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Transition-Metal-Free Sonogashira-Type Cross-Coupling of Alkynes with Fluoroarenes

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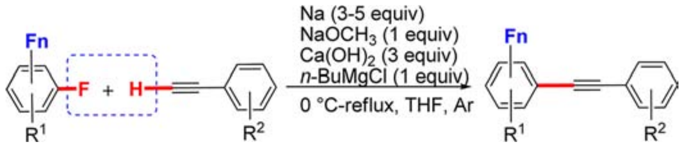
ABSTRACT



A novel, inexpensive, and efficient palladium-, copper-, ligand-, and amine-free Sonogashira-type cross-coupling reaction of terminal alkynes with unreactive aryl fluorides in the presence of sodium, sodium methoxide, and calcium hydroxide under the assistance of a Grignard reagent was developed. A plausible mechanism was also suggested.

The Sonogashira cross-coupling reaction is one of the most applied synthetic tools for the construction of internal acetylenic compounds.[1] Typical procedures for the Sonogashira reaction involve the use of palladium phosphine complexes with CuI as the cocatalyst and large amounts of amines as the solvents or cosolvents.[2] However, the use of expensive palladium phosphine complexes, high Pd loadings, and Pd contamination of the products rendered Pd catalysts unpopular, in particular, for potential large-scale industrial applications.[3] Furthermore, the presence of the copper salt can facilitate the homocoupling reaction of the terminal alkynes and the diyne byproduct is difficult to separate from the target product due to similar chromatographic properties.[4]

Up to now, an impressive variety of modifications of the traditional Sonogashira reaction have been developed such as varying the type of palladium complex, ligand, copper salts, and transition metals and performing the reaction in the absence of palladium, or copper.[5] However, examples of Sonogashira cross-coupling reactions without a transition metal still remain limited.[6] In 2003, Leadbeater reported the first example of a transition-metal-free microwave-assisted Sonogashira-type coupling reaction using water as a solvent, poly(ethylene glycol) as a phase-transfer agent, and sodium hydroxide as a base.[7] In 2011, Daugulis et al. described another practical transition-metal-free alkynylation of aryl

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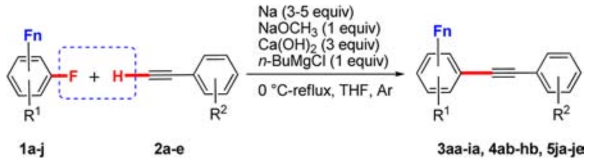
chlorides which involved the use of the hindered TMPLi base in a pentane/THF mixture at rt or a metal alkoxide base in dioxane at elevated temperatures.[8]

Recently, nonactivated aryl chlorides and unreactive alkyl halides have been successfully coupled with terminal alkynes.[9] However, less reactive organofluorine compounds are scarcely used as coupling partners in Sonogashira reactions due to the strong C−F bond.[10] Up to now, only a few reports can be found on the successful coupling of aryl fluorides.[11] For example, Yoakim have demonstrated that the nucleophilic aromatic substitution reaction between 2-fluoronitrobenzene derivatives and terminal alkynes can proceed efficiently using sodium bis(trimethylsilyl)-amide (NaHMDS) as a base in the absence of transition metal catalyst.[12] More recently, Sandford described efficient Pd-catalyzed Sonogashira-type cross-coupling reactions of highly fluorinated nitrobenzene derivatives with terminal acetylenes.[13] However, these two approaches are limited by the narrow choice of aryl fluorides and the strong electron-withdrawing nitro group in fluoroarenes is essential for activation of the C−F bond. Therefore, it is highly desirable to develop an efficient and mild method for the construction of aryl acetylenes from unreactive aryl fluorides.

In continuation of our research on the activation of C−F bonds,[14] here, we report a transition-metal-free method for the Sonogashira coupling reaction of aryl fluorides with terminal acetylenes in the presence of sodium, calcium hydroxide, and sodium methoxide under the assistance of a Grignard reagent (Scheme 1).

