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Sequential and domino Sonogashira coupling: Efficient tools for the synthesis of diarylalkynes ☆

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Abstract

The Sonogashira coupling reaction of aryl halides with a masked acetylene, leading to the formation of diarylethynes is reviewed. The process is either run in a sequential coupling–deprotection–coupling manner, or sometimes it is carried out in one-pot, a reaction we coined domino coupling. The procedures were also extended to the synthesis of compound libraries.

Keywords: Sonogashira reaction; Cross-coupling; Diarylalkynes; Palladium

1. Introduction

The palladium-catalyzed coupling of terminal acetylenes with aryl and vinyl halides is an important and widely used carbon–carbon bond forming reaction in organic synthesis. The Sonogashira coupling is a very useful method for the introduction of the acetylene function into aromatic ring systems and olefins [1]. The reaction has been extended to alternate solvent systems (fluorous solvents [2], ionic liquids [3]) and its applications in the fields of fine chemicals synthesis [4] and pharmaceutical chemistry [5] have been highlighted recently. The Sonogashira reaction also offers a very powerful tool for the preparation of conjugated oligomers and polymers [6]. The conformational rigidity of the acetylene bond makes these conjugated systems one of the key building blocks of optical [7] and molecular electronic applications [8].

The key step in the construction of the **3** diarylacetylenes (Scheme 1) is the Sonogashira coupling of an aryl halide (**1**) and a terminal arylacetylene (**2**) [9]. The way the acetylene (**2**) is employed might serve as the basis for the (arbitrary) division of these reactions. In cases, where the arylacetylene (**2**) is available, we coin the coupling conventional (Eq. a). When the synthesis starts from the protected form of the arylacetylene (**4**) and carries out its deprotection and the following coupling parallel, then we term the process sequential coupling (Eq. b). A third possibility is the coupling of the aryl halide (**1**) with a protected acetylene (**5**), followed by the parallel removal of the protecting group and subsequent Sonogashira coupling with an aryl halide in the same pot, a process we call domino coupling (Eq. c). While other sources discuss the conventional coupling in detail, the present article is aimed at reviewing the recent progress in sequential and domino Sonogashira coupling reactions.

Key to the success of sequential and domino Sonogashira couplings is the proper choice of the protected acetylene (**5**). Probably the most frequently used mono protected acetylene derivative in lab-scale experiments is trimethylsilyl-acetylene (**5a**) [10]. Removal of the protecting group usually requires the presence of fluoride ion or a base at ambient temperature enabling the preparation of terminal acetylene derivatives under mild

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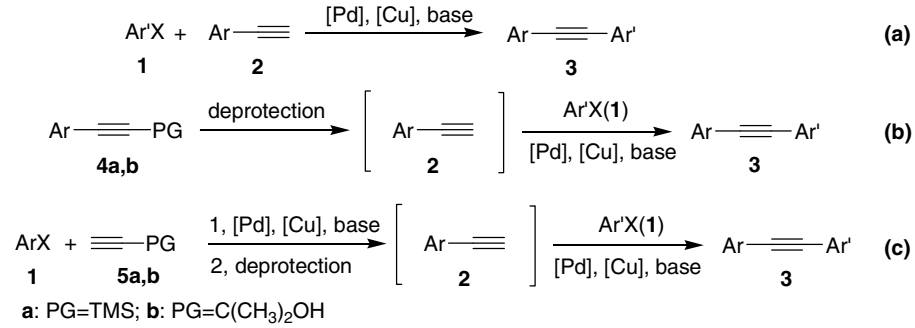


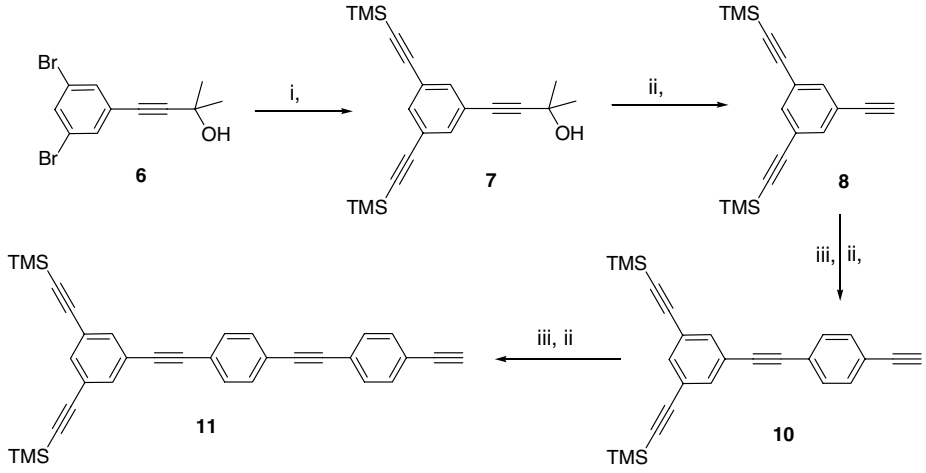
Scheme 1. Synthesis of diarylalkynes in (a) conventional, (b) sequential and (c) domino Sonogashira coupling.

