Organic LETTERS

Letter

pubs.acs.org/OrgLett

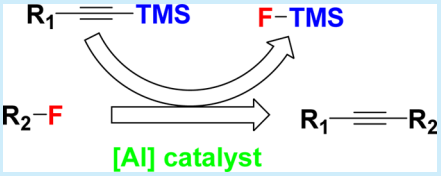
Aluminum-Catalyzed Cross-Coupling of Silylalkynes with Aliphatic C−F Bonds

Amit K. Jaiswal, Kelvin K. K. Goh, Simon Sung, and Rowan D. Young*

Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543

Supporting Information

ABSTRACT: We report the generation of aliphatic and benzylic acetylenes via reaction of primary, secondary, and tertiary aliphatic fluorides with various trimethylsilyl acetylides. These reactions are catalyzed by Al and B Lewis acids, most effectively by the extremely fluorophilic tris(pentafluorophenyl)alane, representing the first example of catalytic incorporation of alkynes into aliphatic C−F positions. The fluorophilicity of the catalysts gives rise to fluorine selectivity over other halogens, allowing orthogonal reactivity pathways.



The challenge of activating C−F bonds, coupled with their ever-increasing abundance in chemical industries, has provided incentive to chemists in pursuing C−F bond functionalization.[1,2] Recently, we reported the catalytic conversion of C−F to higher C−X functional groups (X = Cl, Br, I) utilizing halosilanes and Al catalysts, allowing access to "traditional" transition-metal cross-coupling chemistry.[3] However, the direct coupling of C−F bonds with organometals for C−C bond formation remains an attractive but difficult means to late-stage functionalization. Direct C−C couplings of sp^2 C−F bonds are known with Zn, Mg, and B organometallic reagents catalyzed by transition metals;[4] however, sp^3 aliphatic and benzylic substrates remain challenging.[5]

Given the unique environmental hazard posed by aliphatic fluorocarbons, their catalytic functionalization through C−C coupling reactions for reuse in the chemical industry remains an important chemical goal. Early examples of Lewis acid catalyzed, aliphatic C−F coupling reactions that proceeded via S_E2' pathways were reported for tertiary fluorides with Si allyl or enolate coupling partners (Figure 1a) and recently extended to benzylic fluorides.[6] Friedel−Crafts alkylations between primary alkyl fluorides and arene solvent were first reported with boron halide catalysts by Olah.[7] Since then, this has been extended to secondary and tertiary alkyl fluorides[8] and, more recently, to benzylic fluoride coupling partners (Figure 1b).[6c,9] Ozerov employed an in situ generated Al catalyst to catalyze the methyldefluorination of benzylic fluorides with $AlMe_3$ (Figure 1c),[10] although this reaction has also been reported to proceed in the absence of catalyst.[11]

Indeed, although a limited number of metal-catalyzed C−F bond Grignard couplings are known,[12] direct stoichiometric functionalization of aliphatic C−F bonds has been accomplished most successfully using highly active organometallic Al reagents, with reports of alkyl, allyl, aryl, and alkynyl transfer.[6a,11] Despite this success, organoalane reagents suffer greatly from their extreme reactivity, being pyrophoric and, in some cases, explosive. Additionally, the incorporation of organogroups into aluminum's coordination sphere requires the use of other highly reactive, dangerous, and/or toxic Sn, Mg, Zn, or Li reagents.

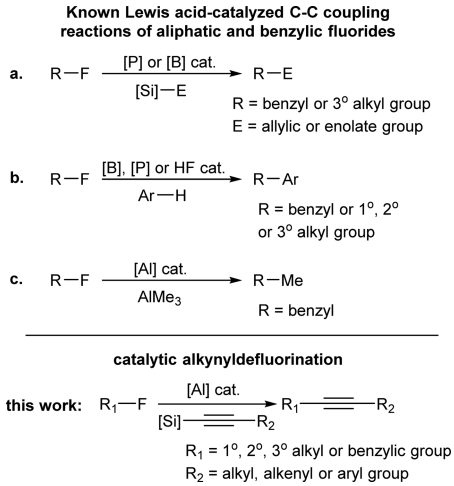


Figure 1. (Top) Previous catalytic systems for C−C coupling of aliphatic fluorides. (Bottom) The installation of acetylenes into C−F bonds using silylalkynes and Al catalysts (this work). [M] = main group complex.

