



Direct preparation of arylethynylzinc bromides and their application to cross-coupling reactions



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ABSTRACT

A novel synthetic protocol for the preparation of arylethynylzinc bromides has been developed. Thus-obtained organozinc reagents were successfully employed in the subsequent cross-coupling reactions with a broad range of aryl halides providing the corresponding alkynylated compounds in good to excellent yields.

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Alkyne motif is one of the most frequently found functionalities in many naturally occurring organic compounds and, more importantly, some of those compounds have been played a crucial role in biologically active molecules and materials.¹ Reflecting the growing interest in the synthesis of alkynyl-substituted aryl and heteroaryl compounds, more diverse and versatile synthetic tools have attracted increasing attention to synthetic chemist. Of those synthetic methodologies reported to date, transition-metal-catalyzed $C_{sp^2}-C_{sp}$ bond forming protocols have been widely and efficiently utilized for the preparation of aromatics bearing internal alkyne moiety represented in [Scheme 1](#).

Among those, a reliable and robust protocol is the direct introduction of carbon triple bond onto the aromatic ring. For completion of this route, the Sonogashira coupling reaction between an aryl halides and a terminal alkyne has been the most widely used method for the construction of $C_{sp}-C_{sp^2}$ bond.² Recently, transition-metal-catalyzed decarboxylative cross-coupling reactions have also been extensively studied and this strategy was successfully employed in the preparation of alkynylated-aromatic compounds.³ In addition, utilizing organometallic compounds has emerged as an extremely powerful tool for the synthesis of the desired cross-coupling products above. For examples, organosilane,⁴ organoaluminum,⁵ organoborane,⁶ organotin,⁷ and organozinc reagents⁸ have been effectively used. By use of this method, a variety of substituted diarylacetylenes were efficiently synthesized in the presence of a suitable catalyst. More recently, transition-metal-

catalyzed direct C–H functionalization also was reported for the construction of aryl-ynes.⁹

As described above, several metal acetylenyl complexes have been used as key intermediates for the synthesis of alkynyl derivatives. Of these, we were immediately interested in the preparation and application of alkynylzinc complexes which were extensively studied by Negishi group.^{8a–c} In their works including others, acetylenyl-metal complexes were prepared exclusively by transmetalation, treatment of pre-synthesized acetylenide or acetylenyl-metal with zinc salt.

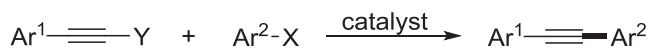
Considering those approaches, we decided to explore a facile route for the synthesis of unsymmetrical diaryl and/or aryl-heteroaryl acetylene derivatives utilizing a versatile zinc route based upon our previous studies of active zinc (Zn^*).¹⁰ The core strategy is to use arylacetylenylzinc bromides (**1a–d**) prepared via direct insertion of active zinc into bromoethynylbenzenes ([Scheme 2](#)).

To challenge this approach, direct preparation of phenylethynylzinc bromide (**1a**) was investigated by treatment of 1.5 equiv of Zn^* with 1.0 equiv of bromoethynylbenzene in THF at room temperature. Completion of Zn^* insertion into carbon-bromine bond was confirmed by G/C analysis of reaction aliquot after acidic quenching, showing a single major peak which was attributed to ethynylbenzene. This protocol worked well for the preparation of more organozinc reagents (**1b–d**) used in this study ([Scheme 2](#)).

Prior to the general application of the resulting organozinc reagent (**1a**) to cross-coupling reactions, the first attempt was executed with 4-iodoanisole to find out a suitable catalyst system. The results are summarized in [Table 1](#). As depicted, two widely used

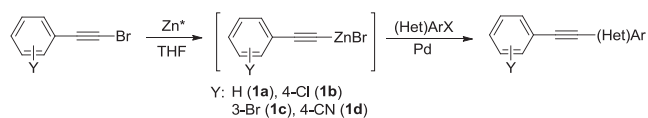
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Y : H (ref. 2), CO₂H (ref. 3), TMS (ref. 4), AIR₂ (ref. 5)
B(OH)₂ (ref. 6), SnBu₃ (ref. 7), ZnCl (ref. 8)

Scheme 1. Representative routes to alkylation of aromatics (previous works).



Scheme 2. Direct preparation and subsequent cross-coupling reaction of arylethynylzinc bromides (**1a** ~ **1d**).