conditions, a possibility that has been exploited by several research groups. An alternative route is offered for the preparation of the same compound class by the use of 2-methyl-3-butyn-2-ol (**5b**) as acetylene source. Its relatively low cost makes this "acetone protected" acetylene molecule an attractive reagent for the preparation of acetylene derivatives. The major drawback of the existing methods based on the application of **5b** is the harshness of the reaction conditions required for the release of the protecting group. The applied hard bases and high temperature in the presence of less tolerant functional groups lead frequently to undesired side reactions. In spite of these limitations 2-methyl-3-butyn-2-ol (**5b**), like trimethylsilyl-acetylene (**5a**) has been used successfully by several groups to introduce the acetylene moiety onto aromatic compounds in a step-by-step manner [11].

The complimentary nature of **5a** and **5b** might even be utilized to build in a series of acetylene groups into polyfunctional molecules in a selective manner. A fine example of this principle was presented by Rodriguez, who introduced three acetylene functions onto the same benzene ring to extend the molecule in the following reactions in only one direction [12]. In the process shown in Scheme 2, the acetone protection was removed selectively in the presence of TMS groups and in a series of coupling and deprotection reactions the dendrimeric **11** was prepared from **7** in good yield. The protected phenylethyne subunits were incorporated in the form of 4-(3′-hydroxy-3′-methyl-1′-butynyl)-iodobenzene (**9**), and the deprotection was achieved using sodium hydroxide in boiling toluene.

2. Sequential coupling reactions

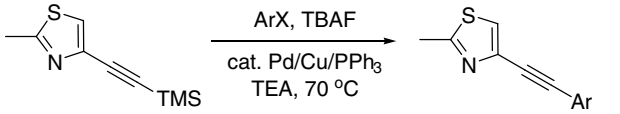
In the sequential Sonogashira coupling the release of the terminal acetylene function and the cross-coupling are carried out in the same vessel, usually by the concurrent addition of all reagents. This approach is frequently utilized in the preparation of "high added value" compounds, which allows for the use of the more expensive trimethylsilyl protecting group. Removal of the silyl protection is easily achieved by the addition of fluorides or bases, the former being compatible with most



(i) TMS-ethyne, $(PPh_3)_2PdCl_2$, CuI, Et_3N. (ii) NaOH, toluene at reflux
(iii) $(PPh_3)_2PdCl_2$, CuI, Et_3N, 4-(3'-hydroxy-3'-methyl-1'-butynyl)-iodobenzene (**9**)

Scheme 2. Selective deprotection of the methylbutynol moiety in the presence of trimethylsilyl-ethyne functions and consecutive Sonogashira coupling of the formed acetylene.

Table 1
The preparation of arylethynyl–thiazoles in sequential Sonogashira coupling



12 13

Entry	Ar–X	Solvent	Time (h)	Yield (%)
1	Iodobenzene	DMF	36	73[a]
2	2-Bromopyridine	DMF	0.5	73
3	3-Bromopyridine	DME	26	65
4	4-Bromopyridine	DME	32	75

[a] The reaction mixture also contained some tetrabutylammonium iodide.

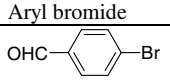
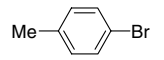
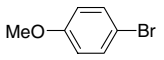
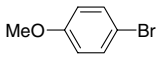
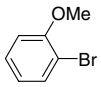
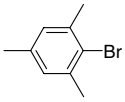
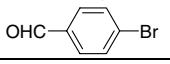
functional groups and therefore providing a very mild way of in situ arylethyne generation. A recent application of this strategy was reported by Cosford et al. (Table 1) [13]. who synthesized 4-arylethynyl-2-methylthiazoles (**13**) from a common intermediate, **12** through sequential coupling. In these reactions the deprotection of the acetylene proceeds probably faster than the following rate-limiting Sonogashira coupling.

