Synthetic Methods

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Arylsulfonylacetylenes as Alkynylating Reagents of C_{sp^2}–H Bonds Activated with Lithium Bases**

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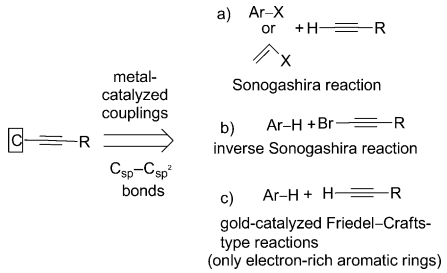
Dedicated to Dr. Amelia Tito.

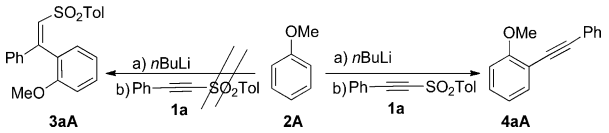
In recent years, acetylene chemistry has become an increasingly attractive topic for chemists because of its importance in the synthesis of bioactive natural products and new materials as well as in biochemistry.[1] A variety of new approaches have appeared for incorporating alkyne moieties into organic molecules. The most common methods for the formation of C_{sp}–C_{sp^2} bonds to provide aryl acetylenes and conjugated enynes are illustrated in Scheme 1,[2] the most powerful being the well-known Sonogashira cross-coupling



Scheme 1. Approaches for the synthesis of C_{sp^2}–C_{sp} bonds.

reaction (Scheme 1a).[3] It starts from aryl or alkenyl halides and terminal alkynes and requires the presence of a palladium(0) catalyst and a copper source (cocatalyst). The scope of this reaction is quite general, with its primary limitation being the availability of the starting halides. Moreover, specialized reaction conditions are often necessary to improve the poor results obtained in some couplings involving electron-rich C_{sp^2} components (which interfere with the oxidative addition step) or electron-poor alkynes (which do not readily form the copper acetylide intermediates).[4] A more recent strategy for the formation of aryl alkynes is the inverse-Sonogashira-type reaction (Scheme 1b)[5] in which the alkyne source is typically a bromo alkyne and aromatic C–H activation is achieved using palladium,[5b] nickel,[5a] or copper[5c] catalysts. This method is generally restricted to substrates susceptible to C–H activation (azoles or activated aromatic rings). A third, but even less general approach is based on a gold-catalyzed Friedel–Crafts-type addition of highly electron-rich aromatic rings[6] (e.g., 2,4,6-trimethoxyphenyl groups,[6a] thiophenes[6b] or indoles[6c]) to electron-poor terminal alkynes or alkynyl iodonium salt derivatives (Scheme 1c). Because all these methods suffer from problems associated with the use of expensive catalysts and harsh reaction conditions, the development of alternative methods able to circumvent these limitations would be highly desirable.

We have recently reported reactions of *ortho*-sulfinyl benzylcarbanions with β-monosubstituted vinylsulfones as the solution for creating carbon skeletons containing two adjacent chiral centers.[7] To evaluate the applicability of this methodology to the synthesis of quaternary centers by reaction with β-disubstituted vinylsulfones, we decided to synthesize **3aA** (Scheme 2, left) by Michael addition of the



Scheme 2. Alkynylation of anisole with arylsulfonylacetylenes.

orthometalated anisole (obtained with *n*BuLi) to the sulfonylacetylene **1a**. Unexpectedly, only the anti-Michael[8] addition product **4aA** was obtained (Scheme 2, right).

