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Synthesis of unsymmetrically disubstituted ethynes by the palladium/copper(I)cocatalyzed sila-Sonogashira—Hagihara coupling reactions of alkynylsilanes with aryl iodides, bromides, and chlorides through a direct activation of a carbon—silicon bond

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ABSTRACT

In this paper, we explore the copper/palladium-cocatalyzed cross-coupling reactions of 1-aryl-2trimethylsilylethynes with aryl iodides, bromides, and chlorides as coupling partners, to furnish unsymmetrically disubstituted ethynes in moderate to excellent yields. Various aryl iodides were subjected to reaction under the optimized conditions with 5 mol % of Pd(PPh₃)₂ and 50 mol % of CuCl. The steric properties of the aryl iodide proved more influential to the outcome of the cross-coupling reaction than electronic factors. In addition, we succeeded in synthesizing unsymmetrical diarylethynes using two different aryl iodides in one-pot. Furthermore, under the same reaction conditions with 10 mol% of PdCl₂, 40 mol % of P(4-FC₆H₄)₃, and 50 mol % of CuCl as catalyst, we succeeded in synthesizing unsymmetrical diarylethynes from various aryl bromides. Finally, we explored reactions with aryl chlorides and duly discovered that unsymmetrical diarylethynes were obtainable in moderate to good yields when 10 mol % of Pd(OAc)₂, 10 mol % of (-)-DIOP, and 10 mol % of CuCl were used. These reactions proceed through a direct activation of a carbon-silicon bond in alkynylsilanes by CuCl to generate the corresponding alkynylcopper species via transmetalation from silicon to copper. Mechanistic investigations on the reaction of alkynylsilanes with anyl bromides confirmed that the trimethylsilyl bromide generated in situ retarded both transmetalation steps between CuCl and alkynylsilane, and between palladium(II) species formed by oxidative addition and alkynylcopper species.

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1. Introduction

The unsymmetrical diarylethyne¹ motif is common in pharmaceutical chemistry,² natural products,³ and materials science.^{1e,4} Compounds incorporating this motif can be conveniently synthesized by use of the Sonogashira–Hagihara cross-coupling reaction of terminal alkynes with aryl halides, or pseudo-halides, to construct of C(sp²)–C(sp) bonds.⁵ This reaction employs a palladium complex in conjunction with a copper(I) salt as a catalyst system under *basic* conditions.^{1f,4f,6–8} The Sonogashira–Hagihara reaction has proven to be one of the most practical routes to unsymmetrical diarylethynes, and, following on from the original protocol, various modifications and improvements have been introduced to overcome its identified limitations.⁹ Besides the original palladium/ copper(I) co-catalyst systems, copper-free,¹⁰ palladium-free,¹¹ silver-cocatalyzed,¹² nickel-,¹³ iron-,¹⁴ silver-,¹⁵ rhodium-,¹⁶ and samarium-catalyzed^{11f} protocols have all been developed.

A direct cross-coupling of alkynylsilanes without any activators, if successful, under modified Sonogashira–Hagihara coupling conditions would provide an interesting and straightforward synthetic method, especially as trimethylsilylated alkynes have previously been believed to be inert to the Sonogashira–Hagihara coupling. Accordingly, the trimethylsilyl group is often used as a protective group in the Sonogashira–Hagihara cross-coupling for the introduction of appropriate peripheral functionalities decorating the alkyne. The silyl group can then, if desired, be removed to furnish the target terminal alkyne,¹⁷ which after a second Sonogashira–Hagihara cross-coupling reaction can be converted to an unsymmetrical diarylethyne. It follows that direct coupling of an alkynylsilane via the C–Si bond activation would improve the efficiency of the overall process. This modification might also avoid the decomposition of the highly reactive terminal alkynes,¹⁸ and



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also formation of the alkyne homocoupling Glaser-type products,¹⁹ owing to the gradual generation of the alkynylcopper species when only catalytic amount of a copper salt is required.²⁰

With these considerations in mind, we have developed a palladium-catalyzed 'sila'-Sonogashira-Hagihara coupling of aryl triflates with alkynylsilanes in the presence of a catalytic amount of CuCl in DMF as solvent to vield unsymmetrical diarylethynes in good to high vields.^{21,22} This reaction is the most straightforward and powerful method for the formation of unsymmetrical diarylethynes via direct carbon-silicon bond activation without desilylation, compared to a typical Sonogashira-Hagihara reaction. In this reaction, transmetalation from silicon to copper has been proposed when a copper(I) co-catalyst was used. Following our studies, a copper-free version of this 'sila'-Sonogashira-Hagihara reaction was achieved using a palladium/imidazolium salt system.²³ This process was applied to the copper-free sila-Sonogashira-type cross-coupling of electron-poor aryl and heteroaryl bromides or iodides, with 1-aryl-2-(trimethylsilyl)ethynes, to afford the cross-coupled product in the presence of tetra-*n*-butylammonium chloride under microwave irradiation.²⁴ However, in the aforementioned reactions, the yields of the desired products from electron-rich aryl iodides were rather low and addition of a base to activate the carbon-silicon bond was required.

Although numerous reports describe the coupling of trimethylsilylethyne with aryl halides under *basic* conditions,²⁵ to the best of our knowledge, there are no reports describing the synthesis of unsymmetrical diarylethynes by Pd/Cu-cocatalyzed cross-coupling of alkynylsilanes with aryl halides (iodides, bromides, and chlorides) under *neutral* conditions. In continuation of our studies

2. Results and discussion

2.1. Cross-coupling reaction of alkynylsilanes with aryl iodides

In order to identify an appropriate palladium catalyst for the sila-Sonogashira-Hagihara cross-coupling reaction of 1-phenyl-2trimethylsilylethyne (1a. 0.3 mmol) with the electron-rich 4methoxyphenyl iodide (2a, 0.2 mmol) was used as a model reaction. Stoichiometric quantities of CuCl (150 mol%) were used in combination with 5 mol% of candidate palladium complexes at 80 °C for 12 h in DMF (1 mL), the solvent of choice for homocoupling of alkynylsilanes^{26a} and cross-coupling of alkynylsilanes with aryl triflates.^{21,22} The results obtained are summarized in Table 1. By using Pd(PPh₃)₄, the desired cross-coupled product, (4methoxyphenyl)(phenyl)ethyne (**3a**) was formed in 90% yield, based on 2a. However, the reaction mixture contained 1,4diphenyl-1,3-butadiyne (4; 7% confirmed by GC and NMR, based on 1a), presumably derived from homocoupling of 1a (entry 1). We continued to explore other palladium catalysts for the reaction of 1a with 2a and determined that the catalyst employed had a considerable influence on the yield of **3a** obtained. Although PdCl₂(PPh₃)₂ alone delivered only a 19% yield of **3a**, PdCl₂(PPh₃)₂ combined with PPh3 (P/Pd=2.0; 5 mol %) gave a 71% yield of 3a (entry 2 vs 3). The basis for the high yield obtained with $Pd(PPh_3)_4$ or PdCl₂(PPh₃)₂ with PPh₃ may well be owing to stabilization of the catalyst through coordination of excess PPh₃ ligands. Among the palladium catalysts examined in the coupling of **1a** with **2a**. Pd(OAc)₂ or Pd(dba)₂ in the presence, or absence, of the added PPh₃

Table 1

Cross-coupling of alkynylsilane 1a with aryl iodide 2a using various palladium catalysts^a

			Pd cat (5 mol %)		
	PhSiMe ₃ +	I	CuCl (150 mol %) DMF	PhOMe	
	1a	2a	80 °C, 12 h	3a	
	(0.3 mmol)	(0.2 mmol)		+	
				PhPh	
				4	
Entry	Pa	lladium catalyst		Yield ^b (%)	
				3a	4
1	Pd	(PPh ₃) ₄		90	7
2	Pd	Cl ₂ (PPh ₃) ₂ /2PPh ₃		71	11
3	Pd	$Cl_2(PPh_3)_2$		19	6
4	Pd	Cl ₂ (NCPh) ₂		<1	<1
5	Pd	(OAc) ₂ /2PPh ₃		12	5
6	Pd	(OAc) ₂		<1	<1
7	Pd	(dba) ₂ /2PPh ₃		10	2
8	Pd	(dba) ₂		8	<1
9	Pd	Cl ₂ (dppf) ^c		46	10

^a Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), Pd catalyst (5 mol %), and CuCl (0.3 mmol) in DMF (1 mL) at 80 °C.

^b GC yields. Yields of **3a** and **4** were based on **2a** and **1a**, respectively.

^c dppf=1,1'-bis(diphenylphosphino)ferrocene.

on a direct activation of a carbon—silicon bond in alkynylsilanes by a copper(1) salt,^{21,22,26} we herein describe the Pd-catalyzed 'sila'-Sonogashira-type cross-coupling reaction of alkynylsilanes with aryl halides, which proceeds in the presence of a catalytic or substoichiometric amounts of CuCl under non-basic reaction conditions, leading to various unsymmetrical diarylethynes.²⁷

gave poor results (entries 5–8). $PdCl_2(dppf)$ bearing a bidentate phosphine ligand gave 46% yield of **3a**, albeit with contamination of a relatively large amount of **4** as a by-product. In addition, other transition metal complexes, such as Ni(cod)₂ and RhCl(PPh₃)₃ did not catalyze the reaction. With Pd(PPh₃)₄, increase of the **1a/2a** ratio to 2:1 attained the formation of **3a** up to 96% yield.