At the outset of our investigations, we carried out the Sonogashira cross-coupling reaction of fluorobenzene **1a** with phenylacetylene **2a** under standard Sonogashira conditions ($PdCl_2(PPh_3)_2$/CuI/Et_3N/DMF). Unfortunately, the desired cross-coupling product was not observed, and a considerable amount of the side product from the homocoupling reaction of two acetylenes was obtained.

Scheme 1. Cross-Coupling between Various Aryl Fluorides **1a−j** and Substituted Phenyl Acetylenes **2a−e**



Inspired by recent developments in the transition-metal-free Sonogashira-type coupling reactions, and also driven by the striking success of C−F activation reactions,[15] we tried to realize the Sonogashira reaction involving various aryl fluorides without a transition metal catalyst. Hence, the reactions of fluorobenzene **1a** with phenylacetylene **2a** were extensively investigated in the presence of sodium, base, and a Grignard reagent to obtain the optimum reaction conditions. The detailed results are summarized in Table 1. As indicated in Table 1 (entries 1−8), the amount of sodium plays a crucial role in achieving high conversion of acetylene to cross-coupling product **3aa**. Attempts to decrease the amount of sodium to less than 2.5 equiv resulted in lower yields of the cross-coupling products (entries 1−5) along with a considerable amount of biphenyl **3aa′**, a homocoupling product from fluorobenzene. Fortunately, the homocoupling reaction of phenylacetylene was sufficiently suppressed and no homocoupling product diphenylbutadiyne **3aa″** was formed under the reaction conditions. No reaction was observed if toluene, benzene, DMSO or DMF were employed instead of THF. Therefore, THF was found to be the best solvent for the coupling reaction involving aryl fluorides (entries 8−12).

The reaction was also influenced significantly by the base employed (entries 8, 13−19). In the absence of a base, only a small amount of the desired product **3aa** was formed. However, when $NaOCH_3$ or $Ca(OH)_2$ was used as the sole base for this coupling reaction, the expected products were obtained in low yields. To our delight, the reaction proceeded smoothly using $Ca(OH)_2$ (3 equiv) combined with $NaOCH_3$ (1 equiv) and a relatively higher yield was obtained (entry 8).

It is well-known that deprotonation of a terminal alkyne with organomagnesium generates an alkynylmagnesium halide.[16] Acetylide anions are reactive carbon nucleophiles and useful for the formation of a C−C bond.[17] To examine the influence of a Grignard reagent on the reactivity of a terminal alkyne toward fluorobenzene, a different amount of *n*-butylmagnesium chloride was added to this novel reaction system. The results in Table 1 (entries 8, 20−22) clearly indicated that without a Grignard reagent, a cross-coupling reaction could not proceed. Upon addition of 1.0 equiv of *n*-BuMgCl, the yield of cross-coupling product **3aa** increased dramatically. Furthermore, too little or too

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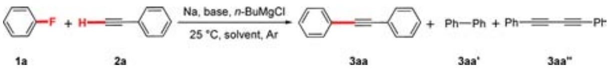
Table 1. Screening for Optimal Reaction Conditions for Cross-Coupling of Fluorobenzene **1a** with Phenylacetylene **2a**[a]