Based on this unexpected behavior, we hypothesized about a new approach for the synthesis of C_{sp^2}–C_{sp} bonds based on the use of sulfonyl acetylenes as general alkynylating reagents of aromatic positions activated with lithium bases to form ArLi. Taking into account that the conditions for this reaction (5 min at −78 °C) are milder than those required by

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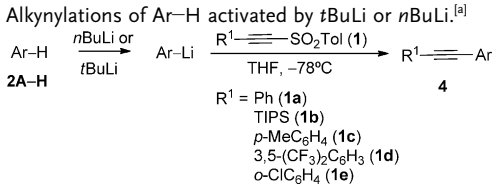
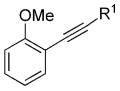
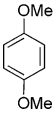
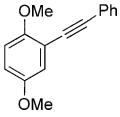
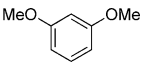
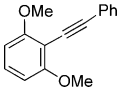
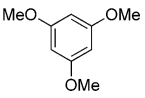
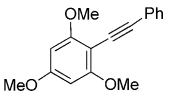
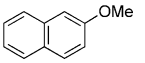
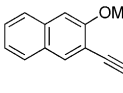
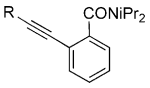
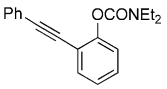
other methods[9] (Scheme 1), and the fact that no transition metals are necessary, we thought this method could be used as an alternative to the methodologies indicated at Scheme 1. Herein, we demonstrate the scope and generality of this method for the alkynylation of a wide variety of C_{sp^2}-lithium substrates.

Under optimized reaction conditions, *ortho* lithiation of anisole (**2A**) using *n*BuLi or *t*BuLi at room temperature with subsequent addition of the sulfonylacetylene **1a** at −78 °C, afforded **4aA** in 5 minutes (81% yield; entry 1, Table 1). Under similar reaction conditions, **2A** reacted with the TIPS-substituted sulfonylacetylene **1b** to afford alkynyl derivative **4bA** in 80% yield (entry 2, Table 1). This result is particularly remarkable because of the potential synthetic utility of **4bA** as an intermediate in the preparation of many other alkynyl derivatives (by previous deprotection of the terminal alkyne), indicating that the anti-Michael behavior of the sulfonylacetylenes is not exclusive of 2-aryl derivatives.[10] Other arylacetylenesulfones (**1c**–**e**) bearing electron-donating and electron-withdrawing groups at the aromatic ring, also reacted with similar yield, thus affording the corresponding acetylenes (entries 3–5, Table 1). Reaction of **2B** with **1a** exclusively provided **4aB** in 85% yield (entry 6, Table 1), which was increased up to 92% (entry 7) on a 4.0 mmol scale. The absence of dialkynylated products indicates that **4aB** is less reactive than **2B**, as would be expected from the deactivating influence of the alkynyl groups on the formation of the corresponding aryl lithium species. The reaction of **2C** was interesting because of its regioselectivity (entry 8, Table 1). Working under the usual reaction conditions (*ortho* lithiation at RT), the reaction affords a 80:20 mixture of **4aC** and its regioisomer 4-alkynyl-1,3-dimethoxybenzene, which were easily separated by chromatography (56% yield of **4aC**). The lower susceptibility of **2D** to *ortho* lithiation, is likely a result of both electronic (high electronic density of the ring) and steric factors, which lead to the need to perform the reaction at room temperature (other reactions were nearly instantaneous at −78 °C). Under these reaction conditions, decomposition of **1a** was very fast,[11] and the use of a large excess of the nucleophile (8 equiv) activated by TMEDA (8 equiv) was necessary to achieve its complete alkynylation[11] to obtain **4aD**[12] in 80% yield (entry 9, Table 1). A particularly interesting result was obtained from 2-methoxynaphthalene (**2E**), which upon lithiation by *n*BuLi and addition of **1a** afforded a 95:5 mixture of the two possible regioisomers. After separation, the major isomer, **4aE**, was obtained in 70% yield (entry 10, Table 1). The observed regioselectivity (attack at C3 is favored) can be explained by assuming that electronic and steric factors both inhibit C1 lithiation and subsequent alkynylation.