In certain cases the too fast release of the terminal acetylene might lead to the emergence of its undesired dimerization. Studying the palladium–carbene catalyzed Sonogashira coupling, Nolan and Yang [14] established that the formation of the dimeric by-product could be suppressed by the use of trimethylsilyl protected acetylenes (Table 2). The choice of base was crucial for the success of the reaction. Amines failed to initiate the coupling, probably not being able to release the acetylene, while of the inorganic bases tested cesium carbonate was found to be the most efficient. Its success was attributed to the measured release of the acetylene in synchrony with its cross-coupling. The active catalyst system allowed for the use of aryl bromides, and in certain cases even the copper co-catalyst could be omitted.

The sequential Sonogashira coupling might in some cases be achieved in the absence of a fluoride source or base. In the reaction of 1-phenyl-2-tri methylsilylethyne and different aryl triflates diarylacetylenes were prepared in good yield by Mori and co-workers (Table 3) [15]. The reported reactions ran in the presence of a palladium catalyst and a copper co-catalyst, the latter being responsible for the deprotection of the acetylene, too. The use of a polar solvent was crucial for the success of the coupling and the procedure, in the absence of the palladium catalyst, was extended to the synthesis of 1,4-diarylbutadiynes, too (Table 4), in a deprotection-dimerization sequence. The authors also studied the ease of removal of different silyl protecting groups and found that trimethoxysilyl was superior to

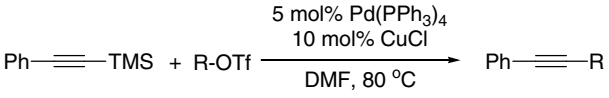
Table 2
The palladium–carbene mediated sequential Sonogashira coupling of TMS protected arylacetylenes and bromoarenes

14 15 16

Entry	R'	Aryl bromide	Time (h)	Yield (%)[a]
1	Ph		0.25	100 (92)[b]
2	Ph		0.5	99
3	Ph		0.5	82[b]
4	Ph		0.5	96 (88)
5	Ph		0.5	100 (93)
6	Ph		1	90 (82)
7	^{n}Bu		1	100

[a] GC yields based on aryl halide; number in parenthesis is isolated yield (average of two runs).
[b] Without CuI.

Table 3
Sequential Sonogashira coupling using copper mediated deprotection



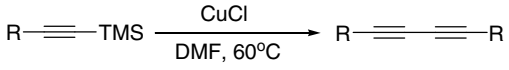
17 18 19

Entry	R	Time (h)	Yield (%)
1	1-Naphtyl	14	64
2	2-Naphtyl	12	65
3	2-Pyridyl	16	68
4	2-Quinolinyl	9	62

the others tested. The proposed intermediate alkynyl-copper complex was also isolated in an independent experiment [16].

The standard deprotection conditions for "acetone-protected" acetylenes include the boiling of the substance in toluene in the presence of excess powdered sodium or potassium hydroxide. Since these conditions are far from ideal with respect to the consecutive Sonogashira coupling, the sequential coupling of arylbutynols is usually carried out in the presence of a phase transfer catalyst in a two phase system consisting of an organic phase favorable for the cross-coupling and a strongly alkaline aqueous phase facilitating the release of the acetylene function. An elegant procedure, developed

Table 4
The copper-catalyzed dimerization of arylethynylsilanes



15 20

Entry	R	Time (h)	Yield (%)
1	Ph	6	>99
2	4-OMe-Ph	12	74
3	4-MeCO-Ph	12	75
4	2-Thienyl	12	70
5	*n*-Hexyl	3	80

recently by Chow et al. (Table 5) [17], utilizes tetrabutyl ammonium iodide in a toluene–5 M aqueous KOH system. The preparation of diarylethynes is usually accompanied by the formation of the acetylene dimer as byproduct. The reaction works well with di- and trihalogenated benzenes, such as tribromobenzene giving the tris-ethynyl coupling product. The sequential coupling was extended to purine derivatives, although with limited success, the conventional coupling giving usually superior results [18].

Although it proceeds through a distinctly different mechanism, a formally analogous coupling between 4-aryl-2-methyl-3-butyn-2-ols (**21**) and olefins giving enynes was reported by Uemura and co-workers [19]. The authors suggest that the release of acetone is promoted by the palladium(II) catalyst through β-carbon elimination of the palladium alkoxide derivative of **21**, giving an alkynylpalladium intermediate.