Optimization of an amount of CuCl in the cross-coupling of 1a with 2a in the presence of Pd(PPh₃)₄ as a catalyst^a



^a Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), Pd(PPh₃)₄ (5 mol %) in DMF (1 mL) at 80 °C.

^b GC yields. Yields of **3a** and **4** were based on **2a** and **1a**, respectively.

With the optimized 2:1 ratio of 1a/2a for the cross-coupling reactions in hand, we next searched the amount of CuCl in the reactions of 2a with 1a. The results are summarized in Table 2. Although the use of an excess (>100 mol %) of CuCl afforded 3a in over 90% yield, a significant amount of homocoupled product 4 was also obtained (7–14%) (entries 1–3). We found a substoichiometric amount (50 mol %) of CuCl to be optimal (entry 4), while use of a catalytic amount (10 mol %) was found to retard the reaction progress (entry 5).

position with **1a** proceeded to give the corresponding unsymmetrical diarylethynes **3a**–**3g** in good to excellent yields (entries 1–7). However, a sterically hindered 2-substituted aryl iodides **2h**–**2k** partially retarded reaction of **1a** and gave the lower yield of the desired products **3h**–**3k**, respectively (entries 8–11). Reactions of iodides **2l** and **2m** having heteroaromatic (e.g., 2-pyridyl and 2thienyl) substituted alkynes proved successful with the desired cross-coupling products **3l** and **3m** being obtained in 69% and 68% yields, respectively (entries 12 and 13).

Table 3

Sila-Sonogashira–Hagihara cross-coupling reaction of alkynylsilanes 1 with aryl iodides 2^a

			Pa(PPn ₃) ₄ (5 r	nol%)		
			CuCl (50 mc	ol %)		
	R ¹ ────SiMe₂ [·]	+ IR ² -		>	$R^1 \longrightarrow R^2$	
			DMF			
	10 1	20.20	80 °C, 1-6	h	20.34	
	Ta-Ij	2d-211			3a=3v	
Entry	Alkynylsilanes 1 , R ¹ =	Iodides 2 , 1	$R^2 =$	Time (h)	Products	Yield ^b (%)
1	$C_6H_5-(1a)$	4-MeOC ₆ H	4 (2a)	3	3a	84
2	1a	4-MeC ₆ H ₄	(2b)	3	3b	75
3	1a	4-NCC ₆ H ₄	(2c)	1	3c	89
4	1a	4-MeCOC ₆	$H_4(2d)$	1	3d	90
5	1a	4-02NC6H4	4 (2e)	3	3e	92
6	1a	4-ClC ₆ H ₄ (2	2f)	1	3f	92
7	1a	4-EtO ₂ CC ₆	$H_4(2g)$	1	3g	93
8	1a	2-MeOC ₆ H	$_{4}(2h)$	3	3h	49
9	1a	2-MeC ₆ H ₄	(2i)	6	3i	66
10	1a	2-MeCOC ₆	H ₄ (2j)	3	3j	77
11	1a	2,4,6-Me ₃ 0	C ₆ H ₂ (2k)	6	3k	36
12	1a	2-Pyridyl (2I)	3	31	69
13	1a	2-Thienyl ((2m)	3	3m	68
14	$4-MeOC_{6}H_{4}-(1b)$	2b		6	3n	73
15	1b	2c		1	30	78
16	1b	2d		1	3р	89
17	$4-NCC_{6}H_{4}(1c)$	2a		6	30	71
18	$4-MeCOC_6H_4$ (1d)	C ₆ H ₅ (2n)		6	3d	88
19	1d	2a		6	3р	83
20	$4-O_2NC_6H_4$ (1e)	2a		6	3q	59
21	$4-F_3CC_6H_4$ (1f)	2n		3	3r	77
22	2-Pyridyl (1g)	2a		3	3s	47
23	2-Thienyl (1h)	2a		6	3t	75
24	4-t-BuMe ₂ SiOC ₆ H ₄ (1i)	2n		1	3u	48
25	$n-C_{6}H_{13}(1j)$	2n		1	3v	49

^a Conditions: 1 (2.0 mmol); 2 (1.0 mmol); CuCl (50 mol %); Pd(PPh₃)₄ (5 mol %); DMF (5 mL).

^b Isolated yields based on aryl iodides **2**.

The generality of the cross-coupling reactions of a wide range of alkynylsilanes 1a-1j with aryl iodides 2a-2n was studied under our optimized conditions, i.e., 50 mol% of CuCl and 5 mol% of Pd(PPh₃)₄ and the results are summarized in Table 3. The reactions of various aryl iodides 2 bearing the substituents in the *para*-

In addition, reaction of alkynylsilanes **1b–1h**, which features various aromatic and heteroaromatic groups also underwent successful cross-coupling reaction and gave the corresponding unsymmetrical diarylethynes **3n–3t** in up to 89% yield (entries 14–23). The reaction was also applied to the cross-coupling

reaction of alkynylsilane **1i** having a *tert*-butyldimethylsilyl (TBDMS) group as a protecting group. In contrast to the palladiumcatalyzed cross-coupling reactions of alkynylsilanes (Hiyama coupling) in the presence of a fluoride ion activator,²⁸ which gives desilylation, 1i smoothly coupled with 2n to give 3u wherein the TBDMS group remained intact (entry 24). Alkyl-substituted alkynvlsilane **1i** also coupled with **2n** to give **3v** in 49% yield (entry 25).

It is of note that this reaction of arvl iodides 2 considerably surpasses those of the corresponding aryl triflates as we reported previously,²² probably owing to the much more reactive nature of the C–I bond in **2**. For instance, the reactions of **1c** with **2a**, **1d** with 2n, and 1d with 2a furnished cross-coupled products 3o, 3d, and 3p in 71%, 88%, and 83% yields, respectively, whereas the corresponding reactions with aryl triflates delivered much lower yields (27%, 30%, and 19%, respectively). Therefore, the use of aryl iodides **2** is superior to aryl triflates for the synthesis of **3**.

The possibility that the in situ generated alkynylcopper species could react with aryl iodides 2 via a direct oxidative addition mechanism to form a copper(III) complex (a proposed intermediate of Stephens–Castro reaction),²⁹ which, by reductive elimination, expels the cross-coupled products **3** cannot be ruled out as very recently we have observed Cu-catalyzed sila-Sonogashira-Hagihara couplings can occur without any addition of a palladium catalyst.³⁰

The direct transformation of a C-Si bond enables the double arylation of bis(trimethylsilyl)ethyne (5) in place of acetylene. Indeed, reaction of 5 with 2 M equiv of 4-methoxyphenyl (2a) and 4cvanophenyl iodides (2c) furnished the corresponding symmetrical diarylethynes 6a and 6b in 19% and 72% yields, respectively (Eq. 1). This new method for the synthesis of symmetrical diarylethynes could prove highly useful since precise manipulation of gaseous acetylene is experimentally difficult, although acetylene is generally used for the synthesis of symmetrical diarylethynes through a typical Sonogashira-Hagihara reaction.



$$= 4 - \text{NCC}_6 \text{H}_4 (2c) \quad \text{R}^2 = 4 - \text{CIC}_6 \text{H}_4 (2f) \qquad 3 \qquad 93 (3w)$$

Scheme 1. The one-pot sequential sila-Sonogashira-Hagihara couplings of bis(trimethylsilyl)ethyne (5).

CuCl and 10 mol% of Pd(dba)₂ as a palladium precursor, the reaction of alkynylsilane **1a** with aryl bromide **7a** was investigated. The results are summarized in Table 4. Since we have found the best ratio of Pd/ligand to be 1:4 in the case of the cross-coupling reactions of alkynylsilanes 1 with aryl iodides 2 (vide supra), 40 mol % of various ligands were added. When PPh₃ was used, the crosscoupled product **3b** was obtained, alongside small amounts (3%) of the undesired homocoupled product 4 (entry 1). Increasing the amount of PPh₃ added to the reaction resulted only in a lowering of reaction yield (entries 2 and 3). Successful cross-coupling reaction utilizing electron-deficient phosphine ligands such as P(4- $F_3CC_6H_4)_3$ and $P(4-ClC_6H_4)_3$ furnished **3b** in 56% yield (entries 4 and 5). The best yield was achieved with $P(4-FC_6H_4)_3$, although a 40 mol % ligand loading was necessary (entry 6-8). An electronwithdrawing bidentate ligand, (4-FC₆H₄)₂P(CH₂)₄P(4-FC₆H₄)₂, was

		Pd(PPh ₃) ₄ CuCl (10	(10 mol %) 0 mol %)	(1)
Me₃Si─────SiMe₃ 5 (1.0 mmol)	+ 2 R—I – 2 (2.0 mmol)	DMF, 8	30 °C R────R 6	(1)
		Time (h)	Isolated Yield (%)	
R = 4-	MeOC ₆ H ₄ (2a)	18	19 (6a)	
R = 4-	NCC ₆ H ₄ (2c)	6	72 (6b)	

Additionally, the utility of the present sila-Sonogashira-Hagihara cross-coupling reaction via a direct activation of a carbon-silicon bond is demonstrated by a more challenging one-pot synthesis of unsymmetrical diarylethynes 3, starting from 5. The one-pot sila-Sonogashira-Hagihara reactions of 5 with a sequential addition of the first aryl iodide (R^1-I) and the second aryl iodide (R^2-I) allowed us to synthesize unsymmetrical diarylethynes **3** as shown in Scheme 1. Subsequent addition of two different aryl iodides resulted in three-component coupling of **5**, R^1 -I, and R^2 -I to give the corresponding products $(R^1 - C \equiv C - R^2)$ **30** and **3w** in 49% and 93% GC yields, respectively.