The use of other *ortho*-directing groups was also successful. The *N*,*N*-diisopropylcarboxamide **2F** underwent reaction with **1a** and **1b** to give **4aF** and **4bF**, respectively (entries 11 and 12, Table 1). The *N*,*N*-diethylcarbamate **2G** also underwent reaction with **1a**, thus affording **4aG** in 86% yield (entry 13, Table 1). If the carbamate occupies the β position of a naphthalene ring, we can expect a similar behavior to that observed for **2E** (entry 10, Table 1). In this sense, the estradiol derivative **5** reacts with *n*BuLi and **1a** to afford **6** in 89% yield

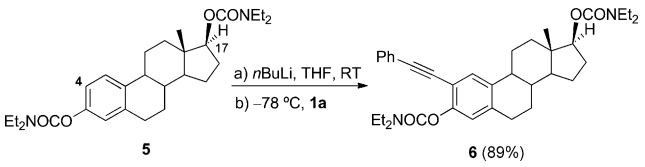
Table 1: Alkynylations of Ar–H activated by *t*BuLi or *n*BuLi.[a]



Entry	Substrate	1 (R^1)	Product	Yield [%][b]
1		1a	 4aA	81
2		1b	4bA	80
3	2A	1c	4cA	55
4		1d	4dA	53
5		1e	4eA	73
6	 2B	1a	 4aB	85
7		1a		92[c]
8	 2C	1a	 4aC	56[d]
9	 2D	1a	 4aD	80[e]
10	 2E	1a	 4aE	70
11	 2F	1a	 4aF	99
12		1b	4bF	90
13	 2G	1a	 4aG	86
14	 2H	1a	 4aH	67

[a] All the reactions were performed with **1** (0.2 mmol) and **2** (0.4 mmol). [b] Yield of isolated product after flash chromatography. [c] Reaction carried out at 4.0 mmol scale. [d] A mixture 4:1 regioisomers was obtained. [e] Full conversion requires 8 equivalents of anion, RT, and TMEDA and hexanes were used to increase the reactivity of the nucleophile. THF = tetrahydrofuran, TIPS = triisopropylsilyl, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylenediamine.

with complete regioselectivity (Scheme 3). This transformation is particularly interesting given that alkyne moieties have previously been used in steroid chemistry as delivery vectors



5 6 (89%)

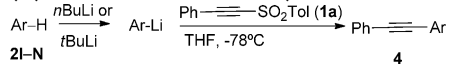
Scheme 3. Alkynylation of the estradiol derivative **5.**

to enhance the activity of different biologically active molecules.[13] For this purpose, alkynes have traditionally been introduced at C17 through acetylide addition. The reaction illustrated in Scheme 3 opens the possibility of an entirely new site for this type of alkyne linker.

Next, we focused our attention on the alkynylation of ferrocene **2H** because this reaction could be useful in the preparation of new materials.[14] To our knowledge, all the methods available for introducing alkynyl groups at ferrocene cores are indirect or give poor yields.[14b] Our method allows the synthesis of **4aH** (67%) by direct reaction of ferrocene with *t*BuLi and **1a** (entry 14, Table 1).

Alkynylated heteroaromatic rings are important intermediates in the preparation of bioactive molecules (Table 2). Given that many C_{sp^2}–H bonds of aromatic heterocycles are sufficiently activated to undergo lithiation with RLi, our method would allow a very simple and direct introduction of an alkyne in such positions. Thus, the α position of furan and thiophene was alkynylated to afford **4aI** and **4aJ**, respectively, in high yields (entries 1 and 2, Table 2) without giving any double alkynylation, which had been observed using other methods. *N*-methylpyrrole gave the expected product **4aK**, although an excess of the nucleophile (8 equiv) at room temperature, and [12]crown-4 ether were required (entry 3, Table 2). Interestingly, *N*-methylindole (**2L**) gave alkynylation at C2 (entry 4, Table 2),[15] whereas the TIPS derivative **2M** afforded the C3-alkynylated product **4aM** after removal of the silyl protecting group (entry 5). These compounds had been previously prepared using both catalytic[15a–c] and non-catalytic methods[15d] that were generally long synthetic sequences. Analogously, the mild reaction conditions used for obtaining **4aN** in 65% yield (−78 °C, 5 min; entry 6, Table 2) by metalation of benzothiazole and then reaction with **1a** contrast with the harsh conditions (toluene, 100 °C, 24 h) previously used for achieving the alkynylation of benzothiazoles.[5d]