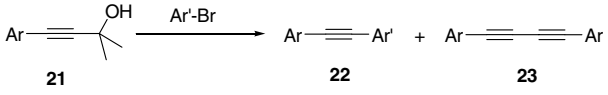
The sequential coupling might also achieved using solid potassium hydroxide in the presence of a phase transfer catalyst. In the example shown below the Sonogashira coupling was run in the presence of a regular palladium–copper catalyst system and triethylamine in benzene and tetrabutylammonium iodide played the role of the phase transfer catalyst. Using this approach a series of "molecular rotors" (e.g. **26**) were prepared from a selection of dihaloarene cores (**25**) and 4-aryl-2-methyl-3-butyn-2-ols such as **24** (Scheme 3) [20]. An analogous double coupling of a chiral bis(trimethylsilylethynyl)fluorene derivative allowed for the synthesis of the chiral bis(pyridylethynyl)-fluorene **27**, which was used to construct the first chiral square-grid coordination polymer [21].

The introduction of acetylene functions between aromatic rings leads to the formation of rigid conjugated systems that have interesting electronic and photophysical properties [22]. The sequential Sonogashira coupling of bifunctional compounds has proved to be an efficient tool for the construction of such molecular frameworks. Metal coordinating bipyridyl units and thiophene rings were coupled, for example, through acetylene bridges using both the trimethylsilyl and acetone protection strategy. Reaction of the 2-bromothiophene derivative **28** shown in Scheme 4 and 4,4′-bis(trimethylsilyl-ethynyl)-2,2′-bipyridyl (**29**) led to the desired conjugated system **30** in 60% yield [23]. The similar three component coupling of the 2,5-dibromothiophene derived bis-butynol derivative **31** and 4-bromo-2,2′-biphenyl (**32**) ran also smoothly to give **33** in 72% yield. An interesting feature of the presented reactions is the fact, that in spite of the different protecting groups used, the reported conditions were the same for both processes.

The oligo(arylethyne) motif through its conjugated system is capable of transferring electrons between its two termini, which makes it a key structural element of molecular wires. The preparation of such a complex is shown in Scheme 5. The cyclometalated ruthenium-complex end groups (**34**) were linked by diethynylarene units such as 9,10-diethynylanthracene to give compounds like **37** [24]. The construction of **37** was attempted both using the "acetone protected" bridge **35** and its silyl-protected analog **36**, the former failing to undergo cross-coupling, and the latter giving rise of the expected product in a mediocre 34% yield. The unsatisfactory yield of the procedure was, in part, attributed to the instability of the intermediate 9,10-diethynylanthracene.

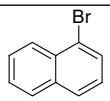
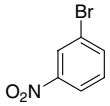
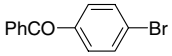
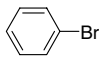
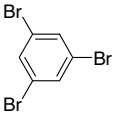
Silyl-protected acetylenes might be deprotected under a variety of conditions. Besides the most commonly used fluoride ions and bases, presented already, metal salts

Table 5
Sequential Sonogashira coupling of 4-aryl-2-methyl-3-butyn-2-ols with bromoarenes

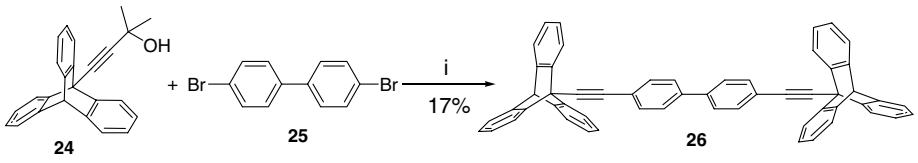


21 22 23

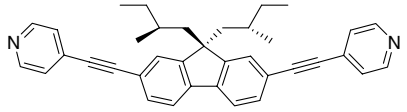
Conditions: 10 mol% $(PPh_3)_2PdCl_2$, 10 mol% CuI, Et_3N, 3 eq. 5 M aq. NaOH, 10 mol% Bu_4NI, toluene, 80 °C

Entry	Ar	Ar'–Br	Diarylethyne (yield %)	Diarylethyne/butadiyne
1	Ph		83	9/1
2	Ph		89	70/1
3	Ph		92	28/1
4	4-NO_2-Ph		57	-[a]
5	Ph		57[b]	4.4/1

