out the participation of transition metals, the present findings indicate the low possibility of the involvement of a transition-metal-mediated process.[19]

In conclusion, we have developed a direct cross-coupling reaction between organoaluminum and aryl halides without any external catalyst. This reaction is efficient, selective, and applicable to a wide range of substrates, including aryl/alkenyl/alkynyl halides. Further studies to further expand the scope of this reaction and its synthetic utility, including its applicability to functional molecules with extended π-conjugated systems is in progress. We are also further investigating the reaction properties/mechanisms with the help of theoretical and spectroscopic methods.[20]

Keywords: C–C bond formation · cross-coupling · organic halides · organoaluminum · selectivity

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[1] a) "Modern organoaluminum reagents: preparation, structure, reactivity and use": *Topics in Organometallic Chemistry*, *Vol. 41* (Eds.: S. Woodward, S. Dagorne), Springer, Berlin, **2013**, pp. 1–322, for the synthesis of organoaluminum compounds, see pp. 173–186, in the chapter on Preparation of organoalanes for organic synthesis, by P. Knochel, T. Blümke, K. Groll, Y.-H. Chen; for cross-coupling reactions of organoaluminum compounds, see pp. 267–276, in chapter on Organoaluminum couplings to carbonyls, imines, and halides, by A. Kolb, P. Zezschwitz; b) W. Hallwachs, A. Schafarik, *Justus Liebigs Ann. Chem.* **1859**, *109*, 206–209.

[2] For reviews on the applications of organoaluminum reagents in organic synthesis, see also a) K. Maruoka, H. Yamamoto, *Tetrahedron* **1988**, *44*, 5001–5032; b) C. Wang, Z. Xi, *Chem. Soc. Rev.* **2007**, *36*, 1395–1406; c) W. Uhl, *Coord. Chem. Rev.* **2008**, *252*, 1540–1563.

[3] T. Blümke, Y.-H. Chen, Z. Peng, P. Knochel, *Nat. Chem.* **2010**, *2*, 313–318. We also reported on the preparation of organoaluminum compounds thorough deprotonative alumination as well as its synthetic application in Pd-catalyzed cross-coupling reactions with organic halides, see Ref. [10].

[4] For selected reviews, see a) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085; *Angew. Chem.* **2012**, *124*, 5150–5174; b) E. Negishi, *Angew. Chem. Int. Ed.* **2011**, *50*, 6738–6764; *Angew. Chem.* **2011**, *123*, 6870–6897; c) A. Suzuki, *Angew. Chem. Int. Ed.* **2011**, *50*, 6722–6737; *Angew. Chem.* **2011**, *123*, 6854–6869; d) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417–1492; e) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**.

[5] a) E. Negishi, S. Baba, *J. Chem. Soc. Chem. Commun.* **1976**, 596b–597b; b) E. Negishi, S. Baba, *J. Am. Chem. Soc.* **1976**, *98*, 6729–6731.

[6] a) E. Negishi, N. Okukado, A. O. King, D. E. van Horn, B. I. Spiegel, *J. Am. Chem. Soc.* **1978**, *100*, 2254–2256; b) M. Qian, Z. Huang, E. Negishi, *Org. Lett.* **2004**, *6*, 1531–1534; c) A. Unsinn, S. H. Wunderlich, A. Jana, K. Karaghiosoff, P. Knochel, *Chem. Eur. J.* **2013**, *19*, 14687–14696; d) T. D. Blümke, K. Groll, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2011**, *13*, 6440–6443; e) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 1501–1504; *Angew. Chem.* **2009**, *121*, 1530–1533.

[7] a) J. Blum, D. Gelman, W. Baidossi, E. Shakh, A. Rosenfeld, Z. Aizenshtat, B. C. Wassermann, M. Frick, B. Heymer, S. Schutte, S. Wernik, H. Schumann, *J. Org. Chem.* **1997**, *62*, 8681–8686; b) H. Schumann, J. Kaufmann, H.-G. Schmalz, A. Böttcher, B. Gotov, *Synlett* **2003**, 1783–1788; c) T. Cooper, A. Novak, L. D. Humphreys, M. D. Walker, S. Woodward, *Adv. Synth. Catal.* **2006**, *348*, 686–690.

[8] S. L. Ku, X. P. Hui, C. A. Chen, Y. Y. Kuo, H. M. Gau, *Chem. Commun.* **2007**, 3847–3849.

[9] a) S. Kawamura, K. Ishizuka, H. Takaya, M. Nakamura, *Chem. Commun.* **2010**, *46*, 6054–6056; b) S. Kawamura, T. Kawabata, K. Ishizuka, M. Nakamura, *Chem. Commun.* **2012**, *48*, 9376–9378.

[10] a) H. Naka, J. V. Morey, J. Haywood, D. J. Eisler, M. McPartlin, F. García, H. Kudo, Y. Kondo, M. Uchiyama, A. E. H. Wheatley, *J. Am. Chem. Soc.* **2008**, *130*, 16193–16200; b) H. Naka, M. Uchiyama, Y. Matsumoto, A. E. H. Wheatley, M. McPartlin, J. V. Morey, Y. Kondo, *J. Am. Chem. Soc.* **2007**, *129*, 1921–1930; c) M. Uchiyama, H. Naka, Y. Matsumoto, T. Ohwada, *J. Am. Chem. Soc.* **2004**, *126*, 10526–10527; for reviews, see d) F. Mongin, A. Harrison-Marchand, *Chem. Rev.* **2013**, *113*, 7563–7727; e) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem. Int. Ed.* **2007**, *46*, 3802–3824; *Angew. Chem.* **2007**, *119*, 3876–3899.