2.2. Cross-coupling reaction of alkynylsilanes with aryl bromides

We progressed to employ 4-methylphenyl bromide (7a) as the coupling partner, since aryl bromides are generally less expensive than aryl iodides.³¹ With a substoichiometric amount (50 mol %) of found to be ineffective (entry 9). The reaction did not occur in the absence of either the palladium catalyst or the copper catalyst.

We next examined the effect of a palladium source in the reaction of 1a with 7a to afford the cross-coupled product 3b, as shown in Table 5. As with cross-coupling reaction performed above with various Pd(0) and Pd(II) species the desired product **3b** was contaminated with the homocoupled product 4. Among the catalysts examined, PdCl₂ was found to be the best catalyst affording the cross-coupled product 3b in 70% yield, when 4 M equiv of P(4- FC_6H_4)₃ were used as an ancillary ligand.

The scope and limitations for the reactions of alkynylsilanes 1 with aryl bromides 7 were investigated under the optimized conditions (i.e., 50 mol % of CuCl, 10 mol % of PdCl₂, and 40 mol % of P(4- $FC_6H_4)_3$). The results obtained are summarized in Table 6. Notable here is that the correlation between substitution of the aryl bromide 7 and their reactivity are considerably similar to that observed for the aryl iodides 2, probably owing to the same trend in oxidative addition of Pd(0) to the C-X bond of 2 (X=I) and 7 (X=Br). In

Ligand effect of cross-coupling of alkynylsilane **1a** with aryl bromide **7a**^a



^a Reaction conditions: **1a** (0.3 mmol), **7a** (0.2 mmol), Pd(dba)₂ (10 mol%), and CuCl (0.1 mmol) in DMF (1 mL) at 100 °C.

^b GC yields. Yields of **3b** and **4** were based on **7a** and **1a**, respectively.

^c $(4-FC_6H_4)_2P(CH_2)_4P(4-FC_6H_4)_2$.

general, electron-rich aryl bromides such as 7a and 7b gave the desired products 3a and 3b in lower yields (entries 1 and 2). On the other hand, aryl bromides with an electron-withdrawing substituent in the para-position, for example, 7c-7h were viable coupling partners and gave the products **3c-3g**, and **3r** in excellent yields (entries 3–8). The reaction of **1a** with bulkier aryl bromides 7i-7k gave the corresponding cross-coupled products 3h, 3i, and 3k in 50%, 52%, and 38% yields, respectively (entry 9-11). 2-Pyridyl-(7l) and 2-thienyl (7m) bromides were treated with 1a to afford 3l and 3m, in 46% and 76% yields, respectively (entries 12 and 13). We further studied the reaction of various alkynylsilanes **1b–1d** and 1f-1h with aryl bromides 7 to afford the corresponding crosscoupled products **3** in moderate yields (entries 14–20). However, a combination of electron-deficient alkynylsilanes and electronrich aryl bromides gave a lower yield of the cross-coupled products (entries 16 and 17). Therefore, the appropriate combination of alkynylsilanes 1 and aryl bromides 7 is important for the formation of 3 in high yield. Again, alkynylsilane 1i bearing a silyl protective

Table 5

8

9

Cross-coupling of alkynylsilane 1a with aryl bromide 7a using various palladium catalysts^a



^a Reaction conditions: **1a** (0.3 mmol), **7a** (0.2 mmol), Pd catalyst (10 mol%), and CuCl (0.1 mmol) in DMF (1 mL) at 100 °C.

Na₂PdCl₄

 $[PdCl(\pi-allvl)]_{2}$

^b GC yields. Yields of **3b** and **4** were based on **7a** and **1a**, respectively.

group cleanly coupled with aryl bromide **7n** to afford **3u** without removal of a TBDMS group in 91% yield (entry 21). This cross-coupling reaction was applicable to an alkyl-substituted alky-nylsilane **1j**, which gave **3v** in 53% yield, upon coupling with an aryl

2.3. Cross-coupling reaction of alkynylsilanes with aryl chlorides

51

45

bromide 7n (entry 22).

We finally examined present sila-Sonogashira—Hagihara crosscoupling reaction using an aryl chloride as a coupling partner. Aryl chlorides are less expensive and more easily available, but generally more challenging substrates for coupling reactions compared to the corresponding aryl bromides and iodides. Although they have been believed to be inert due to a difficulty of an insertion of palladium(0) to the C–Cl bond of the aryl chloride, recently, significant progress of the efficient palladium catalyst

4

6

<1

4

4

3 2

< 1

3

3

Sila-Sonogashira–Hagihara cross-coupling reaction of alkynylsilanes **1** with aryl bromides **7**^a

		PdCl ₂ (10 mol %) P(4-FC ₆ H ₄) ₃ (40 mol %)		
	R ¹ ————————————————————————————————————	2 CuCl (50 mol %)	$R^1 R^2$	
	1a-1d, 1f-1j 7a-7	n 100 C, 12 h	3	
Entry	Alkynylsilanes 1 , R ¹ =	Bromides 2 , $R^2 =$	Products	Yield ^b (%)
1	$C_6H_5-(1a)$	$4-MeC_{6}H_{4}(7a)$	3b	70
2	1a	4-MeOC ₆ H ₄ (7b)	3a	54
3	1a	$4-NCC_{6}H_{4}(7c)$	3c	99
4	1a	4-MeCOC ₆ H ₄ (7d)	3d	99
5	1a	$4-O_2NC_6H_4$ (7e)	3e	92
5	1a	$4-ClC_{6}H_{4}(7f)$	3f	84
7	1a	$4-EtO_2CC_6H_4$ (7g)	3g	93
3	1a	$4-F_3CC_6H_4$ (7h)	3r	97
Ð	1a	2-MeOC ₆ H ₄ (7i)	3h	50
10	1a	$2-MeC_{6}H_{4}(7j)$	3i	52
11	1a	2,4,6-Me ₃ C ₆ H ₂ (7k)	3k	38
12	1a	2-Pyridyl (7l)	31	46
13	1a	2-Thienyl (7m)	3m	76
14	$4-MeOC_{6}H_{4}-(1b)$	7c	30	98
15	1b	7d	3р	42
16	$4-NCC_{6}H_{4}(1c)$	7b	30	50
17	$4-MeCOC_6H_4$ (1d)	7b	3р	32
18	$4-CF_{3}C_{6}H_{4}(1f)$	C ₆ H ₅ - (7n)	3r	73
19	2-Pyridyl (1g)	7n	31	44
20	2-Thienyl (1h)	7n	3m	38
21	4-t-BuMe ₂ SiOC ₆ H ₄ (1i)	7n	3u	91
22	$n-C_{6}H_{13}(1\mathbf{j})$	7n	3v	53

^a Conditions: 1 (0.3 mmol); 7 (0.2 mmol); CuCl (50 mol %); PdCl₂ (10 mol %); P(4-FC₆H₄)₃ (40 mol %); DMF (1 mL) at 100 °C.

^b GC yields based on aryl bromides **7**.

systems for Sonogashira–Hagihara couplings of aryl chlorides has been made. $^{\rm 8d,32}$