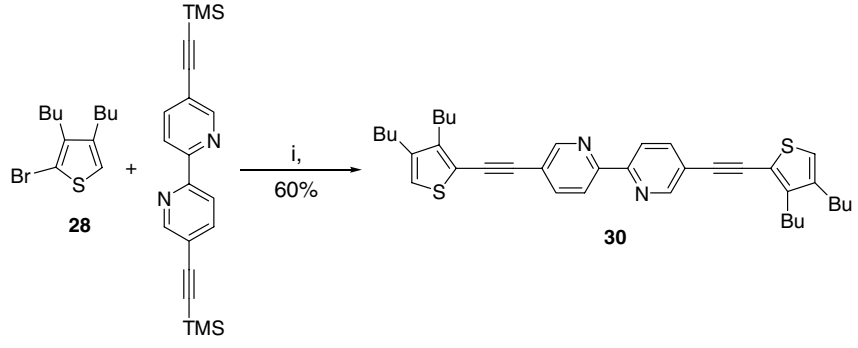
[a] No detectable butadiyne formation.
[b] Yield of the tris-coupling product.

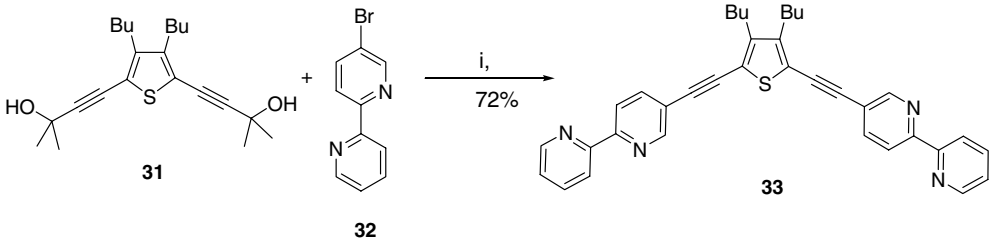


(i): KOH, Bu_4NI, 2% $(PPh_3)_2PdCl_2$, Et_3N, CuI, PPh_3, Ph-H



Scheme 3. The preparation of conjugated systems in double sequential Sonogashira coupling.





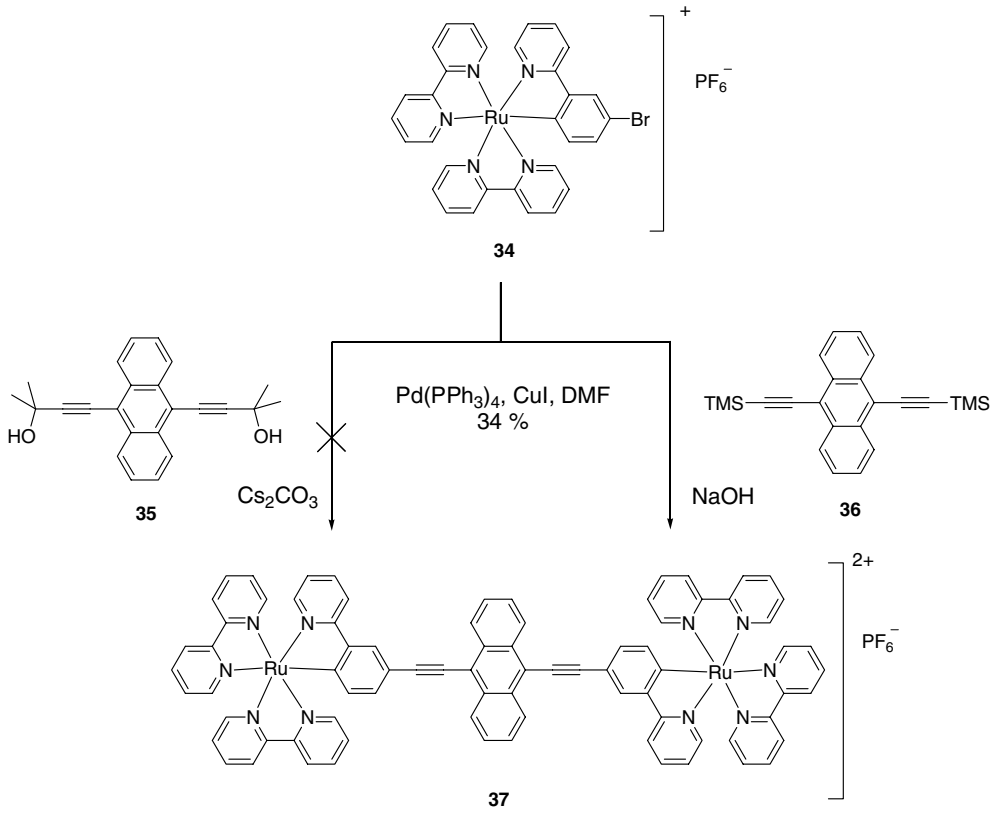
(i) Et_3BnNCl, 6 mol% $Pd(PPh_3)_4$, 10 mol% CuI, benzene, aq. NaOH.