In contrast, organosilanes are stable under atmospheric conditions, commercially available, and/or safe and easy to synthesize. Organosilanes have been employed as leaving groups in allylic and enolic nucleophilic reactions with tertiary fluorides and as co-reagents in the reaction of benzylic and allylic fluorides with a range of nucleophilic organyls.[6] Given our recent success utilizing silicon halides as nucleophilic reagents in the substitution of organofluorides,[3] we envisioned the reaction may be extended to silyl acetylides.

Sonogashira couplings between terminal alkynes and sp^2 fluoroarenes can be catalyzed by indium chloride,[13] and the base-induced attack of allylic fluorides by phenyl acetylide has been reported.[5] However, prior to this study, the direct catalytic coupling of aliphatic C−F bonds with alkyne nucleophiles was

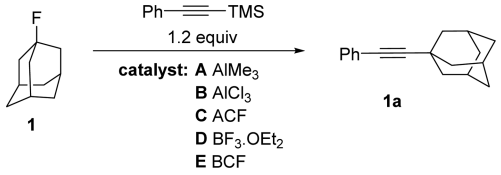
Received: March 20, 2017

DOI: 10.1021/acs.orglett.7b00712
Org. Lett. XXXX, XXX, XXX−XXX

undocumented. Herein, we report the development of a method that utilizes silyl acetylides and Al catalysts in the transfer of acetylides to primary, secondary, and tertiary aliphatic C−F positions.

When 1-TMS-2-phenylacetylene and adamantyl fluoride (**1**) were stirred for 18 h overnight in the presence of 10 mol % $AlMe_3$, methyladamantane (18%) and 1-adamantyl-2-phenylacetylene (**1a**, 78%) were produced as the dominant products (Table 1, entry 1). Concurrently, complete consumption of **1** and formation of TMSF were observed by ^{19}F NMR spectroscopy. Alkylation of aliphatic fluorides by Al alkyls has been reported to be facile, but alkynyldefluorination catalysis continued to proceed after methylation occurred.[6b] Thus, the generation of methyladamantane may be indicative of an induction process that generates an active catalyst. In agreement with this, lower loadings of $AlMe_3$ led to less methyladamantane byproduct and higher observed yields of **1a** (Table 1, entries 1, 2). Similarly, when 10 mol % $AlCl_3$ was utilized as a catalyst, chloroadamantane (16%) was observed as a reaction byproduct (Table 1, entry 3). However, aluminum halides were less effective catalysts compared to $AlMe_3$ due to their lower solubility in organic solvents.

Table 1. Optimization of Reaction between 1 and 1-TMS-2-phenylacetylene[a,b]



entry	catalyst	solvent	conv (%)	yield (%)
1	**A** (10 mol %)	PhCl	>99	78 (67)
2	**A** (3 mol %)	PhCl	91	84
3	**B** (10 mol %)	DCE	79	61
4	**C** (5 mol %)	PhCl	100	98
5	**C (5 mol %)**	**DCE**	**100**	**98 (96)**
6	**D** (10 mol %)	DCE	99	88
7	**E** (5 mol %)	DCE	100	>95
8		DCE	8	6

[a]General conditions: **1** (1.0 M), 18 h at rt. [b]Yields and conversions are based on GC−MS, isolated yields in parentheses.