We have already reported that a catalytic amount of CuCl (10 mol %) and PdCl₂(dppb) (10 mol %) is the most effective catalyst system in the cross-coupling reaction of trimethylsilylethyne 1a with 4-acetylphenyl chloride (8a); this reaction gives rise to the cross-coupled product 4-(phenylethynyl)phenylethanone (3d) in 47% yield.²² Accordingly, we first reexamined the ligand effect as shown in Table 7. As a model reaction, we conducted the crosscoupling reaction of 1a (0.48 mmol) with 8a (0.4 mmol) in the presence of a catalytic amount of CuCl (10 mol %) and 10 mol % of Pd(dba)₂ (dba=dibenzylideneacetone) in DMF at 120 °C for 48 h. The results of our studies are summarized in Table 7. Combination of Pd(dba)₂ with PPh₃ (P/Pd=2.0; 10 mol %) gave only 5% yield of a cross-coupled product, 3d (entry 1). Other electron-deficient and -rich monodentate phosphine ligands did not give the satisfactory results (entries 2-5). In regard to the smooth oxidative addition step, foregoing studies of the palladium-catalyzed cross-couplings of aryl chlorides suggested that electron-rich phosphine ligands may activate the less reactive carbon-chlorine bond. Although PCy₃ and Pt-Bu₃ are known to accelerate various cross-coupling reactions using aryl chlorides, in this case they proved ineffective (entries 6 and 7). In conjunction with these observations, we postulate that a mutual decelerating effect between the nucleophilic phosphine ligands and the added CuCl as a phosphine scavenger in the oxidative addition and transmetalation steps for the catalytic cycle can impede reaction. Systematically, the series of bidentate phosphine ligands $Ph_2P(CH_2)_nPPh_2$ (n=1-5) was examined. The reactions were carried out with the 1:1 molar ratio of Pd(dba)₂ to dppm (n=1, 1,1-bis(diphenylphosphino)methane) resulting in the formation of the cross-coupled product **3d** in only 7% yield (entry 9). The reaction using other diphosphine ligands with increasing numbers of the methylene spacer units revealed that up to a 43% yield of **3d** could be obtained when dppb (n=4, 1,4bis(diphenylphosphino)butane) was used, indicating that an appropriate bite angle is highly important to successful crosscoupling reaction in this case (entries 9–13). We next explored various bidentate phosphine ligands bearing cyclic moieties, including dppf (1,1'-bis(diphenylphosphino)ferrocene) (entries 14–19). Among the ligands examined, (-)-DIOP (2,2-dimethyl-1,3dioxolane-4,5-(diyl)bis(methylene)bis(diphenylphosphine)) was found to be the best, with a 58% yield of **3d** (entry 16). Again, this indicated that a C4-tethered bidentate phosphine ligand could improve the yield of **3d**. As a palladium precursor, Pd(OAc)₂ provided the best yield of the cross-coupled product in 62% yield in combination with (-)-DIOP, which markedly surpasses the yield previously obtained with PdCl₂(dppb). However, other transition metal catalyst systems, for example, Ni(cod)₂/(-)-DIOP and Pt(cod)₂/dppb were completely ineffective. Increasing the $Pd(OAc)_2/(-)$ -DIOP ratio had a significant effect on yield of **3d**; 62% vield (1:1) and 25% (1:2), respectively.

The reactions with other copper salts than CuCl were also explored, although lower yields of **3d** were obtained with CuTC³³ (18%), CuOAc (15%), Cu(OAc)₂ (17%), and CuO*t*-Bu·KCl (20%) under our optimized conditions. In all cases the reaction mixture contained unreacted starting materials, but 1,4-diphenyl-1,3-butadiyne (**4**) derived from homocoupling of **1a** was not detectable by either GC or ¹H NMR spectroscopy.

An important observation was made for a catalyst derived from $Pd(OAc)_2$ and (–)-DIOP: the presence of CuCl has a deleterious effect on the desired cross-coupling reaction.³⁴ More than 10 mol % of CuCl was found to suppress the cross-coupling. Although the use of 10 mol % amounts of CuCl did not disturb the reaction progress and produced **3d** in 62% yield, the use of 30 mol % and 50 mol % of CuCl afforded **3d** in 13% and 8% yields, respectively. Thus 10 mol % of CuCl appears optimal.

Reactions of a variety of aryl chlorides **8** under the optimized conditions were conducted to the cross-coupling with **1**. The results

Ligand effect of cross-coupling of alkynylsilane **1a** with aryl chloride **8a**^a



^a Reaction conditions: **1a** (0.48 mmol), **8a** (0.4 mmol), Pd(dba)₂ (10 mol %), and CuCl (0.04 mmol) in DMF (1 mL) at 120 °C.

^b GC yields. Yield of **3d** was based on **1a**.



are shown in Table 8. Unfortunately, electronically rich aryl chlorides, such as 4-methoxyphenyl chloride (8a) and 4-methylphenyl chloride (8b), completely retarded reaction and gave no desired product (entries 1 and 2). However, reactions of 1a with activated aryl chlorides 8c and 8d at 120 °C did take place and gave the corresponding cross-coupled products 3c and 3d in moderate yields (entries 3 and 4). However, the reactions of 1a with 4nitrophenyl chloride (8e) and 4-trifluoromethylphenyl chloride (8f) gave the lower yields (10% and 34%, respectively) of 3e and 3f (entries 5 and 6). Heteroaromatic chlorides such as the 2-pyridyl and 2-thienyl systems gave contrasting results with crosscoupling products **31** and **3m** being obtained in 66% and <1% yields, respectively (entries 7 and 8). With these results in hand, aryl chlorides 8c, 8d, and 8g were subjected to reaction with various alkynylsilanes 1, since it was evident that only activated aryl chlorides underwent effective reaction. Alkynylsilane 1b bearing an electron-donating methoxy group coupled smoothly with 8c, 8d, and 8g to give the corresponding unsymmetrical diarylethynes 3o, **3p**, and **3s** in 90%, 50%, and 51% yields, respectively. Alkynylsilanes **1f** and **1g** having a CF₃ group in the 3- or 4-position furnished the moderate yields of cross-coupled products 3 (entries 13–16). An advantage of the fluoride-free conditions is evident for the reaction of TBDMS-protected alkynylsilane 1i with 8d when compared to the reaction under typical Hiyama coupling conditions^{28,35} (entry 19). Under the conditions in the presence of CuCl, selective crosscoupling occurred to generate 3dd in 50% yield. Under Hiyama coupling conditions with TBAF as an activator, the reactions gave

rise to the formation of multiple products including disiloxane derived from the starting material. Alkyl-substituted alkynylsilane **1j** smoothly reacted with **8c** afforded the desired product **3ee** in 81% yield (entry 20).

2.4. Reaction mechanism

Concerning the mechanism, we proposed catalytic cycles of the cross-coupling reaction using alkynyltrimethylsilanes 1 and aryl halides 2, 7, and 8, as depicted in Scheme 2. On the basis of our previous studies, in a first step, it seems reasonable to propose transmetalation between CuCl and the alkynylsilanes 1 to generate an alkynylcopper species 9.26e In the case of PdCl₂ (for aryl bromides) and Pd(OAc)₂ (for aryl chlorides), the Pd(II) complexes might be reduced by the formed alkynylcopper species 9 to the unsaturated Pd(0) complexes, generating homocoupled conjugated diyne **4** as a by-product. This process results in the requirement for a slightly excess of alkynylsilanes 1 in the reaction. Oxidative addition of aryl halides to Pd(0) generates the arylpalladium(II) halide 10. Subsequently, alkynylcopper species 9 causes another transmetalation to palladium to produce an intermediate 11, whose reductive elimination can then afford the unsymmetrical diarylethynes $\mathbf{3}$, and regenerate the Pd(0) catalyst. It is noteworthy that the reaction between 9 and 10 generates copper(I) halides, which can serve as the reagent for transmetalation with alkynylsilanes 1 in the other catalytic cycles.

Sila-Sonogashira–Hagihara cross-coupling reaction of alkynylsilanes 1 with aryl chlorides 8a^a

			Pd(OAc) ₂	(10 mol %)					
			(-)- DIOP	(10 mol %)					
	R1SiMe	$P \cap \mathbb{R}^2$		→ 0 11101 /8)	$R^1 \longrightarrow R^2$				
			DI	ИF					
	1	8a-8h	120 °C	, 3-48 h	3				
Entry	Alkynylsilanes 1 , R ¹ =	Chlorides	8 , R ² =	Time (h)	Products	Yield ^b (%)			
1	$C_6H_5-(1a)$	4-MeOC ₆	H ₄ (8a)	48	3a	<1			
2	1a	4-MeC ₆ H	4 (8b)	48	3b	<1			
3	1a	4-NCC ₆ H ₄	4 (8c)	6	3c	51 (47)			
4	1a	$4-MeCOC_6H_4$ (8d)		24	3d	62 (57)			
5	1a	$4 - O_2 NC_6 H_4 (8e)$		3	3e	(10)			
6	1a	4-F ₃ CC ₆ H ₄ (8f)		6	3r	(34)			
7	1a	2-Pyridyl	(8g)	3	31	56 (60)			
8	1a	2-Thienyl	(8h)	3	3m	<1			
9	$4-MeOC_{6}H_{4}-(1b)$	8c		12	30	90 (71)			
10	1b	8d		12	3р	50 (34)			
11	1b	8g		3	3s	51 (45)			
12	$4-MeCOC_6H_4$ (1d)	8g		3	3x	44 (36)			
13	4-CF ₃ C ₆ H ₄ (1f)	8c		24	Зу	75 (54)			
14	$3-CF_3C_6H_4$ (1k)	8c		24	3z	74 (63)			
15	1k	8d		12	3aa	(48)			
16	1k	8g		12	3bb	(65)			
17	2-Pyridyl (1g)	8c		48	3cc	(38)			
18	1g	8d		48	3x	(37)			
19	4-t-BuMe ₂ SiOC ₆ H ₄ (1i)	8d		12	3dd	(50)			
20	<i>n</i> -C ₆ H ₁₃ (1j)	8c		12	3ee	81 (70)			
21	1j	8d		12	3ff	(12)			

^a Conditions: 1 (1.2 mmol); 8 (1.0 mmol); CuCl (10 mol%); Pd(OAc)₂ (10 mol%); (-)-DIOP (10 mol%); DMF (5 mL).

^b GC yields based on aryl iodides **8**. Isolated yields were shown in parentheses.