Scheme 4. Construction of conjugated systems from thiophene and bipyridyl units.

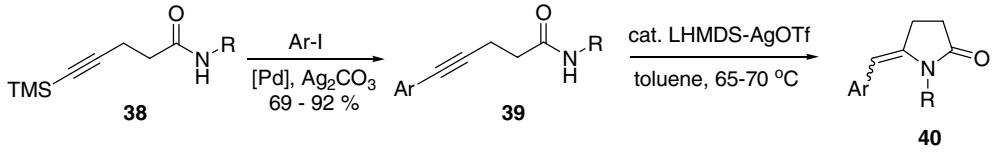
such as copper(I) or silver(I) compounds are also efficient. A recent report by Nagasaka and co-workers disclosed the conversion of the **38** 5-trimethylsilyl-4-pentynoic amide into its 5-aryl derivative (**39**) using a palladium acetate–triphenylphosphine catalyst system, 0.5 equiv of silver(I) carbonate (1 equiv of silver) and a phase transfer catalyst, tetrabutylammonium chloride (Scheme 6). Besides removing the TMS group, the silver salt also facilitates the cross-coupling reaction [25]. The coupling products were used in the preparation of pyrrolidinone derivatives containing arylidene substituents (**40**). In a similar reaction the combination of tetrabutylammonium fluoride and a catalytic amount of silver iodide were used to facilitate the conversion of a TMS-protected aliphatic alkyne into an aryl-alkylacetylene [26].

The sequential Sonogashira reaction might in certain cases also be coupled with carbon monoxide insertion as shown in Scheme 7. The **41** 3-ethynylpyridine derivative reacted with different aryl iodides in the presence of a suitable palladium catalyst, tetrabutylammonium fluoride and triethylamine under a CO pressure of 3 bar to give the **42** aroyl-alkynes in acceptable yield. The formed acetylene derivatives were used to construct [1,8]naphthyridines, a compound class of significant pharmaceutical and biomedical interest [27].

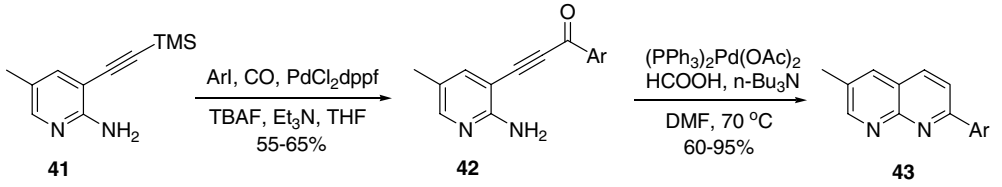
The examples of the sequential Sonogashira coupling reported by Kang et al. are somewhat unusual (Scheme 8). They replaced the commonly used aryl halides in the coupling with organoantimony compounds, namely triarylantimony diacetates (**45**) [28]. The reaction of **45** with alkynylsilanes (**44**) in the presence of a



Scheme 5. Preparation of a "molecular wire" in sequential Sonogashira coupling.



Scheme 6. Silver promoted sequential Sonogashira coupling.

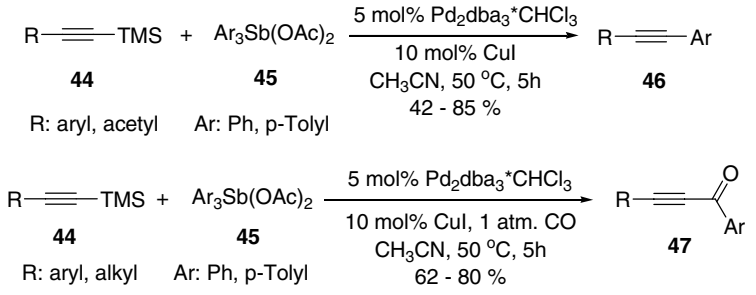


Scheme 7. Carbonylative sequential Sonogashira coupling in the synthesis of [1,8]naphthyridines.

palladium(0) complex and copper iodide gave a disubstituted acetylene derivative (**46**). In the reaction, unfortunately, only one aryl group was transferred from antimony to palladium. It is interesting to note that the cross-coupling ran in the absence of any common, strongly coordinating ligand (phosphine, carbene) or base. Under an atmospheric pressure of carbon monoxide the same reagents underwent carbonylative coupling to give the expected ynones (**47**) in good yield.

