Alkynylation of α-halocarbonyl compounds—a Stille-type cross-coupling for the formation of C(sp)–C(sp^3) bonds under neutral conditions†

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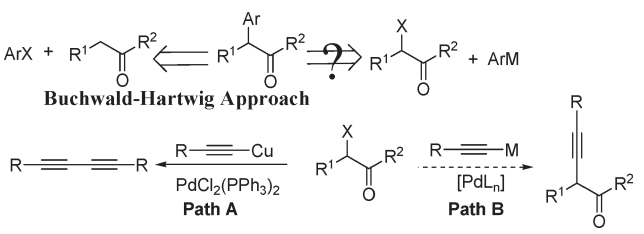
A direct alkynylation of readily available α-halo esters and amides with high yields is described herein; a distinct switch from diyne formation to alkynylation products was attained under neutral conditions.

Palladium-catalyzed arylation of esters, amides, nitriles *etc.* has been a breakthrough in the transition-metal mediated carbon–carbon bond formation, which involves aryl halide electrophiles and enolates (Scheme 1, Buchwald–Hartwig approach).[1–15] Initially, this transformation was carried out in strong base, such as KO^{t}Bu. Hartwig recently has developed mild conditions employing zinc enolates and trialkylsilyl enolates.[16–18] Theoretically, an alternative route for the arylation can come from using α-halo esters or amides, as the electrophile, and aryl metallic reagents (refer to Scheme 1). But, there are few examples in the literature taking this route.[19–21] The use of α-halo esters, as the electrophilic reagents, and aryl boronic acids in the presence of $PdCl_2$(*rac*-BINAP) yielded biaryl homo-coupling products rather than the desired arylation products.[22] Up to now, there are still few reports on attaining alkynylation through this protocol. Williams *et al.* reported the coupling of haloglycinates with alkyne stannanes under Lewis acid conditions.[23–25] In addition, the coupling of alkyne stannanes with activated C(sp^2)–X (Ar–X or vinyl halides) are well documented.[26,27] Attempting to perform the alkynylation of ethyl bromoacetate with an alkyne cuprate, in the presence of $PdCl_2(PPh_3)_2$ as the catalyst, produced a high yield of the diyne product (Scheme 1, path A).[28]

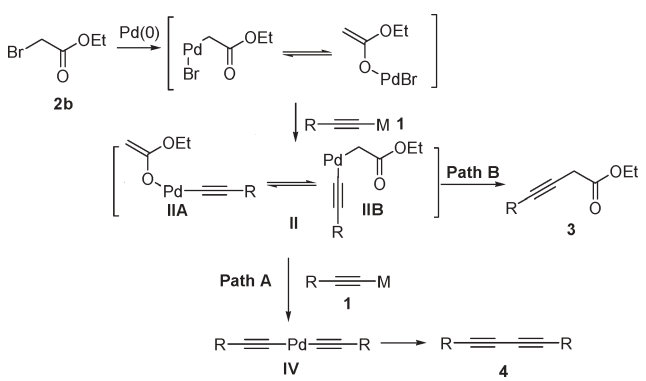
With the rapid development of transition-metal chemistry in the past decade, organometallic reagents (R–M) are becoming more and more abundant. This provides great opportunity for variation in coupling approaches. Considering that α-halo esters or amides are usually readily available, the couplings between R–M's and α-halo esters or amides can be very attractive to synthetic chemists. Potentially, such coupling can be applied widely in organic synthesis if it can be carried out under mild conditions and tolerate a broad range of functional groups. We applied this coupling strategy to C(sp)–C(sp^3) bond formation *via* alkynylation of α-halo esters or amides with alkyne metal (Scheme 1, path B). There are very limited reports regarding such transformations, even though the expected products are especially attractive as building blocks.[26,27,29–31] From a mechanistic perspective, we rationalized the possibility of achieving high selectivity for C(sp)–C(sp^3) cross-coupling through competition between reductive elimination and transmetallation by tuning the reaction conditions. Herein, we communicate a distinct switch from diyne formation *via* homo-coupling (Scheme 1, path A) to high yielding alkynylation of α-halo esters or amides (Scheme 1, path B) under neutral conditions.



Scheme 1

The reaction of alkyne cuprates (formed *in situ* from terminal alkynes and CuI in the presence of amines) and ethyl bromoacetate can be described mechanistically by Scheme 2. Diynes **4** were produced in high yield *via* the second transmetallation of intermediate **II** with alkyne cuprates (Scheme 2, path A).[28] It is the direct reductive elimination of the C-bound palladium enolate intermediate that furnishes the alkynylation product **3** (Scheme 2, path B). To enhance the selectivity for formation of **3**, one needs to either accelerate the reductive elimination of the C-bound palladium enolate **II** or inhibit the second transmetallation of intermediate **II**.