Table 1
Catalyst screening for the coupling of **1a** with 4-iodoanisole.

catalyst	conversion ^a	
	1 h	3 h
2 mol % Pd(PPh ₃) ₂ Cl ₂	54	>99
2 mol % Ni(PPh ₃) ₂ Cl ₂	<1	6
10 mol % Ni(PCy ₃) ₂ Cl ₂	<1	2
5 mol % Ni(dppe)Cl ₂	0	0
2 mol % Pd(OAc) ₂ /10 mol % PPh ₃	30	40

^a Area ratio by G/C.

catalysts, Ni- and Pd-catalysts, were examined, and the use of 2 mol% of Pd(PPh₃)₂Cl₂ alone turned out to be the best tool in terms of conversion ratio to the cross-coupled product. Unfortunately, no or inefficient coupling reaction was observed in the presence of Ni-catalysts (Table 1).

With the above optimized catalyst system, we explored the scope of coupling reaction of **1a** with readily available aryl and heteroaryl halides. The results are summarized in Table 2. Carbon-iodine bond in the aromatics was easily incorporated with **1a** at room temperature in THF resulting in the formation of alkylnated aromatics (**2a–c**, Table 2) in excellent isolated yields. In addition, it has been found that higher isolated yields were obtained from the coupling reactions when 3.0 equiv of **1a** was used compared with 1.5 equiv of **1a**. Even though the excess amounts of **1a** presented in the reaction system, no critical obstacle was observed to complete coupling reaction.¹¹ Thus, the rest of the coupling reactions have been carried out using 3.0 equiv of organozinc reagents. It should be also mentioned that use of freshly prepared organozinc reagent was crucial for the efficient coupling reaction. Carbon-bromine bond also worked well with **1a** to give rise to the coupled product in good yield (entry 4, Table 2). Heteroaromatics bearing carbon-halogen were also employed to the coupling reactions of **1a** providing phenyl/heteroaryl-substituted ethyne derivatives in moderate yields (entries 5–8, Table 2).

Table 2
Coupling of **1a** with aryl and heteroaryl halides.

Entry	(Het)ArX	Time	Product	Yield (%) ^a
1		3 h		98
2		8 h		95
3		8 h		96
4		14 h		84
5		21 h		56
6		21 h		67(33) ^b
7		6 h		70(30) ^b
8		8 h		59(27) ^b

^a Isolated yield (based on (Het)ArX).

^b 1.5 eq of **1a** used.

To expand our strategy, we next investigated the scope of phenylacetylnylzinc reagents. As depicted in Table 3, functionalized organozinc reagents such as 4-chlorophenylacetylnylzinc bromide (**1b**), 3-bromophenylacetylnylzinc bromide (**1c**), and 4-cyanophenylacetylnylzinc bromide (**1d**) were successfully prepared by treatment of Zn* with the corresponding phenylacetylnyl bromide¹² under the same conditions mentioned above. To our satisfaction, Zn* was selectively inserted into C_{sp}-Br bond, remaining the other functional groups (Cl, Br, and CN) intact on the ring.

Thus-obtained new organozinc reagents (**1b–d**, Table 3) were reacted with aryl halides, and the coupling reaction went smoothly in the presence of a catalytic amounts of Pd-catalyst to provide the products (**3a–g**) in good to excellent yields (entries 1–7, Table 3). Of interest, not only phenylacetylene compounds but also bromoethynylthiophene was also an excellent candidate for the preparation of organozinc reagent, thiophene-2-ylethynylzinc bromide (**1e**) which was easily obtained from the same conditions employed in this study. The subsequent couplings of **1e** with aryl halides also took place gently to give the desired coupling products (**3h–j**, Table 3) in the range of 88–92% isolated yields.

To address further challenge, an additional effort has been performed to prepare mono- and di-alkynylated heteroaryl compounds in one-pot reaction utilizing dibromothiophenes or dibromopyridines as a coupling partner.¹³ As described in Table 4, 2,5-dibromopyridine and 2,6-dibromopyridine were reacted with 3.0 equivalent of **1a** in the presence of Pd(PPh₃)₂Cl₂ (2 mol%) catalyst in THF. As observed in previous reactions, the coupling reaction took place nicely at room temperature providing both 2-alkynylated pyridine (**4a**) and 2,5-dialkynylated pyridine (**4aa**) in 62% and 4% isolated yields, respectively. Even though relatively lower total yields were obtained, higher ratio (25% of **4b** and 10% of **4bb**) of di-substituted pyridine derivative was obtained from the reaction with 2,6-dibromopyridine bearing two chemically equivalent carbon-bromine bonds (entry 2, Table 4).

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