The use of the highly Lewis acidic $[Al(C_6F_5)_3]$[14] (ACF) was also found to catalyze the reaction effectively (Table 1, entries 4, 5). In this case, very little C_6F_5 transfer was observed (0.5%), with 5 mol % catalyst loading allowing near-quantitative formation of **1a**. Both DCE and PhCl were found to be suitable solvents; however, the higher boiling point of chlorobenzene and small quantities (<5%) of Friedel−Crafts alkylation products rendered DCE the solvent of choice for obtaining analytically pure products. $BF_3{\cdot}OEt_2$ and $[B(C_6F_5)_3]$(BCF) catalysts also proved efficient for the alkynyldefluorination of **1** (Table 1, entries 6, 7); however, ACF proved more effective with challenging fluorides (discussed below) and thus was chosen as the catalyst of choice for the remainder of this study. A control experiment in the absence of Al catalyst resulted in almost no reaction, confirming the active role of Lewis acid in alkynyldefluorination (Table 1, entry 8).

Using optimized conditions, the scope of TMS acetylides for the alkynyldefluorination of adamantyl fluoride was explored (Figure 2). Generally, arylacetylenes gave excellent conversions

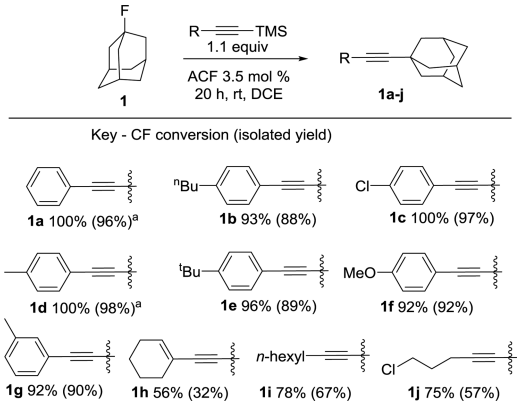


Figure 2. Alkyne reaction scope with **1**. Conditions: **1** (1 M), 1 mL reaction volume, 1.1 equiv alkyne, ACF 3.5 mol %, rt, reaction stopped after 20 h for analysis, conversion determined by ^{19}F NMR and GC−MS. (a) Reaction run with 5 mol % ACF and stopped after 8 h.

and yields (**1a−g**, ≥88%), and alkynyldefluorination products were highly favored over Friedel−Crafts alkylation products. Notably, the yields remained high when the *para* position contained electron-donating methoxy (**1f**, 92%) or electron-withdrawing chloro (**1c**, 97%) substituents. Moderate conversions were observed for alkenyl (**1h**) and alkyl (**1i,j**) acetylenes, although the corresponding moderate yields showed the reaction to be relatively clean. The reaction was also selective for sp^3 C−F activation in the presence of sp^3 C−Cl as demonstrated by the absence of C−Cl cleavage in **1j**.

The use of terminal TMS acetylide in the alkynyldefluorination reaction of **1** resulted in a mixture of three products, adamantylacetylene (**1k**), 1-adamantyl-2-TMS-acetylene (**1l**), and bis-adamantylacetylene as the dominant product. Increasing the relative concentration of TMS-acetylene to 5 times that of **1** greatly reduced the yield of bis-adamantylacetylene (<10%) to give a mixture of **1k** and **1l** (2.2:1, 70% combined yield) (Figure 3). Conveniently, desilylation of **1l** forms **1k** (1.0 M TBAF in THF,[15] 12 h, 89% conversion), representing an effective route of acetylide delivery to organofluorides.

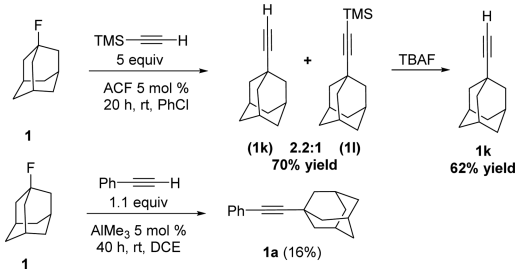


Figure 3. (Top) TMS and H compete as leaving groups to produce **1k** and **1l**. Only **1k** is generated after treatment with TBAF, offering a convenient route to adamantylacetylene. (Bottom) Without TMS present, H performed poorly as a leaving group, suggesting that silicon plays an important role in catalysis turnover.