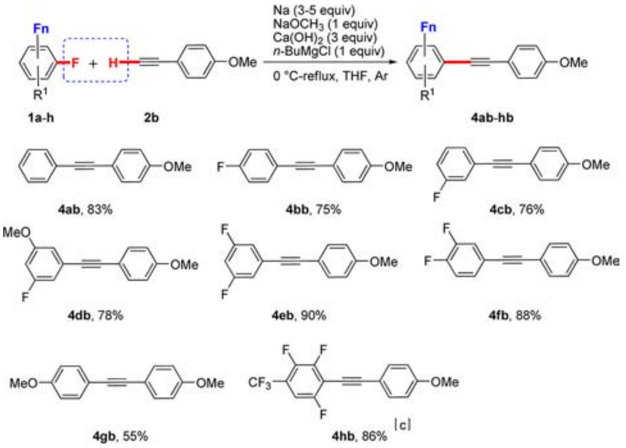
entry	Na (equiv)	base (equiv)	n-BuMgCl (equiv)	solvent	yield (%)[b]
1	0.5	$Ca(OH)_2$ (3), $NaOCH_3$ (1)	1	THF	0
2	1.0	$Ca(OH)_2$ (3), $NaOCH_3$ (1)	1	THF	0
3	1.5	$Ca(OH)_2$ (3), $NaOCH_3$ (1)	1	THF	10
4	2.0	$Ca(OH)_2$ (3), $NaOCH_3$ (1)	1	THF	37
5	2.5	$Ca(OH)_2$ (3), $NaOCH_3$ (1)	1	THF	55
6	3.0	$Ca(OH)_2$ (3), $NaOCH_3$ (1)	1	THF	69
7	4.0	$Ca(OH)_2$ (3), $NaOCH_3$ (1)	1	THF	72
8	5.0	$Ca(OH)_2$ (3), $NaOCH_3$ (1)	1	THF	77
9	5.0	$Ca(OH)_2$ (3), $NaOCH_3$ (1)	1	toluene	0
10	5.0	$Ca(OH)_2$ (3), $NaOCH_3$ (1)	1	benzene	0
11	5.0	$Ca(OH)_2$ (3), $NaOCH_3$ (1)	1	DMSO	0
12	5.0	$Ca(OH)_2$ (3), $NaOCH_3$ (1)	1	DMF	0
13	5.0	none	1	THF	38
14	5.0	Et_3N (3)	1	THF	21
15	5.0	$NaOCH_3$ (2)	1	THF	30
16	5.0	$NaOCH_3$ (3)	1	THF	41
17	5.0	$Ca(OH)_2$ (1)	1	THF	51
18	5.0	$Ca(OH)_2$ (2)	1	THF	57
19	5.0	$Ca(OH)_2$ (3)	1	THF	62
20	5.0	$Ca(OH)_2$ (3), $NaOCH_3$ (1)	0	THF	0
21	5.0	$Ca(OH)_2$ (3), $NaOCH_3$ (1)	0.5	THF	30
22	5.0	$Ca(OH)_2$ (3), $NaOCH_3$ (1)	1.5	THF	41

[a] Reaction conditions: fluorobenzene (5 mmol), phenylacetylene (1 mmol), solvent (8 mL), 25 °C, 5 h. [b] Yields referred to the desired product **3aa**. Yields determined by GC analysis and based on **2a**.

much n-BuMgCl would lead to incomplete conversion of **2a** to **3aa** and a notable amount of byproduct **3aa′** was produced.

Encouraged by these preliminary interesting results, we studied the scope and limitation of this sodium and Grignard reagent-promoted Sonogashira-type cross-coupling reaction. First, the reactions of various aryl fluorides **1a**–**h** with (p-methoxyphenyl)acetylene **2b** under the optimized reaction conditions (Table 1, entry 8) were examined, and the results are summarized in Scheme 2. In most cases, the cross-coupling products were obtained in high yields. The cross-coupling reaction of unactivated fluorobenzene **1a** with **2b** worked well. We were also delighted to find that the less reactive 1,3-difluoro-5-methoxybenzene **1d**, and 1-fluoro-4-methoxybenzene **1g** proceeded smoothly and afforded the desired products in moderate yields (**4db**, **4gb**) (the substrates **1a**–**j** and **2a**–**e**; see Supporting Information).