[11] a) E. Negishi, T. Takahashi, S. Baba, D. E. van Horn, N. Okukado, *J. Am. Chem. Soc.* **1987**, *109*, 2393–2401; b) B. H. Lipshutz, G. Bulow, R. F. Lowe, K. L. Stevens, *Tetrahedron* **1996**, *52*, 7265–7276; c) B. H. Lipshutz, P. Mollard, S. S. Pfeiffer, W. Chrisman, *J. Am. Chem. Soc.* **2002**, *124*, 14282–14283; d) D. B. Biradar, H. M. Gau, *Chem. Commun.* **2011**, *47*, 10467–10469.

[12] D. Nečas, P. Drabina, M. Sedlák, M. Kotora, *Tetrahedron Lett.* **2007**, *48*, 4539–4541.

[13] a) B. Wang, M. Bonin, L. Micouin, *Org. Lett.* **2004**, *6*, 3481–3484; b) H. Gao, P. Knochel, *Synlett* **2009**, 1321–1325; c) K. Groll, T. D. Blümke, A. Unsinn, D. Haas, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 11157–11161; *Angew. Chem.* **2012**, *124*, 11319–11323; d) T. Klatt, K. Groll, P. Knochel, *Chem. Commun.*

2013, *49*, 6953 – 6955; e) X. Chen, L. Zhou, Y. Li, T. Xie, S. Zhou, *J. Org. Chem.* **2014**, *79*, 230 – 239.

[14] C. Hawner, D. Müller, L. Gremaud, A. Felouat, S. Woodward, A. Alexakis, *Angew. Chem. Int. Ed.* **2010**, *49*, 7769 – 7772; *Angew. Chem.* **2010**, *122*, 7935 – 7938.

[15] For details on screening of the conditions, see the Supporting Information. Note that lithium salts such as LiCl influence many chemical transformations (see E. Hevia, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2011**, *50*, 6448 – 6450; *Angew. Chem.* **2011**, *123*, 6576 – 6578). We are currently investigating salt effects in the present reaction.

[16] For reviews, see a) J. Cornella, C. Zarate, R. Martin, *Chem. Soc. Rev.* **2014**, *43*, 8081 – 8097; b) S. Z. Tasker, E. A. Standley, T. F. Jamison, *Nature* **2014**, *509*, 299 – 309; c) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A. M. Resmerita, N. K. Garg, V. Percec, *Chem. Rev.* **2011**, *111*, 1346 – 1416; d) B. Li, D. Yu, S. Sun, Z. Shi, *Chem. Eur. J.* **2011**, *17*, 1728 – 1759.

[17] a) E. Shirakawa, Y. Hayashi, K. I. Itoh, R. Watabe, N. Uchiyama, W. Konagaya, S. Masui, T. Hayashi, *Angew. Chem. Int. Ed.* **2012**, *51*, 218 – 221; *Angew. Chem.* **2012**, *124*, 222 – 225; b) N. Uchiyama, E. Shirakawa, T. Hayashi, *Chem. Commun.* **2013**, *49*, 364 – 366; c) S. Murarka, A. Studer, *Angew. Chem. Int. Ed.* **2012**, *51*, 12362 – 12366; *Angew. Chem.* **2012**, *124*, 12528 – 12532; d) E. Shirakawa, R. Watabe, T. Murakami, T. Hayashi, *Chem. Commun.* **2013**, *49*, 5219 – 5221.

[18] a) H. Minami, X. Wang, C. Wang, M. Uchiyama, *Eur. J. Org. Chem.* **2013**, 7891 – 7894; b) E. Shirakawa, F. Tamakuni, E. Kusano, N. Uchiyama, W. Konagaya, R. Watabe, T. Hayashi, *Angew. Chem. Int. Ed.* **2014**, *53*, 521 – 525; *Angew. Chem.* **2014**, *126*, 531 – 535.

[19] ICP-MS was performed to analyze **1a**, **2a**, THF, and Et_2O (solvent for the lithation of the iodide to prepare **1**) as representative reactants and solvents. As a result, the concentrations of Fe, Co, Ni, Cu, Ru, Rh, Pd, Ag, Ir, Pt, and Au were found to be less than 1 ppb (below the detection limit).

[20] For a pioneering DFT calculation on the mechanism of a $S_{RN}1$ substitution between a Grignard reagent and an aryl iodide induced by single-electron transfer (SET), see a) B. E. Haines, O. Wiest, *J. Org. Chem.* **2014**, *79*, 2771 – 2774; for similar mechanistic studies, see Refs. [17, 18]; for recent reviews on SET-induced C–C bond-formation reactions, see b) A. Studer, D. P. Curran, *Nat. Chem.* **2014**, *6*, 765 – 773; c) C.-L. Sun, Z.-J. Shi, *Chem. Rev.* **2014**, *114*, 9219 – 9280; d) N. Zhang, S. R. Samanta, B. M. Rosen, V. Percec, *Chem. Rev.* **2014**, *114*, 5848 – 5958; e) T. L. Chan, Y. Wu, P. Y. Choy, F. Y. Kwong, *Chem. Eur. J.* **2013**, *19*, 15802 – 15814.

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