Attempts to employ terminal acetylenes without TMS groups failed to produce the reactivity observed in the presence of TMS-acetylenes. For instance, the reaction of **1** with phenylacetylene under optimized conditions led to only 40% conversion after 40 h, with a yield of 16% of **1a** (Figure 3) (cf. 84% yield for the synthesis of **1a** using 1-TMS-2-phenylacetylene; see Table 1,

DOI: 10.1021/acs.orglett.7b00712
Org. Lett. XXXX, XXX, XXX−XXX

entry 2). The ability of silicon to sequester fluoride and promote defluorination reactions has been previously noted.[6c]

To pursue a more efficient and selective reaction, we explored the effect of substituents on silicon's ability to act as a leaving group. The electronic effects of incorporating either a phenyl or *tert*-butyl group into silicon's coordination sphere were investigated through the use of bis-silylacetylenes **2a** and **2b** (Figure 4). However, the distribution of products suggested that

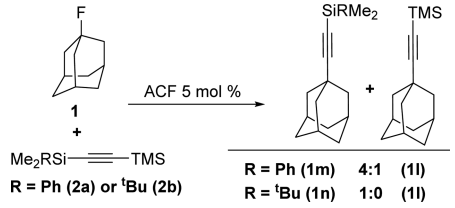


Figure 4. Competitive reactions between different silyl leaving groups determined preference based on sterics. The use of reagent **2b** offers a selective desilylation protocol.

steric factors were decisive in product distribution, with TMS dominating as the leaving group when in competition with either $SiMe_2{}^tBu$ or $SiMe_2Ph$ groups.

Hoping to extend this method to other organofluorides, we attempted alkynyldefluorination of primary and secondary fluoride derivatives (Figure 5).

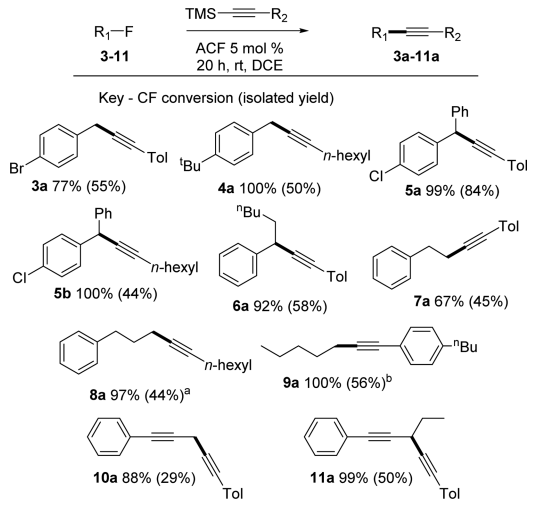


Figure 5. Alkynyldefluorination of primary and secondary aliphatic fluorides. Conditions: **3**–**11** (1 M), 1 mL reaction volume, 2 equiv alkyne, ACF 5 mol %, rt, reaction stopped after 20 h for analysis, conversion determined by ^{19}F NMR and GC–MS. (a) Yield based on GC–MS. (b) Isomerization products accounted for remainder of conversion products and could not be separated from **9a** using flash chromatography; 5 equiv of alkyne used.

The alkynyldefluorination reaction of benzyl fluorides tolerated both electron-donating and -withdrawing substituents in the benzyl fluoride *para* position, allowing incorporation of alkyl (**4a**) and halide (**3a**, **5a**,**b**) functional groups. α-, β- and γ-fluoroalkylbenzenes were also found to be stable toward alkynyldefluorination, albeit in reduced yields (**6a**–**8a**). Although alkynyldefluorination of 1-fluoropentane (**9a**) proceeded to complete conversion under our reaction conditions, only 56% of the desired linear product was observed. Rearrangement products accounted for the remainder of the conversion, suggestive of a pathway invoking a carbocation intermediate, which agrees with previous reports of similar reactions.[3] Substrates containing an alkyne functional group generated moderate yields of diyne product (**10a**, **11a**), signifying that disubstituted alkynes did not interfere with the reaction.