Scheme 2. Plausible catalytic cycles of sila-Sonogashira–Hagihara cross-coupling reactions of aryl halides (X=I (2), Br (7), and Cl (8)) with alkynylsilanes 1 in Cu(1)/Pd(0) co-catalyst system.

We have already reported that counter ions of a halogenated copper(I) salt dramatically affected the sila-Sonogashira–Hagihara cross-couplings of alkynylsilanes **1**. CuCl seems to play an important role for generation of an alkynylcopper species **9** via cleavage of the carbon–silicon bond owing to the high affinity of silicon and the chloride anion. Thus, CuCl is the most effective among copper(I) salts for transmetalation of alkynylsilanes **1**, while CuBr and CuI are less effective for the transmetalation from silicon to copper, even though they were reportedly effective for coupling reactions using organoboron³⁶ and organotin³⁷ reagents. These chemical properties of CuBr and CuI caused the excessive addition of CuCl as a cocatalyst up to 50 mol% in the case of the cross-couplings using aryl iodides and bromides. On the contrary, if the regenerated copper catalyst is effective for the transmetalation of the alkynyl

group from silicon to copper, an initial addition of 10 mol % of CuCl is enough for completion of the catalytic cycles in the case of reactions with aryl chlorides.

In regard to a different effect of a copper salt, another important factor to be discussed is the formation of SiMe₃X (X=I, Br, Cl), generated by transmetalation between alkynylsilanes **1** and CuCl and/or the regenerated CuI and CuBr during the reaction. In order to gain a mechanistic insight into the effect of SiMe₃X, we investigated the reaction of an alkynylsilane **1a** with an aryl bromide **5a** in the presence or absence of SiMe₃X as shown in Eq. 2. Unambiguously, the reaction without an addition of SiMe₃X gave the cross-coupled product **3b** in 70% yield, but the yields are decreased (X=Cl; 58%, X=Br; 12%) when an equimolar amount of SiMe₃X was added.



Since we additionally confirmed that the oxidative addition step of **7a** to Pd was not affected by the addition of SiMe₃Br, we elucidated transmetalation of **1a** with CuBr in the presence or absence of SiMe₃X (X=Cl and Br). As shown in Eq. 3, we found that transmetalation from silicon to copper was obviously retarded by addition of SiMe₃X (X=Cl and Br) and that the effect of SiMe₃Br is much more remarkable. Based on these comparisons, we postulated the retardation process as follows: CuCl first coordinates to a triple bond in alkynylsilanes 1, followed by the alkynyl group transfer from silicon to copper to generate alkynylcopper species 9. But, SiMe₃Br would interact with alkynylsilanes **1** and inhibit the approach of CuCl to a triple bond of alkynylsilanes, leading to the suppression for the generation of alkynylcopper species 9. In crosscouplings with aryl bromides, 50 mol% of CuCl was essential to proceed the reaction, because the generated CuBr is not so effective for transmetalation of alkynylsilanes 1 and the formed SiMe₃Cl also disturbs the transmetalation.

4. Experimental section

4.1. General

All the reactions were carried out under an Ar atmosphere using standard Schlenk techniques. Glassware was dried in an oven (150 °C) and heated under reduced pressure before use. For thin layer chromatography (TLC) analyses throughout this work, Merck precoated TLC plates (silica gel 60 GF₂₅₄, 0.25 mm) were used. Silica gel column chromatography was carried out using Silica gel 60N (spherical, neutral, 40–100 μ m) from Kanto Chemicals Co., Ltd. Copper(I) chloride, bromide, and iodide were purified by the literature method.³⁸

4.2. Materials

The following alkynylsilanes were prepared by literature procedures: trimethyl(phenylethynyl)silane (**1a**),³⁹ {(4-methoxyphenyl)

	Me ₃ SiX (0.4 mmol)) CuBr (100 mol %)	H⁺			(3)
1a (0.2 mmol)	DMF 60 °C, 12 h		Ph	Π	(0)
		none	•	62%	
		X = 0	CI	33%	
		X = I	Br	3%	

3. Conclusion

In conclusion, we have successfully developed a preparative synthetic method for the generation of unsymmetrical disubstituted ethynes from the cross-coupling reactions of three types of aryl halides with alkynylsilanes in the presence of palladium/CuCl co-catalysts. Because the presented method is carried out using the alkynes masked with the silicon moiety, side reactions leading to symmetrical conjugated divnes by the homocoupling of non-protected terminal alkynes by Glaser coupling, can be avoided more successfully than the case for 'traditional' Pd-Cucatalyzed Sonogashira-Hagihara cross-couplings. This reaction is synthetically useful from a viewpoint of the straightforward carbon-carbon bond formation via a direct activation of carbon--silicon bond using a stable, nontoxic, and functional group tolerant organosilicon compounds. Because these coupling reactions take place under neutral conditions, this catalytic system is compatible with a wide range of sensitive functional groups and should find synthetic application for the construction of not only unsymmetrical diarylethynes, but also other novel molecules bearing a carbon-carbon triple bond.

ethynyl}trimethylsilane (**1b**),³⁹ {(4-cyanophenyl)ethynyl}trimethylsilane (**1c**),⁴⁰ {(4-acetylphenyl)ethynyl}trimethylsilane (**1d**),⁴¹ {(4-nitorophenyl)ethynyl}trimethylsilane (**1e**),⁴¹ trimethyl{(4-trifluoromethylphenyl)ethynyl}silane (**1f**),³⁹ trimethyl(2-pyridylethynyl)silane (**1g**),³⁹ trimethyl(2-thienylethynyl)silane (**1h**),³⁹ [{4-(1,1-dimethylethyl)dimethylsiloxyphenyl}ethynyl]trimethylsilane (**1i**),²² trimethyl(1-oct-1-ynyl)silane (**1j**),⁴¹ and trimethyl{(3-trifluoromethylphenyl)ethynyl}silane (**1k**).⁴²

4.3. General procedure for synthesis of unsymmetrically disubstituted ethynes with aryl iodides. Formation of (4-methoxyphenyl)(phenyl)ethyne (3a)^{29a}

To a solution of CuCl (50 mg, 0.5 mmol, 50 mol%), tetrakis(-triphenylphosphine)palladium (58 mg, 0.05 mmol, 5 mol%), and 4-iodoanisole (**2a**) (234 mg, 1 mmol) in DMF (5 mL) in a 20 mL of Schlenk tube was added trimethyl(phenylethynyl)silane (**1a**) (0.39 mL, 2 mmol). The reaction mixture was stirred for 3 h at 80 °C, quenched with 1.0 M HCl, and extracted with diethyl ether (20 mL×3). The combined ethereal layer was washed with brine

and dried over MgSO₄. Filtration and evaporation afforded a dark yellow oil. Column chromatography (silica gel, hexane/diethyl ether=9:1, R_{f} =0.14) gave the title compound (197 mg, 0.84 mmol, 84% yield) as white solid. ¹H NMR (300 MHz, CDCl₃, rt): δ 3.83 (s, 3H), 6.86–6.90 (m, 2H), 7.32–7.34 (m, 3H), 7.46–7.53 (m, 4H). MS (EI, *m*/*z* (relative intensity)): 208 (M⁺, 100), 193 (50), 165 (41), 139 (10), 104 (6), 88 (5), 75 (2), 63 (4).

The following unsymmetrically disubstituted ethynes **3** are synthesized according to the optimized reaction conditions described above.

4.3.1. (4-Methylphenyl)(phenyl)ethyne (**3b**).⁴³ ¹H NMR (300 MHz, CDCl₃, rt): δ 2.37 (s, 3H), 7.16 (d, *J*=8.4 Hz, 2H), 7.33–7.35 (m, 3H), 7.43 (d, *J*=8.4 Hz, 2H), 7.51–7.54 (m, 2H). MS (EI, *m*/z (relative intensity)): 192 (M⁺, 100), 176 (3), 165 (15), 152 (3), 139 (4), 126 (2), 115 (6), 96 (5), 82 (5), 74 (2), 63 (4).

4.3.2. (4-Cyanophenyl)(phenyl)ethyne (**3c**).⁴⁴ ¹H NMR (300 MHz, CDCl₃, rt): δ 7.39 (m, 3H), 7.53–7.56 (m, 2H), 7.59–7.63 (m, 4H). MS (EI, *m*/*z* (relative intensity)): 203 (M⁺, 100), 176 (8), 164 (2), 151 (5), 124 (2), 101 (7), 88 (7), 75 (6), 63 (3).

4.3.3. 4-(Phenylethynyl)phenylethanone (**3d**).⁴³ ¹H NMR (300 MHz, CDCl₃, rt): δ 2.62 (s, 3H), 7.26–7.38 (m, 3H), 7.53–7.55 (m, 2H), 7.61 (d, *J*=8.7 Hz, 2H), 7.94 (d, *J*=8.4 Hz, 2H). MS (EI, *m/z* (relative intensity)): 220 (M⁺, 70), 205 (100), 176 (54), 165 (2), 151 (20), 126 (5), 103 (7), 88 (17), 75 (8), 63 (3).

4.3.4. (4-Nitrophenyl)(phenyl)ethyne (**3e**).⁴⁴ ¹H NMR (300 MHz, CDCl₃, rt): δ 7.39–7.41 (m, 3H), 7.55–7.57 (m, 2H), 7.66–7.68 (m, 2H), 8.22–8.24 (m, 2H). MS (EI, *m*/*z* (relative intensity)): 223 (M⁺, 100), 207 (3), 193 (45), 176 (73), 165 (37), 151 (32), 126 (4), 88 (8), 75 (13).