Scheme 2. Cross-Coupling between Various Aryl Fluorides **1a**–**h** and (p-Methoxyphenyl)acetylene **2b**[a,b]



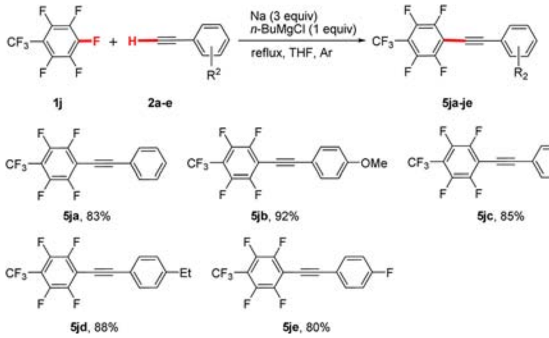
[a] Reaction conditions: aryl fluorides (3–5 mmol), (p-methoxyphenyl) acetylene **2b** (1 mmol), THF (8 mL). [b] Yields of isolated product after chromatographic purification and based on **2b**. [c]Without sodium methoxide and calcium hydroxide.

The functional group tolerance was also demonstrated by the successful reactions of different substituted phenyl acetylenes with octafluorotoluene **1j** (Scheme 3). The results showed that the electronic nature of the substituents on the benzene ring (**2a**–**e**) did not play a significant role in the reaction. Both electron-rich and -poor substituted phenyl acetylenes could afford the corresponding products in good yields (**5jb**, **5je**). It is noteworthy that octafluorotoluene **1j** reacted smoothly with various phenyl acetylenes in the absence of bases ($Ca(OH)_2$ and $NaOCH_3$) due to the exceptional reactivity of octafluorotoluene toward an anion. Furthermore, addition of 1 equiv of octafluorotoluene **1j** in the reaction system is enough to make the reaction proceed smoothly.

Finally, this novel synthetic protocol was further applied to the reactions of unreactive aryl fluorides (**1a**, **1b**, **1d**, and **1e**) with nonactivated phenyl acetylenes (**2a**, **2c**, **2d**) under the optimized reaction conditions (Scheme 4). It was found that these reactions also proceeded smoothly and gave the desired product in an acceptable yield. Similar to octafluorotoluene **1j**, 1-fluoro-2-nitrobenzene **1i** is a more reactive substrate. Only 1 equiv of **1i** could make the coupling reaction proceed smoothly, and no bases were required; however, the yield of cross-coupling product **3ia** was relatively low.

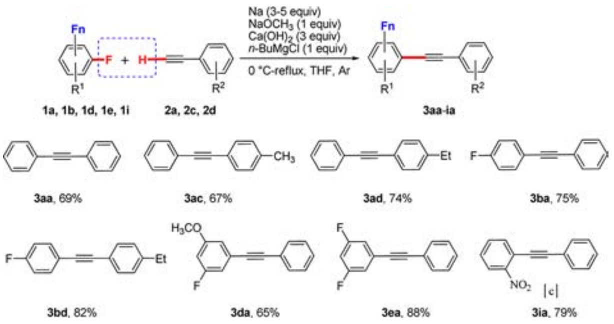
Based on the above observations, it can be concluded that the presence of electron-withdrawing groups such as CF_3, NO_2 on the aryl fluorides or phenyl acetylenes bearing electron-donating groups such as CH_3O significantly promotes the cross-coupling reactions and affords internal alkynes in good to high yields, whereas electron-rich fluoroarenes or electron-poor aryl acetylenes appear to be unfavorable for the reaction; only moderate yields were obtained. Aliphatic terminal alkynes such as 1-pentyne were

Scheme 3. Cross-Coupling between Various Substituted Phenyl Acetylenes **2a**−**e** and Octafluorotoluene **1j**[a,b]



[a] Reaction conditions: octafluorotoluene **1j** (1 mmol), substituted phenyl acetylenes **2a**−**e** (1 mmol), THF (8 mL). [b] Yields of isolated product after chromatographic purification and based on **2a**−**e**.