The activity of other halides was tested to examine if the reaction was specific to organofluorides.[16] When 1-bromoadamantane was reacted with 1-TMS-2-phenylacetylene under optimized conditions, negligible quantities (<5%) of **1a** were observed by GC–MS (Figure 6). The preference of fluorine over

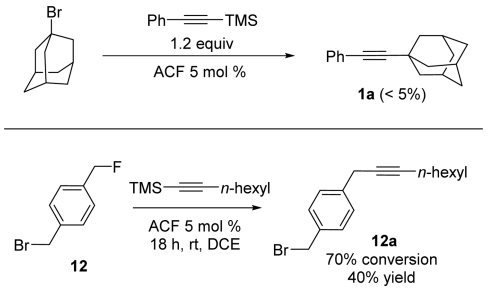


Figure 6. Under optimized reaction conditions, aliphatic bromides were found to be largely unreactive, allowing selective functionalization of aliphatic fluoro positions.

bromine for this reaction stands in contrast to that of transition-metal-catalyzed cross-couplings, offering the opportunity to access divergent reactivity. Indeed, this was demonstrated through the use of 1-(bromomethyl)-4-(fluoromethyl)benzene (**12**). Reaction of 1-*n*-hexyl-2-TMS-acetylene with **12** resulted in 70% conversion after 18 h (Figure 4). The major product of this reaction was found to be **12a** (40% yield), where alkynyldefluorination had occurred. Alkynyldebromination represented less than 1% of the reaction products. Thus, alkynyldefluorination offers a new method to access orthogonal reactivity.

To explore the mechanism for alkynyl transfer, in separate experiments, ACF was mixed solely with stoichiometric quantities of **1** or (TMS)-2-phenylacetylene. No notable reaction was observed in the mixture of ACF/TMS-2-phenylacetylene; however, the reaction between **1** and ACF produced (pentafluorophenyl)adamantane (Ad-C_6F_5), as judged by ^{19}F NMR spectroscopy and later identified by GC–MS. This is in contrast to producing a carbocation/aluminate ion pair (i.e., $[Ad][AlF(C_6F_5)_3]$), which has been reported in a similar fluoride abstraction of fluorotriphenylmethane to generate $[CPh_3][AlF(C_6F_5)_3]$[14b,17] and may be expected to be stable given the high stability of the adamantium cation.[18]

Indeed, ^{19}F NMR spectroscopy revealed the formation of small quantities of Ad-C_6F_5 during catalysis, and Ad-C_6F_5 (ca. 1% yield) was routinely identified in post-reaction GC–MS analyses (see the SI). As described above, transfer products arising from initial constituents on aluminum were even more prominent when using $AlMe_3$ or $AlCl_3$ catalysts. The presence of Ad-X (X = C_6F_5, Me, Cl) byproducts may indicate an initiation process to generate an active aluminum fluoride catalyst. Although undocumented, aluminum fluoride exchange with silyl acetylide would produce silicon fluoride and aluminum acetylide, which is known to be capable of undergoing alkynyldefluorination (Figure 7, cycle B).[11b]

Given the very high conversion of **1** to products in alkynyldefluorination with ACF and the lower production of Ad-C_6F_5 (cf. Ad-Me and Ad-Cl), X transfer could be a competing reaction, and the active catalytic pathway could proceed via Lewis

DOI: 10.1021/acs.orglett.7b00712
Org. Lett. XXXX, XXX, XXX–XXX

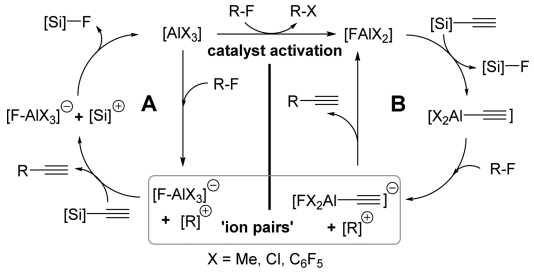


Figure 7. Proposed catalytic cycles for alkynyldefluorination reaction. See text for mechanism discussion.