4.3.5. (4-*Chlorophenyl*)(*phenyl*)*ethyne* (**3***f*).⁴⁵ ¹H NMR (300 MHz, CDCl₃, rt): δ 7.32–7.36 (m, 5H), 7.45–7.47 (m, 2H), 7.51–7.53 (m, 2H). MS (El, *m*/*z* (relative intensity)): 212 (M⁺, 100), 176 (34), 151 (11), 125 (2), 106 (7), 88 (8), 75 (6), 62 (2).

4.3.6. *Ethyl* 4-(*phenylethynyl*)*benzoate* (**3g**).⁴⁶ ¹H NMR (300 MHz, CDCl₃, rt): δ 1.41 (t, *J*=4.2 Hz, 3H), 4.39 (q, *J*=4.2 Hz, 2H), 7.36–7.37 (m, 3H), 7.54–7.60 (m, 4H), 8.03 (dd, *J*=4.2, 1.2 Hz, 2H). MS (EI, *m*/*z* (relative intensity)): 250 (M⁺, 96), 222 (34), 205 (100), 176 (49), 151 (20), 126 (4), 102 (8), 88 (18), 75 (5), 63 (2).

4.3.7. (2-Methoxyphenyl)(phenyl)ethyne (**3h**).⁴⁷ ¹H NMR (300 MHz, CDCl₃, rt): δ 3.92 (s, 3H), 6.90–6.96 (m, 2H), 7.29–7.36 (m, 4H), 7.49–7.57 (m, 3H). MS (EI, *m*/*z* (relative intensity)): 208 (M⁺, 100), 189 (6), 178 (22), 165 (37), 152 (4), 139 (11), 131 (33), 115 (9), 102 (3), 89 (8), 76 (7), 63 (5).

4.3.8. (2-Methylphenyl)(phenyl)ethyne (**3i**).⁴⁸ ¹H NMR (300 MHz, CDCl₃, rt): δ 2.52 (s, 3H), 7.15–7.26 (m, 3H), 7.33–7.36 (m, 3H), 7.48–7.56 (m, 3H). MS (EI, *m/z* (relative intensity)): 192 (M⁺, 100), 191 (86), 165 (25), 152 (3), 139 (4), 115 (12), 95 (8), 82 (6), 63 (5).

4.3.9. 2-(Phenylethynyl)phenylethanone (**3j**).⁴⁹ ¹H NMR (300 MHz, CDCl₃, rt): δ 2.80 (s, 3H), 7.36–7.38 (m, 3H), 7.42 (d, *J*=7.5 Hz, 1H), 7.48 (t, *J*=7.5 Hz, 1H), 7.54–7.57 (m, 2H), 7.64 (d, *J*=7.8 Hz, 1H), 7.76 (d, *J*=7.8 Hz, 1H). MS (EI, *m/z* (relative intensity)): 220 (M⁺, 77), 205 (100), 189 (5), 176 (51), 151 (19), 126 (4), 103 (4), 88 (17), 75 (6), 63 (3).

4.3.10. (Phenyl)(2,4,6-trimethylphenyl)ethyne (**3k**).⁵⁰ ¹H NMR (300 MHz, CDCl₃, rt): δ 2.30 (s, 3H), 2.48 (s, 6H), 6.90 (s, 2H), 7.33–7.37 (m, 3H), 7.52–7.55 (m, 2H). MS (EI, *m/z* (relative

intensity)): 220 (M⁺, 100), 205 (80), 189 (14), 178 (10), 165 (9), 152 (4), 128 (8), 115 (7), 101 (9), 89 (6), 77 (6), 63 (3).

4.3.11. (Phenyl)(2-pyridyl)ethyne (**3I**).⁴³ ¹H NMR (300 MHz, CDCl₃, rt): δ 7.24 (td, *J*=6.3, 1.2 Hz, 1H), 7.35–7.38 (m, 3H), 7.53 (dd, *J*=8.2, 0.9 Hz, 1H), 7.59–7.61 (m, 2H), 7.68 (td, *J*=7.5, 1.8 Hz, 1H), 8.62 (dd, *J*=5.7 Hz, 1H). MS (EI, *m/z* (relative intensity)): 179 (M⁺, 100), 167 (2), 151 (15), 126 (9), 100 (4), 89 (4), 76 (13), 63 (6).

4.3.12. (*Phenyl*)(2-thienyl)ethyne (**3m**).⁴³ ¹H NMR (300 MHz, CDCl₃, rt): δ 7.00–7.03 (m, 1H), 7.27–7.36 (m, 5H), 7.50–7.54 (m, 2H). MS (EI, *m*/*z* (relative intensity)): 184 (M⁺, 100), 152 (18), 139 (22), 126 (6), 113 (5), 98 (3), 92 (6), 74 (4), 63 (4).

4.3.13. (4-Methoxyphenyl)(4-methylphenyl)ethyne (**3n**).⁵¹ ¹H NMR (300 MHz, CDCl₃, rt): δ 2.36 (s, 3H), 3.83 (s, 3H), 6.87 (d, J=8.4 Hz, 2H), 7.14 (d, J=8.4 Hz, 2H), 7.39–7.47 (m, 4H). MS (EI, *m/z* (relative intensity)): 222 (M⁺, 100), 207 (54), 178 (25), 152 (10), 111 (8), 89 (4), 76 (5), 63 (3).

4.3.14. (4-Cyanophenyl)(4-methoxyphenyl)ethyne (**30**).⁴⁶ ¹H NMR (300 MHz, CDCl₃, rt): δ 3.84 (s, 3H), 6.90 (d, *J*=9.0 Hz, 2H), 7.48 (d, *J*=9.0 Hz, 2H), 7.58–7.61 (m, 4H). MS (EI, *m/z* (relative intensity)): 233 (M⁺, 100), 213 (40), 190 (47), 175 (2), 163 (13), 140 (5), 137 (4), 117 (3), 111 (2), 87 (4), 74 (3), 63 (4).

4.3.15. (4-Acetylphenyl)(4-methoxyphenyl)ethyne (**3p**).²² ¹H NMR (300 MHz, CDCl₃, rt): δ 2.61 (s, 3H), 3.84 (s, 3H), 6.89 (d, *J*=9.0 Hz, 2H), 7.49 (d, *J*=9.0 Hz, 2H), 7.58 (d, *J*=8.7 Hz, 2H), 7.93 (d, *J*=8.7 Hz, 2H). MS (EI, *m*/*z* (relative intensity)): 250 (M⁺, 91), 235 (100), 207 (24), 192 (14), 176 (10), 163 (40), 137 (6), 118 (8), 103 (4), 88 (4), 75 (4).

4.3.16. (4-*Methoxyphenyl*)(4-*nitrophenyl*)*ethyne* (**3q**).⁵² ¹H NMR (300 MHz, CDCl₃, rt): δ 3.85 (s, 3H), 6.91 (d, *J*=8.4 Hz, 2H), 7.50 (d, *J*=8.1 Hz, 2H), 7.63 (d, *J*=8.1 Hz, 2H), 8.21 (d, *J*=8.4 Hz, 2H). MS (EI, *m*/*z* (relative intensity)): 253 (M⁺, 100), 223 (19), 207 (16), 192 (8), 176 (7), 163 (40), 152 (11), 137 (5), 113 (4), 87 (4), 75 (4), 63 (4).

4.3.17. (*Phenyl*)(4-trifluoromethylphenyl)ethyne (**3r**).⁵³ ¹H NMR (300 MHz, CDCl₃, rt): δ 7.36–7.38 (m, 3H), 7.54–7.57 (m, 2H), 7.59–7.66 (m, 4H); ¹⁹F{¹H} NMR (300 MHz, CDCl₃, rt): δ –62.83. MS (EI, *m/z* (relative intensity)): 246 (M⁺, 100), 227 (10), 207 (3), 196 (9), 176 (10), 150 (6), 123 (8), 98 (29), 85 (13), 75 (10), 63 (6).

4.3.18. (4-Methoxyphenyl)(2-pyridyl)ethyne (**3s**).⁴³ ¹H NMR (300 MHz, CDCl₃, rt): δ 3.82 (s, 3H), 6.88 (d, *J*=8.9 Hz, 2H), 7.18–7.22 (m, 1H), 7.47–7.55 (m, 3H), 7.66 (td, *J*=7.5, 1.8 Hz, 1H), 8.60 (dq, *J*=4.8, 0.9 Hz, 1H). MS (EI, *m/z* (relative intensity)): 209 (M⁺, 100), 194 (41), 166 (20), 140 (26), 113 (8), 105 (3), 87 (5), 75 (4), 63 (6).

4.3.19. (4-*Methoxyphenyl*)(2-*thienyl*)*ethyne* (**3t**).⁵⁴ ¹H NMR (300 MHz, CDCl₃, rt): δ 3.83 (s, 3H), 6.86–6.89 (m, 2H), 7.00–7.01 (m, 1H), 7.24–7.27 (m, 2H), 7.44–7.47 (m, 2H). MS (EI, *m/z* (relative intensity)): 214 (M⁺, 100), 199 (68), 171 (23), 145 (5), 127 (21), 107 (6), 87 (5), 74 (3), 63 (4).