The homo-coupling of phenylethynyltributylstannane (**1a**) using ethyl bromoacetate as the oxidant was reported to be a sluggish process compared with the alkyne cuprate compounds.[28] In other



Scheme 2

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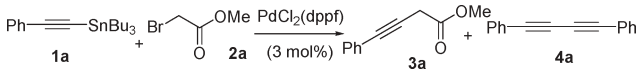
Table 1 Solvent effects in the reaction of **1a** and **2a**[a]



Entry	Solvent	**3a** (%)[b]	**3a** : **4a**[c]
1	MeCN	7.1	18 : 82
2	Toluene	12	53 : 47
3	THF	33	60 : 40
4	Dioxane	Trace	—

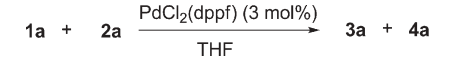
[a] Performed by treatment of **1a** (0.15 mmol) with **2a** (0.15 mmol) in 15 ml solvent. [b] Determined from GC using naphthalene as the internal standard. [c] Molar ratio of **3a** : **4a**.

words, different types of organometallic reagents may affect differently the competition between homo-coupling (Scheme 2, path A) and cross-coupling (Scheme 2, path B). For example, if the transmetallation step between the C(sp)–Sn and Pd–O (Scheme 2, path A) is relatively slow, path B in the Scheme 2 can become dominant, leading to high selectivity for cross-coupling product **3**. With this rationale in mind, the reaction of methyl bromoacetate and **1a** was investigated further to fine tune the conditions for selective alkynylation. First, the reaction solvents were examined with $PdCl_2$(dppf) as the catalyst. The results are listed in Table 1. Among the tested solvents, THF gave the highest selectivity for the cross-coupling product.

According to the mechanism in Scheme 2, two equivalents of **1a** are needed for the formation of intermediate **IV** (Scheme 2, path A) from **2a**, while only one equivalent of **1a** is needed for the cross-coupling (Scheme 2, path B). Thus, lowering the concentration of **1a** might promote selectivity for the cross-coupling product over the homo-coupling product. Indeed, the examination of the concentration effects showed a positive change in the ratio of **3a** : **4a** with decreasing **1a** concentration (refer to Table 2). Higher concentration (0.1 M) of **1a** favored homo-coupling product **4a**, while the diluted reaction mixture yielded higher selectivity for cross-coupling product **3a**. The selectivity for **3a** : **4a** was enhanced further when **1a** was added dropwise into the reaction mixture (Table 2, entry 4). However, this direction of fine tuning is not enough since the yields of all these trials were poor (less than 45% of **3a**).

The next examination was on the effect to reactivity of different types of ligands, and the results are summarized in Table 3. The monophosphines tested were shown to be ineffective ligands for this transformation. Although the sterically hindered electron-rich

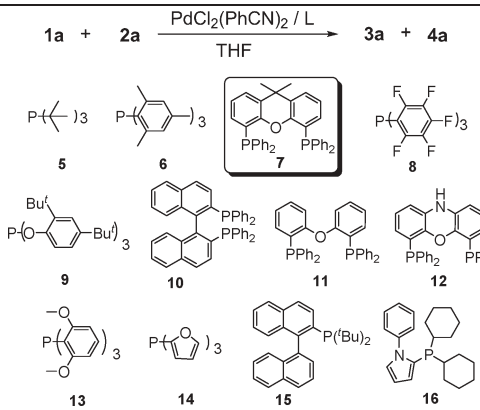
Table 2 Effect of concentration[a]



Entry	[**1a**]	**3a** (%)[b]	**3a** : **4a**[c]
1	0.1	Trace	9 : 91
2	0.04	20	38 : 62
3	0.01	43	65 : 35
4[d]	0.01	30	94 : 6

[a] All reactions were performed at the reflux temperature of THF for 20 h. [b] Determined from GC using naphthalene as the internal standard. [c] The molar ratio of **3a** : **4a**. [d] **1a** was added dropwise over 2 h to the reaction mixture.