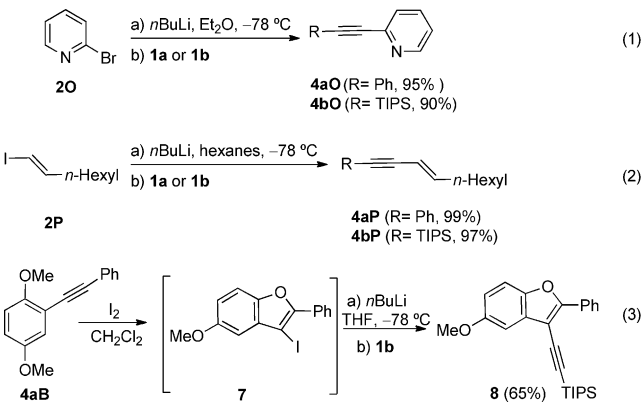
Table 2: Alkynylations of Ar–H activated by *t*BuLi or *n*BuLi.[a]



Entry	Substrate	Product	Yield [%][b]
1	**2I** (X = O)	**4aI**	89
2	**2J** (X = S)	**4aJ**	87
3	**2K** (X = NMe)	**4aK**	69[c]
4	**2L**	**4aL**	80
5	**2M**	**4aM**	32[d]
6	**2N**	**4aN**	64

[a] All the reactions were performed with **1** (0.2 mmol) and **2** (0.4 mmol). [b] Yield of isolated product after flash chromatography. [c] Full conversion requires 8 equiv of anion, RT, and [12]crown-4 ether (1 equiv). [d] TMEDA and hexanes as the solvent was used to increase the reactivity of the nucleophile.

From the above results, it seemed obvious that alkynylation of organolithiums generated by conventional methods involving lithium–halogen interchange, would also be possible with sulfonylacetylenes.[16] In this work, we have illustrated this reaction with five examples (Scheme 4). The first



Scheme 4. Alkynylation of pyridines and double bonds.

two involve the synthesis of 2-alkynyl pyridines[17] (lithiation of pyridines cannot be achieved by *ortho* metallation). Reaction of 2-bromopyridine (**2O**) with *n*BuLi and then addition of either **1a** or **1b** under the standard reaction conditions (in these cases, both Br/Li interchange and reaction with the sulfonylethylene are performed at −78 °C) afforded **4aO** and **4bO**, respectively, in very high yields (Eq (1), Scheme 4). In a similar way, the alkynylation of iodoalkenes would provide a simple and new entry to enynes, which are commonly found in naturally occurring compounds.[18] Thus, reaction of (*E*)-1-iodo-1-octene (**2P**) with *n*BuLi and then addition of **1a** and **1b** allows the synthesis of the enynes **4aP** and **4bP**, respectively, in almost quantitative yield with retention of the *E* configuration at the double bond (Eq. (2), Scheme 4).[19] Finally, a more elaborate method for synthesizing enynes is shown in Equation (3), Scheme 4. It has

been reported that *ortho*-alkynyl anisoles react with I_2 to afford 3-iodobenzofurans.[20] Under these conditions, **4aB** (entry 3, Table 1) was transformed into **7**, which reacted in situ with *n*BuLi and then with alkyne **1b**, thus yielding 3-alkynylbenzofurane **8** in 65% yield (two steps from **4aB**). The three-step sequence from **2B** to deliver **8** illustrates an efficient method for the synthesis of 3-alkynylbenzofuranes that involves two alkynylation reactions.