acid halide abstraction, as proposed by Paquin and Stephan in related Lewis acid catalyzed C−F arylation reactions.[6c,9] Indeed, fluoride abstraction from Ph_3CF to generate $[CPh_3][AlF(C_6F_5)_3]$ is documented.[14b,17] It is plausible that a carbocation generated in this manner may be susceptible to nucleophilic attack by silyl acetylide. The catalytic loop in such a cycle would be closed by silylium recombination with fluoro aluminate to liberate the catalyst and generate silicon fluoride byproduct, whose formation provides thermodynamic drive for catalysis (Figure 7, cycle **A**).[19] It unlikely that in situ generated HF is responsible for catalysis given that alkynyldefluorination only proceeded in high yield in the presence of TMS leaving groups, which are known to sequester HF.[8b]

Thus, we have developed a transition-metal-free method for coupling silylalkynes with aliphatic organofluorides. This method is applicable to primary, secondary, and tertiary fluorides and works for a range of TMS alkynes. In contrast to many previous examples of transition-metal-free C−F functionalization, the use of Si as a leaving group allows regioselectivity control. The preference of the Al catalysts employed for fluoro over other halogen positions enables access to orthogonal synthetic strategies in cooperation with traditional transition-metal couplings, which typically prefer chloro, bromo, and iodo to fluoro positions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00712.

Experimental details and spectra of obtained compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rowan.young@nus.edu.sg.

ORCID

Kelvin K. K. Goh: 0000-0001-6740-2176
Simon Sung: 0000-0002-7864-7694
Rowan D. Young: 0000-0001-7437-8944

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National University of Singapore and the Singapore Ministry of Education for financial support (WBS R-143-000-586-112, R-143-000-666-114).

■ REFERENCES

(1) (a) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432. (b) Theodoridis, G. Advances in Fluorine Science. In *Fluorine and the Environment Agrochemicals, Archaeology, Green Chemistry & Water*; Tressaud, A., Ed.; Elsevier, 2006; Vol. 2, pp 121−175. (c) Sandford, G. *Philos. Trans. R. Soc., A* **2000**, *358*, 455. (d) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (e) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315.

(2) (a) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119. (b) Stahl, T.; Klare, H. F. T.; Oestreich, M. *ACS Catal.* **2013**, *3*, 1578. (c) Ahrens, T.; Kohlmann, J.; Ahrens, M.; Braun, T. *Chem. Rev.* **2015**, *115*, 931. (d) Shen, Q.; Huang, Y.-G.; Liu, C.; Xiao, J.-C.; Chen, Q.-Y.; Guo, Y. *J. Fluorine Chem.* **2015**, *179*, 14.

(3) Goh, K. K. K.; Sinha, A.; Fraser, C.; Young, R. D. *RSC Adv.* **2016**, *6*, 42708.

(4) Examples: (a) Yoshikai, N.; Mashima, H.; Nakamura, E. *J. Am. Chem. Soc.* **2005**, *127*, 17978. (b) Cargill, M. R.; Sandford, G.; Tadeusiak, A. J.; Yufit, D. S.; Howard, J. A. K.; Kilickiran, P.; Nelles, G. *J. Org. Chem.* **2010**, *75*, 5860. (c) Nakamura, Y.; Yoshikai, N.; Ilies, L.; Nakamura, E. *Org. Lett.* **2012**, *14*, 3316. (d) Tobisu, M.; Xu, T.; Shimasaki, T.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 19505. (e) Saijo, H.; Sakaguchi, H.; Ohashi, M.; Ogoshi, S. *Organometallics* **2014**, *33*, 3669.

(5) Shibata reported base-catalyzed C−C couplings for fluoro allylic esters. Such couplings are specific to specialized allylic fluoro substrates and not applicable to more general aliphatic substrates. See: (a) Nishimine, T.; Taira, H.; Tokunaga, E.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2016**, *55*, 359. (b) Okusu, S.; Okazaki, H.; Tokunaga, E.; Soloshonok, V. A.; Shibata, N. *Angew. Chem., Int. Ed.* **2016**, *55*, 6744.