Table 3 Scanning of ligands[a]



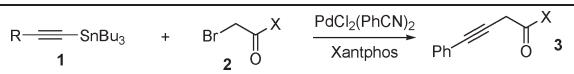
Entry	Ligand[b]	**3a** (%)[c]	**3a** : **4a**
1	**5**	11	58 : 42
2	**6**	9	66 : 34
3	**7**	**60**	**95 : 5**
4	**8**	0	—
5	**9**	3	25 : 75
6	**10**	21	78 : 22
7	**11**	32	84 : 16
8	**12**	34	88 : 12
9	**13**	20	68 : 32
10	**14**	10	79 : 21
11[d]	None	0	—
12[d]	**7**	58	95 : 5
13[e]	None	0	—
14	**15**	12	75 : 25
15	**16**	44	84 : 16

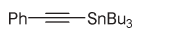
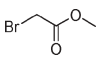
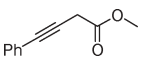
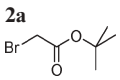
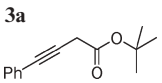
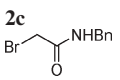
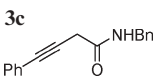
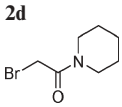
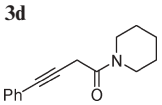
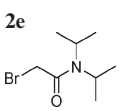
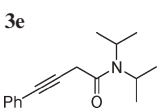
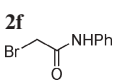
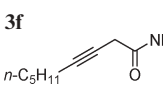
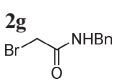
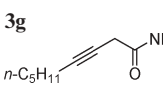
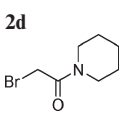
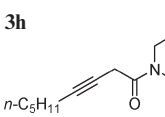
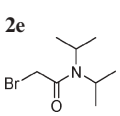
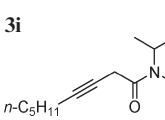
[a] All reactions were carried out in THF (0.02 M) at 66 °C with 3 mol% of Pd catalyst with the exception of entries 11, 12 and 13. [b] The molar ratio of Pd : ligand was 1 : 1 for bidentate ligands and 1 : 2.2 for monodentate ligands. [c] Yields were determined from GC using naphthalene as the internal standard. [d] Using $Pd(dba)_2$ as catalyst precursor. [e] Using $Pd(PPh_3)_4$ as catalyst precursor.

P^tBu_3 was proven to be one of the most efficient ligands for the arylation of amides,[2,10,11,16,18] it only yielded 11% alkynylation product with relatively low selectivity (58 : 42) (Table 3, entry 1) in this reaction. No reaction was observed when $Pd(dba)_2$ or $Pd(PPh_3)_4$ was used. However, the Pd-catalyzed reactions with bidentate ligands showed promising results. The selectivity for the alkynylation product with BINAP, DPEPhos *etc.* reached over 80% (Table 3, entries 3, 7, 8, 12 and 15). Up to 95% selectivity for alkynylation product **3a** in moderate yield (60%) was obtained with xantphos (**7**) (Table 3, entry 3).

These conditions were subsequently investigated with different substrates, and the results are given in Table 4. With xantphos as the bidentate ligand, high isolated yields were achieved when α-bromo amides were employed as the substrates (in less than 12 h). The diynes, *via* competitive homo-coupling, were undetectable or trace in amount so easily removable by flash chromatography. Moreover, we were pleased to find that with xantphos (**7**) as the ligand the reactions were not sensitive to substrate concentration, allowing the use of less solvent to achieve the same result. We hypothesize that this insensitivity to concentration might be due to significant acceleration of the reductive elimination of **IIB** (*via* Path B in Scheme 2) by using the xantphos ligand, to afford the cross-coupling product.

Table 4 Coupling of bromo amides and esters with organotin reagents **1**[a]



Entry	1	2	3	Yield of 3 (%)[b]
1[c]				62
	1a	**2a**	**3a**	
2[d]				46
		2c	**3c**	
3				92
		2d	**3d**	
4[e]				95
		2e	**3e**	
5				83
		2f	**3f**	
6				94
	1b	**2g**	**3g**	
7				95
		2d	**3h**	
8				95
		2e	**3i**	
9				82
		2f	**3j**	

[a] Reactions were carried out with **1** (0.275 mmol) and **2** (0.25 mmol) in 2 ml THF at 66 °C using 2 mol% of Pd catalyst with exception of entries 1, 2 and 4. [b] Isolated yields. [c] 0.5 mmol **1** and 1.0 mmol **2** were used. [d] 0.3 mmol of **1** was used. [e] 0.13 mmol of **2** was used.

In conclusion, we have successfully developed a mild and efficient alkynylation of α-carbonyl compounds *via* the palladium-catalyzed C(sp)–C(sp^3) cross-coupling between alkynyltin reagents and α-halo esters or amides using xantphos as a bidentate ligand. The tuning of the reaction conditions was guided by mechanistic rationale. This coupling method can provide 3-alkynoates and 3-alkynoamides in moderate to high yields under neutral conditions. Broader substrate scope and an asymmetric version of this transformation are currently being investigated in our laboratory and will be reported in due course.

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