To understand the unexpected electrophilic behavior of substituted sulfonylacetylenes, we first performed theoretical calculations using density functional theory (DFT; Gaussian09[21] using the B3LYP functional[22]) on the relative electrophilic character of the α and β carbon atoms of **1a** (for details see the Supporting Information). However, these calculations revealed that the β-carbon atom is the most electrophilic position, thus suggesting that any intermolecular nucleophilic attack should take place through a more typical Michael-type approach. Therefeore, we assume that the formation of species **A** (Figure 1), with the lithium associated

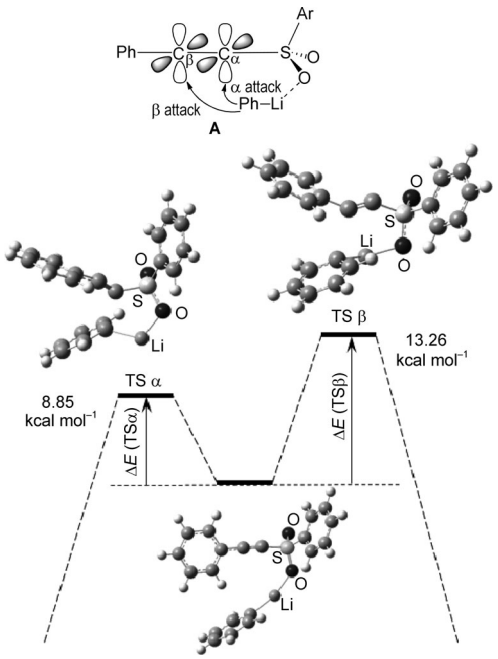


Figure 1. Energies of the transition states for the α and β attacks on species **A**.

to the sulfonyl oxygen atoms, is the first step of an intramolecular transfer of the nucleophilic alkynyl group[23] (Figure 1) and could explain the preferred attack at the α position. To confirm this assumption, a more detailed picture of the reaction mechanism of **1a** with PhLi has been obtained using additional DFT calculations. Beginning from noncomplexed starting materials, the calculations indicate the formation of a complex with the nucleophile coordinated to the electrophile (**A**) by association of lithium to one of the sulfonyl oxygen atoms. It corresponds to a minimum in the potential energy surface. From this point, we then obtained the transition states corresponding to attack at the α and β positions (right and left structures in diagram at Figure 1). The attack at the α position shows a smaller energy barrier, and the ΔE with respect to the β attack is so large (4.40 kcal mol^{-1}) that it would explain the complete selectivity observed in these reactions.

In summary, we have explored a new strategy for the alkynylation of a wide variety of C_{sp^2}–H bonds activated by lithium bases with 2-aryl- and 2-TIPS-substituted sulfonylacetylenes, based on the unexpected anti-Michael addition. The main advantage of this method with respect to those usually employed for the construction of the C_{sp^2}–C_{sp} bonds, derives from the mild reaction conditions (−78 °C, 5 min) and the absence of transition metals. In addition, the broad scope of the reaction, the high yields, and the simple experimental manipulation make this procedure an excellent alternative to the formation of aryl and vinyl alkynes.[24]

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[1] *Modern Acetylene Chemistry* (Eds.: P. J. Stang, F. Diederich), VCH, Weinheim, **1995**.
[2] Scheme 1 does not include other powerful methods such as alkyne metathesis or Corey–Fuchs reaction which create the alkyne moiety instead of formation of a C_{sp}–C_{sp^2} bond.
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[7] J. L. García Ruano, C. Schoepping, C. Alvarado, J. Alemán, *Chem. Eur. J.* **2010**, *16*, 8968–8971.
[8] For a definition and review of anti-Michael reactions, see: E. Lewandowska, *Tetrahedron* **2007**, *63*, 2107–2122.

[9] For Sonogashira's reaction, temperature ranges between RT and 100 °C and reaction times from several hours to several days, depending on the substrates.
[10] We are currently studying the behavior of the 2-alkyl sulfonylacetylenes.
[11] Reactions performed at −78 °C with 1 equiv of **2d** and base only afforded 20 % yield after 1 hour.
[12] The synthesis of this compound in 22 % yield has been reported in Ref. [6a] and involves using Au catalysis (Scheme 1c).
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[24] Although this reaction may not appear to be atom economical, the generated lithium *p*-toluenesulfinate can be easily recovered and used again for the synthesis of ethynylsulfones.