3. Domino coupling reactions

The domino Sonogashira coupling, in principle, allows for the convenient assembly of diarylethynes starting from the easily accessible aryl halides and a masked acetylene, usually trimethylsilyl-acetylene (**5a**) or 2-methyl-3-butyn-2-ol (**5b**). In site of its synthetic potential and the fact, that the first such reaction was published by Rossi in 1984 [29], surprisingly the field laid

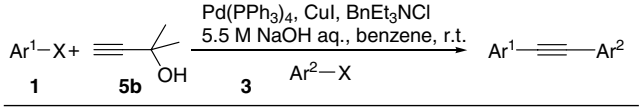


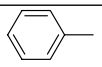
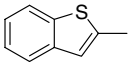
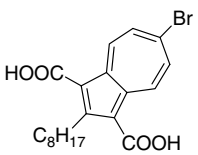
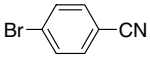
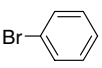
Scheme 8. Sequential Sonogashira coupling of organoantimony compounds with silyl-protected acetylenes.

dormant for nearly 20 years, except for an application of Rossi's method by Dehmlow and Balschukat [30].

In the original report different haloarenes were coupled with **5b** in a two-phase system consisting of benzene and a 5.5 M sodium hydroxide solution. Unfortunately the original report does not specify the halogens attached to the phenyl, benzothiophene and pyridine rings (Table 6, entries 1, 2, 4). The reactions were run in the presence of a conventional palladium–copper catalyst system and benzyl-triethylammonium chloride was used as phase transfer catalyst. On completion of the first coupling the second aryl halide was added and the reactions were run at elevated temperatures for 40–50 h to give the domino Sonogashira coupling products in good yield (Table 6, entries 1–4). The authors claim, that in the absence of the second aryl halide they were unable to detect the formation of any arylacetylene under the applied conditions, suggesting that the intermediate is present only in a small amount in the deprotection equilibrium.

Table 6
The first domino Sonogashira couplings of aryl halides using 2-methyl-3-butyn-2-ol (**5b**) as acetylene source



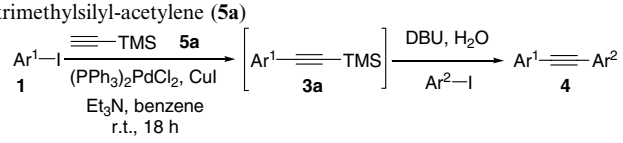
Entry	Ar^1X	Ar^2X	Yield(%)
1[a]			80
2[a]			45
3			75
4[a]			67
5			40
6			42

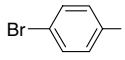
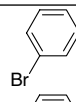
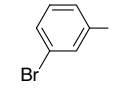
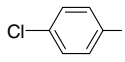
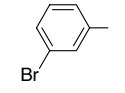
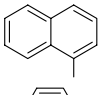
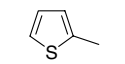
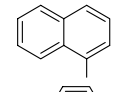
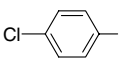
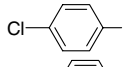
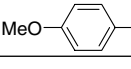
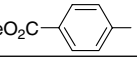
[a] The nature of halide not specified in the article.

The same reaction conditions were used with moderate success by Dehmlow and co-workers in the functionalization of azulene derivatives (Table 6, entries 5 and 6) [30]. They coupled a bromoazulene derivative with **5b** and bromoarenes to obtain the desired arylethynyl-azulenes in ca. 40% yield.