Scheme 4. Cross-Coupling Reaction of Various Aryl Fluorides with Phenyl Acetylenes[a,b]

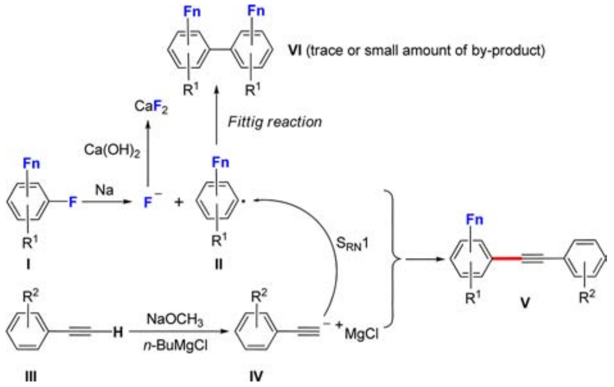


[a] Reaction conditions: Aryl fluorides (3−5 mmol), substituted phenyl acetylenes **2a**, **2c**, **2d** (1 mmol), THF (8 mL). [b] Isolated yields and based on **2a**, **2c**, **2d**. [c] 1-Fluoro-2-nitrobenzene **1i** (1 mmol), without addition of $Ca(OH)_2$ and $NaOCH_3$.

also investigated, however, no obvious product was detected. In addition, if the model reaction was performed under dark conditions, the reaction also proceeded efficiently.

In order to gain insight into this novel reaction, three additional experiments were carried out using the model reaction (reaction of **1a** with **2a**). First, when 1 or 5 equiv of KF were added to the reaction system under the optimized reaction conditions, the yields of coupling product **3aa** decreased to 52% or 35% (GC), respectively. It indicated that the addition of F^- would inhibit the C−F bond cleavage. Second, if the reaction was performed under an air atmosphere, the yield of **3aa** was decreased and the yield of **3aa′** was increased; however, only a trace amount of **3aa″** was detected. Finally, the replacement of fluorobenzene with benzaldehyde underwent the reaction under identical reaction conditions, and acetylenic alcohol (1,3-diphenylprop-2-yn-1-ol) was obtained in moderate yield. The latter two experiments suggested that it might be the acetylide anion, not the alkyne radical, that reacted with the phenyl radical to form the cross-coupling product **3aa**.

Scheme 5. Proposed Mechanism



According to the mechanism of the Wurtz−Fittig reaction and $S_{RN}1$ reaction, we proposed a simplified reaction mechanism of this novel Sonogashira-type cross-coupling protocol (Scheme 5). In the first step, electron transfer from an electron-donor species, sodium, to aryl fluoride **I** results in the formation of free aryl radical **II** and the fluoride anion. The fluoride anion reacts with the calcium ion to form insoluble calcium fluoride which is favorable for the cleavage of the C−F bond. Another key intermediate, alkynylmagnesium chloride **IV**, could be generated by the reaction of aryl acetylene **III** with *n*-butylmagnesium chloride with the assistance of $NaOCH_3$. In the next step, the phenyl acetylide anion attacks aryl radical **II** in an $S_{RN}1$ manner, forming the desired product **V**. Since the aryl radicals are formed, a side reaction such as the Fittig reaction leading to biphenyl derivatives **VI** is also possible; however, only a trace or small amount of **VI** was detected. When 1 equiv of a radical scavenger, galvinoxyl, was added to the reaction system, the reaction could not proceed smoothly. It is indicated that a radical intermediate is involved in this Sonogashira-type coupling reaction.

In conclusion, we have successfully achieved the Sonogashira-type reaction of aryl fluorides and terminal acetylenes in the presence of sodium, calcium hydroxide, and sodium methoxide with the assistance of Grignard reagent under Pd-, Cu-, and ligand-free conditions. The commercially available reagents, exceptional functional group tolerance, and good to high isolated yields make this an interesting alternative for the synthesis of substituted C−C triple bonds.

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Supporting Information Available. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.