4.3.20. {4-(1,1-Dimethylethyl)dimethylsiloxyphenyl}(phenyl)ethyne (**3u**).^{55 1}H NMR (300 MHz, CDCl₃, rt): δ 0.21 (s, 6H), 0.98 (s, 9H), 6.81 (dt, *J*=6.6, 2.1 Hz, 2H), 7.30–7.35 (m, 3H), 7.41 (dt, *J*=8.7, 2.1 Hz, 2H), 7.49–7.52 (m, 2H). MS (EI, *m/z* (relative intensity)): 308 (M⁺, 55), 251 (100), 235 (10), 221 (3), 208 (2), 191 (4), 165 (6), 151 (4), 126 (9), 111 (1), 89 (1), 73 (8).

4.3.21. 1-Oct-1-ynylbenzene (3ν).⁴³ ¹H NMR (300 MHz, CDCl₃, rt): δ 0.91 (t, *J*=6.9 Hz, 3H), 1.29–1.34 (m, 4H), 1.42–1.48 (m, 2H), 1.60 (quin, *J*=8.1 Hz, 2H), 2.40 (t, *J*=7.2 Hz, 2H), 7.26–7.28 (m, 3H),

7.37–7.41 (m, 2H). MS (El, *m*/*z* (relative intensity)): 186 (M⁺, 25), 157 (14), 143 (51), 129 (57), 115 (100), 102 (19), 91 (28), 77 (8), 63 (10).

4.4. General procedure for synthesis of symmetrically disubstituted ethynes by the reaction of bis(trimethylsilyl)-ethyne with 2 equiv of aryl iodides. Di(4-cyanophenyl)ethyne (6b)⁵⁶

To a solution of Pd(PPh₃)₄ (116 mg, 0.1 mmol), CuCl (99 mg, 1 mmol), and 4-iodobenzonitrile (**2c**) (458 mg, 2 mmol) in DMF (8 mL) in a 20 mL of Schlenk tube was added bis(trimethylsilyl) ethyne (**5**) (0.23 mL, 1 mmol) at rt. The reaction mixture was stirred for 6 h at 80 °C before quenching with 1 M HCl and extracted with diethyl ether (20 mL×3). The combined layers were washed with brine and dried over MgSO₄. Filtration and evaporation gave a brown solid, which was purified by column chromatography (silica gel, hexane/ethyl acetate=9:1; R_f =0.21) to give the titled compound (164 mg, 0.72 mmol, 72% yield) as white solid. ¹H NMR (300 MHz, CDCl₃, rt): δ 7.61–7.69 (m, 8H). MS (EI, *m/z* (relative intensity)): 228 (M⁺, 100), 201 (10), 175 (5), 151 (5), 114 (5), 101 (3), 87 (5), 74 (5), 63 (2).

4.4.1. *Di*(4-*methoxyphenyl*)*ethyne* (**6a**).⁵⁷ ¹H NMR (300 MHz, CDCl₃, rt): δ 3.82 (s, 6H), 6.87 (d, *J*=8.4 Hz, 4H), 7.45 (d, *J*=8.4 Hz, 4H). MS (EI, *m*/*z* (relative intensity)): 238 (M⁺, 100), 223 (69), 195 (19), 180 (9), 163 (5), 152 (21), 126 (5), 119 (9), 98 (2), 87 (2), 75 (2), 63 (2).

4.5. One-pot synthesis of unsymmetrically disubstituted ethynes from bis(trimethylsilyl)ethyne. Formation of (4-cyanophenyl)(4-methoxyphenyl)ethyne (30)⁵⁸

To a solution of Pd(PPh₃)₄ (116 mg, 0.1 mmol, 10 mol%), CuCl (99 mg, 1 mmol 100 mol%), and 4-iodobenzonitrile (2c) (458 mg, 2 mmol) in DMF (5 mL) in a 20 mL of Schlenk tube was added bis(trimethylsilyl)ethyne (5) (0.91 mL, 4 mmol) at rt. The mixture was stirred for 30 min at 80 °C. Then, the unreacted 5 was evacuated under reduced pressure. Again, Pd(PPh₃)₄ (57 mg, 0.05 mmol, 5 mol %), CuCl (50 mg, 0.5 mmol 50 mol %), and 4-iodoanisole (2a) (234 mg, 1 mmol) in DMF (5 mL) were added to the reaction mixture and the resulting mixture was stirred for 9 h at 80 °C, quenched with 1 M HCl, and then extracted with diethyl ether (20 mL×3). The combined ethereal layer was washed with brine, and dried over MgSO₄. Filtration and evaporation provided dark brown solid. Column chromatography (silica gel, hexane/ethyl acetate=19:1; R_f =0.15) gave the title compound (109 mg, 0.47 mmol, 47% yield) as white solid. GC yield was 49%. ¹H NMR (300 MHz, CDCl₃, rt): δ 3.84 (s, 3H), 6.90 (d, J=9.0 Hz, 2H), 7.48 (d, *I*=9.0 Hz, 2H), 7.58–7.61 (m, 4H). MS (EI, *m/z* (relative intensity)): 233 (M⁺, 100), 213 (40), 190 (47), 175 (2), 163 (13), 140 (5), 137 (4), 117 (3), 111 (2), 87 (4), 74 (3), 63 (4),

4.5.1. (4-Chlorophenyl)(4-cyanophenyl)ethyne (3w).⁵⁸ ¹H NMR (300 MHz, CDCl₃, rt): δ 7.36 (d, *J*=8.4 Hz, 2H), 7.47 (d, *J*=8.4 Hz, 2H), 7.62 (quin, *J*=8.0 Hz, 4H). MS (EI, *m*/*z* (relative intensity)): 237 (M⁺, 100), 201 (18), 175 (14), 151 (4), 125 (3), 118 (5), 101 (4), 87 (6), 75 (5), 63 (2).

4.6. General procedure for synthesis of unsymmetrically disubstituted ethynes with aryl bromides. Determination of GC yield of cross-coupled products

To a solution of $PdCl_2$ (4 mg, 0.02 mmol, 10 mol%), tri(4-fluorophenyl)phosphine (25 mg, 0.08 mmol, 40 mol%), and CuCl (10 mg, 0.1 mmol, 50 mol%) in dry DMF (1 mL) in a 20 mL of Schlenk tube were added an aryl bromide (0.2 mmol) and an alkynylsilane (0.3 mmol) at rt. The reaction mixture was heated at

100 °C for 12 h and monitored by GC. GC yields of the corresponding cross-coupled products **3** were determined using hep-tylbenzene as an internal standard.

4.7. General procedure for synthesis of unsymmetrically disubstituted ethynes with aryl chlorides. Formation of 4-(phenylethynyl)phenylethanone (3d)⁴³

To a solution of $Pd(OAc)_2$ (45 mg, 0.2 mmol, 10 mol%) and (–)-DIOP (100 mg, 0.2 mmol, 10 mol%) in DMF (5 mL) in a 20 mL of Schlenk tube were added 4-chloroacetophenone (**8d**) (0.26 mL, 2 mmol) and trimethyl(phenylethynyl)silane (**1a**) (0.47 mL, 2.4 mmol), and CuCl (20 mg, 0.2 mmol, 10 mol%) at rt. The reaction mixture was stirred for 24 h at 120 °C, quenched with 1 M HCl, and then extracted with diethyl ether (20 mL×3). The combined ethereal layer was washed with brine, and dried over MgSO₄. Filtration and evaporation provided dark yellow solid. Column chromatography (silica gel, hexane/diethyl ether=8:2) gave **3d** (251 mg, 1.14 mmol, 57% yield) as white solid.

4.7.1. (4-Acetylphenyl)(2-pyridyl)ethyne (**3x**).⁴³ ¹H NMR (300 MHz, CDCl₃, rt): δ 2.62 (s, 3H), 7.29 (td, *J*=4.8, 1.2 Hz, 1H), 7.55 (dt, *J*=7.8, 1.1 Hz, 1H), 7.66–7.74 (m, 3H), 7.95 (dt, *J*=8.4, 1.6 Hz, 2H), 8.64 (dt, *J*=3.9, 0.9 Hz, 1H). MS (EI, *m*/*z* (relative intensity)): 221 (M⁺, 59), 206 (100), 178 (37), 151 (24), 125 (9), 103 (14), 99 (13), 89 (18), 78 (26), 75 (31), 63 (12).