A major development in the domino Sonogashira coupling was reported by Brisbois and co-workers recently [31], who described an efficient method for the preparation of symmetrical and non-symmetrical diaryl alkynes from aryl halides and trimethylsilyl-acetylene (**5a**) along the reaction sequence depicted in Table 7. Key to the success of the reaction was the use of an excess (12 equiv) of DBU as desilylating agent. The

Table 7
DBU mediated domino Sonogashira coupling of aryl iodides and trimethylsilyl-acetylene (**5a**)

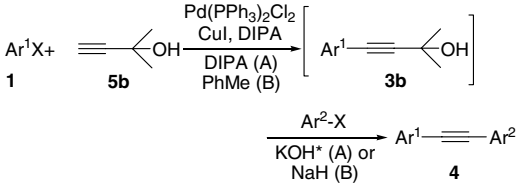


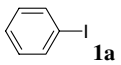
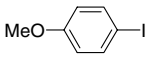
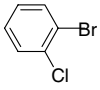
Entry	Ar^1	Ar^2	Yield (%)
1			61
2			79
3			90
4			81
5			62
6			64
7			62
8			71

authors also found that addition of substoichiometric amounts of water (40%) was beneficial to the reaction. A series of different aryl iodides (**1**) were coupled (Table 7, entries 1–8) to give the non-symmetrical bisarylethynes (**4**) in good yield, both the first and the second coupling taking usually around 18 h at ambient temperature. Bromoarenes were also subjected to the domino coupling conditions but most of them failed to give discernible products. The preparation of symmetrical bisarylethynes was usually achieved in good to excellent yield starting from the appropriate aryl iodide or triflate. The deprotection required the presence of 6 equiv of DBU.

In a recent report by Kotschy and co-workers [32] a series of aryl halides (**1**) were converted into bisarylethynes (**4**) using 2-methyl-3-butyn-2-ol (**5b**) as acetylene source (Table 8). The authors developed two complementary sets of conditions to achieve the domino Sonogashira coupling. The first coupling between the aryl halide (**1**) and **5b** in the appropriate solvent in the presence of a conventional palladium–copper catalyst reached complete conversion in less than 1 h (except for entries 7–9, which required 24 h). Potassium hydroxide in diisopropylamine (A) or sodium hydride in toluene (B) both gave good results for the deprotection and subsequent coupling in general, the former method being superior when less reactive, or electron deficient halides were coupled in the second step (entries 6, 9), while the second being favorable when coupling electron rich halides (cf. entries 2 and 5). The second coupling was usually over in 1–3 h at elevated temperatures. Using the KOH-diisopropylamine conditions a second batch of the catalyst system had to be added to the reaction mixture along with the KOH before the second coupling to achieve full conversion.

Table 8
Synthesis of diarylalkynes in domino Sonogashira coupling using 2-methyl-3-butyn-2-ol (**5b**) as acetylene source



Entry	Ar^1X	Ar^2X	Yield
1	 **1a**	**1a**	84(A), 56(B)
2		**1b**	29(A), 57(B)
3		**1c**	38(A), 47(B)
4	 **1b**	**1a**	64(A), 68(B)
5		**1b**	17(A), 66(B)
6		**1c**	68(A), 41(B)
7	 **1c**	**1a**	71(B)
8		**1b**	75(B)
9		**1c**	67(A), 32(B)

A: 5% Pd complex, 5% CuI; B: 2.8% Pd complex, 2.8% CuI.
* Another portion of the palladium-coppercatalyst system was also added.

The developed protocol was also efficient in the preparation of bisarylethyne mixtures. Starting from 3-bromopyridine and adding a mixture of aryl halides in the second step the authors got a near equimolar mixture of the possible products. Certain physical properties of the mixture components (e.g., fluorescence behavior) can be screened using the simple TLC separation of the components, therefore the domino mixture synthesis allows for the fast preliminary screening of arylethynes. A successful application of this approach was the synthesis of 9,10-bisarylethynyl-anthracene libraries, where the otherwise difficult-to-obtain nonsymmetrical compounds were also present in the mixture and could be screened [33].

4. Conclusion

The synthesis of bisarylethynes, due to their interesting physical, optical, and electronic properties as well as their synthetic value, has been in the forefront of acetylene chemistry. Besides the conventional synthetic methods, the sequential and domino Sonogashira couplings offer a convenient and efficient alternative. The reported synthetic procedures usually rely on the cross-coupling of a monoprotected acetylene with an aryl halide, followed by the removal of the protecting group and the subsequent Sonogashira coupling of the released acetylene.

A survey of the literature reveals that besides the multistep procedures the sequential couplings are the method of choice for the preparation of diarylacetylenes, but the recent emergence of efficient domino Sonogashira coupling protocols for both trimethylsilyl-acetylene and 2-methyl-3-butyn-2-ol based approaches suggests that these reactions are also coming of age.

Acknowledgments

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