(6) (a) Ooi, T.; Uraguchi, D.; Kagashima, N.; Maruoka, K. *Tetrahedron Lett.* **1997**, *38*, 5679. (b) Hirano, K.; Fujita, K.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **2004**, *45*, 2555. (c) Zhu, J.; Pérez, M.; Stephan, D. W. *Angew. Chem., Int. Ed.* **2016**, *55*, 8448.

(7) Olah, G. A.; Kuhn, S.; Olah, J. A. *J. Chem. Soc.* **1957**, *0*, 2174.

(8) (a) Lühmann, N.; Panisch, R.; Müller, T. *Appl. Organomet. Chem.* **2010**, *24*, 533. (b) Dryzhakov, M.; Moran, J. *ACS Catal.* **2016**, *6*, 3670.

(9) (a) Zhu, J.; Pérez, M.; Stephan, D. W. *Angew. Chem., Int. Ed.* **2016**, *55*, 8448. (b) Champagne, P. A.; Benhassine, Y.; Desroches, J.; Paquin, J.-F. *Angew. Chem., Int. Ed.* **2014**, *53*, 13835.

(10) Gu, W.; Haneline, M. R.; Douvris, C.; Ozerov, O. V. *J. Am. Chem. Soc.* **2009**, *131*, 11203.

(11) (a) Terao, J.; Nakamura, M.; Kambe, N. *Chem. Commun.* **2009**, 6011. (b) Terao, J.; Begum, S. A.; Shinohara, Y.; Tomita, M.; Naitoh, Y.; Kambe, N. *Chem. Commun.* **2007**, 855.

(12) Metal-catalyzed Grignard reactions with alkyl fluorides: (a) Iwasaki, T.; Min, X.; Fukuoka, A.; Kuniyasu, H.; Kambe, N. *Angew. Chem., Int. Ed.* **2016**, *55*, 5550. (b) Mo, Z.; Zhang, Q.; Deng, L. *Organometallics* **2012**, *31*, 6518. (c) Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2003**, *125*, 5646. (d) Terao, J.; Todo, H.; Watanabe, H.; Ikumi, A.; Kambe, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6180. (e) Iwasaki, T.; Takagawa, H.; Singh, S. P.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2013**, *135*, 9604.

(13) Borah, H. N.; Prajapati, D.; Boruah, R. C. *Synlett* **2005**, 2823.

(14) (a) Hair, G. S.; Cowley, A. H.; Jones, R. A.; McBurnett, B. G.; Voigt, A. *J. Am. Chem. Soc.* **1999**, *121*, 4922. (b) Chen, J.; Chen, E. Y.-X. *Angew. Chem., Int. Ed.* **2015**, *54*, 6842.

(15) Gallagher, W. P.; Maleczka, R. E. *J. Org. Chem.* **2003**, *68*, 6775.

(16) Reaction tolerance of aliphatic chloride is evident through the use of DCE solvent and the stability of product **1j**.

(17) (a) Chen, M.-C.; Roberts, J. A. S.; Marks, T. J. *J. Am. Chem. Soc.* **2004**, *126*, 4605. (b) Chen, M.-C.; Roberts, J. A. S.; Seyam, A. M.; Li, L.; Zuccaccia, C.; Stahl, N. G.; Marks, T. J. *Organometallics* **2006**, *25*, 2833.

(18) Schleyer, P. R.; Fort, R. C.; Watts, W. E.; Comisarow, M. B.; Olah, G. A. *J. Am. Chem. Soc.* **1964**, *86*, 4195.

(19) Under the assumption that cycle **A** is responsible for catalysis, Al fluoride byproducts arising from a competitive transfer reaction (i.e., AlX_2F, $AlXF_2$, and AlF_3) may also act as Lewis acid catalysts.

DOI: 10.1021/acs.orglett.7b00712
Org. Lett. XXXX, XXX, XXX−XXX