4.7.2. (4-Cyanophenyl)(4-trifluoromethylphenyl)ethyne(**3***y*). Isolated in 54% as white solid. R_{f} =0.43 (hexane/diethyl ether=8:2); mp 119 °C; FTIR (KBr, cm⁻¹): 2229 (m), 1611 (m), 1497 (w), 1322 (s), 1163 (s), 1120(s), 1063 (s), 834 (m), 554 (m); ¹H NMR (300 MHz, CDCl₃, rt): δ 7.61–7.68 (m, 8H); ¹³C{¹H} NMR (75 MHz, CDCl₃, rt): δ 89.7, 91.9, 112.0, 118.3, 123.7 (q, ¹ J_{C-F} =270.7 Hz), 125.4 (q, ³ J_{C-F} =3.8 Hz), 126.0 (q, ⁴ J_{C-F} =1.3 Hz), 127.4, 130.6 (q, ² J_{C-F} =32.1 Hz), 132.0, 132.1, 132.2; ¹⁹F{¹H} NMR (300 MHz, CDCl₃, rt): δ –62.97. MS (EI, *m/z* (relative intensity)): 271 (M⁺, 100), 252 (10), 221 (8), 201 (5), 175 (4), 151 (2), 126 (2), 110 (12), 97 (4), 75 (4), 63 (2). Anal. Calcd for C₁₆H₈F₃N: C, 70.85; H, 2.97; N, 5.16%. Found: C, 70.88; H, 3.14; N, 5.17%.

4.7.3. (4-Cyanophenyl)(3-trifluoromethylphenyl)ethyne (**3z**).⁴⁶ ¹H NMR (300 MHz, CDCl₃, rt): δ 7.51 (t, *J*=7.8, 1H), 7.61–7.73 (m, 6H), 7.81 (s, 1H); ¹⁹F{¹H} NMR (300 MHz, CDCl₃, rt): δ –63.05. MS (EI, *m/z* (relative intensity)): 271 (M⁺, 100), 252 (8), 221 (5), 201 (4), 175 (4), 169 (3), 151 (2), 135 (5), 126 (2), 110 (3), 99 (3), 87 (4), 75 (4), 63 (2).

4.7.4. (4-Acetylphenyl)(3-trifluoromethylphenyl)ethyne (**3aa**). Isolated in 48% as white solid. R_f =0.35 (hexane/diethyl ether=7:3); mp 73 °C; FTIR (KBr, cm⁻¹): 3057 (w), 2930 (w), 1689 (s), 1600 (s), 1346 (s), 1264 (s), 1116 (s), 900 (m), 802 (m), 693 (m); ¹H NMR (300 MHz, CDCl₃, rt): δ 2.63 (s, 3H), 7.50 (t, *J*=7.2 Hz, 1H), 7.61–7.64 (m, 3H), 7.72 (d, *J*=7.5 Hz, 1H), 7.82 (br s, 1H), 7.95–7.98 (m, 2H); ¹³C{¹H} NMR (75 MHz, CDCl₃, rt): δ 2.66, 89.9, 90.8, 123.6, 123.6 (q, ¹*J*_{C-F}=271 Hz), 125.3 (q, ³*J*_{C-F}=3.5 Hz), 127.4, 128.3, 128.5 (q, ³*J*_{C-F}=1.2 Hz), 136.5, 197.2; ¹⁹F{¹H} NMR (300 MHz, CDCl₃, rt): δ –63.03. MS (EI, *m/z* (relative intensity)): 288 (M⁺, 51), 273 (100), 245 (18), 225 (24), 176 (20), 136 (6), 122 (5), 111 (4), 99 (6), 87 (5), 75 (10), 63 (5). Anal. Calcd for C₁₇H₁₁F₃O: C, 70.83; H, 3.85%. Found: C, 70.88; H, 3.98%.

4.7.5. (2-Pyridyl)(3-trifluoromethylphenyl)ethyne (**3bb**). Isolated in 65% as white solid. R_{f} =0.15 (hexane/diethyl ether=9:1); mp 38 °C; FTIR (KBr, cm⁻¹): 3045 (w), 2365 (w), 1580 (m), 1465 (m), 1339 (s), 1152 (s), 1114 (s), 897 (m), 813 (m), 775 (m); ¹H NMR (300 MHz, CDCl₃, rt): δ 7.26–7.31 (m, 1H), 7.47–7.57 (m, 2H), 7.62 (d, *J*=7.8 Hz,

1H), 7.72 (dt, *J*=7.8, 1.7 Hz, 1H), 7.77 (d, *J*=7.8 Hz, 1H), 7.87 (br s, 1H), 8.64 (dt, *J*=4.8, 0.9 Hz, 1H); $^{13}C{^{1}H}$ NMR (75 MHz, CDCl₃, rt): δ 87.9, 89.4, 123.0, 123.2, 123.5 (q, $^{1}J_{C-F}$ =271 Hz), 125.5 (q, $^{3}J_{C-F}$ =3.7 Hz), 127.3, 128.8 (q, $^{3}J_{C-F}$ =3.8 Hz), 129.0, 130.9 (q, $^{2}J_{C-F}$ =3.25 Hz), 135.0 (q, $^{4}J_{C-F}$ =1.1 Hz), 136.6, 142.4, 149.7; $^{19}F{^{1}H}$ NMR (300 MHz, CDCl₃, rt): δ -63.05. MS (EI, *m/z* (relative intensity)): 247 (M⁺, 100), 226 (15), 219 (5), 208 (4), 197 (6), 178 (10), 169 (5), 151 (7), 124 (3), 99 (4), 75 (6), 69 (2). Anal. Calcd for C₁₄H₈F₃N: C, 68.02; H, 3.26; N, 5.67%. Found: C, 68.05; H, 3.39; N, 5.64%.

4.7.6. (4-Cyanophenyl)(2-pyridyl)ethyne (3cc).⁵⁹ ¹H NMR (300 MHz, CDCl₃, rt): δ 7.27–7.32 (m, 1H), 7.55 (dt, *J*=7.8, 1.1 Hz, 1H), 7.63–7.75 (m, 5H), 8.64 (dt, *J*=5.7, 0.9 Hz, 1H). MS (EI, *m/z* (relative intensity)): 204 (M⁺, 100), 177 (14), 151 (13), 124 (6), 102 (9), 99 (11), 88 (14), 75 (25), 62 (9).

4.7.7. (4-Acetylphenyl){4-(1,1-dimethylethyl)dimethylsiloxyphenyl} ethyne (**3dd**). Isolated in 50% as white solid. R_{f} =0.25 (hexane/ethyl) acetate=9:1); mp 109 °C; FTIR (KBr, cm⁻¹): 2930 (m), 2858 (m), 2217 (w), 1678 (s), 1595 (s), 1514 (m), 1496 (m), 1268 (s), 912 (s), 842 (s), 782 (m); ¹H NMR (300 MHz, CDCl₃, rt): δ 0.22 (s, 6H), 0.99 (s, 9H), 2.61 (s, 3H), 6.83 (d, *J*=8.7 Hz, 2H), 7.43 (d, *J*=8.7 Hz, 2H), 7.58 (d, *J*=8.7 Hz, 2H), 7.93 (d, *J*=8.7 Hz, 2H); ¹³C{¹H} NMR (75 MHz, CDCl₃, rt): δ -4.4, 18.2, 25.6, 26.6, 87.6, 93.0, 115.3, 120.3, 128.2, 128.6, 131.5, 133.2, 135.9, 156.5, 197.3. MS (EI, *m/z* (relative intensity)): 350 (M⁺, 52), 335 (2), 293 (100), 235 (8), 189 (5), 176 (7), 163 (3), 139 (8), 125 (5), 112 (4), 88 (2), 75 (15), 73 (21). Anal. Calcd for C₂₂H₂₆O₂Si: C, 75.38; H, 7.48%. Found: C, 75.22; H, 7.50%.

4.7.8. 4-(1-Oct-1-ynyl)benzonitrile (**3ee**).^{9a} ¹H NMR (300 MHz, CDCl₃, rt): δ 0.90 (t, *J*=6.7 Hz, 3H), 1.29–1.47 (m, 6H), 1.61 (quin, *J*=7.8, 2H), 2.42 (t, *J*=7.0 Hz, 2H), 7.45 (dd, *J*=6.6, 1.8 Hz, 2H), 7.56 (dd, *J*=6.3, 1.5 Hz, 2H). MS (EI, *m/z* (relative intensity)): 211 (M⁺, 39), 182 (59), 168 (100), 154 (83), 140 (89), 127 (44), 116 (45), 95 (22), 82 (10), 69 (21), 67 (15), 63 (14).

4.7.9. 4-(1-Oct-1-ynyl)phenylethanone (**3ff**).²² ¹H NMR (300 MHz, CDCl₃, rt): δ 0.91 (t, *J*=6.4 Hz, 3H), 1.29–1.34 (m, 4H), 1.45–1.48 (m, 2H), 1.58–1.64 (m, 2H), 2.43 (t, *J*=7.0 Hz, 2H), 2.59 (s, 3H), 7.46 (dd, *J*=6.6, 1.5 Hz, 2H), 7.87 (dd, *J*=6.6, 1.5 Hz, 2H). MS (EI, *m/z* (relative intensity)): 228 (M⁺, 47), 213 (62), 119 (17), 185 (34), 171 (21), 157 (41), 143 (49), 129 (100), 114 (51), 101 (10), 95 (10), 88 (14), 77 (13), 63 (12).

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Supplementary data

Experimental procedures, spectroscopic data, and copies of ${}^{1}\text{H}$ and ${}^{13}\text{C}{}^{1}\text{H}$ NMR spectra of new compounds **3y**, **3aa**, **3bb**, and **3dd**. Supplementary data related to this article can be found in the online version, at doi:10.1016/j.tet.2012.03.093.

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