Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2017, **15**, 3901

"Anti-Michael addition" of Grignard reagents to sulfonylacetylenes: synthesis of alkynes†

Francisco Esteban,[a] Lazhar Boughani,[a] José L. García Ruano,[a] Alberto Fraile *[a,b] and José Alemán *[a,b]

Received 29th March 2017,
Accepted 6th April 2017

DOI: 10.1039/c7ob00783c

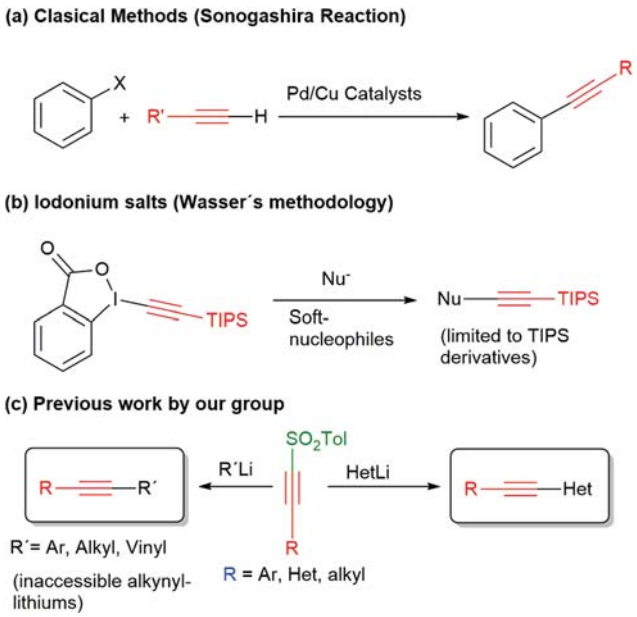
rsc.li/obc

In this work, the addition of Grignard reagents to arylsulfonylacetylenes, which undergoes an "anti-Michael addition", resulting in their alkynylation under very mild conditions is described. The simplicity of the experimental procedure and the functional group tolerance are the main features of this methodology. This is an important advantage over the use of organolithium at –78 °C that we previously reported. Moreover, the synthesis of diynes and other examples showing functional group tolerance in this anti-Michael reaction is also presented.

Introduction

Acetylene chemistry is a very attractive field, because this functional group has been applied in important fields such as the synthesis of bioactive natural products[1] or the synthesis of new materials.[1,2] The triple bond is extremely important in the assembly of different nano-scale molecules, such as fullerenes, nano-tubes or porphyrins. Moreover, the triple bond moiety has been employed as a starting material for a large number of different reactions, such as click chemistry,[3] alkyne hydroamination,[4] Pd-catalyzed cross-coupling,[5] olefin metathesis,[6] and [2 + 2 + 2] cycloaddition arene formation.[7] In the last decade, the 1,3-dipolar cycloadditions of azides and alkynes have been used in polymer and materials sciences,[8] in biology,[9] and in medicinal chemistry[10] (bioconjugates). Therefore, the development of new methodologies for the synthesis of alkynes is crucial for the progress of all these fields.

In the literature, a wide variety of new approaches for incorporating alkyne moieties into organic molecules using metals (formation of C_{sp}–C_{sp^2} or C_{sp}–C_{sp^3} bonds) have appeared.[11–13] However, all these methods have some limitations derived from the price of the catalytic system and, mainly, from the waste generated in reactions catalyzed by Pd and other metals, which seriously limits their use in the pharmaceutical industry (*e.g.* Sonogashira reaction, top, Scheme 1). Other approaches to alkynes are based on the use of hypervalent iodine.



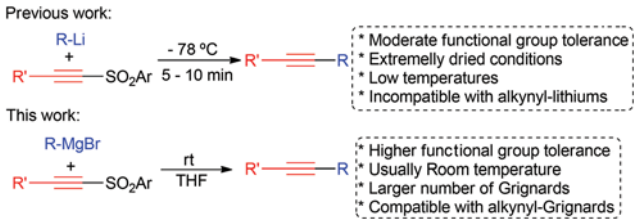
Scheme 1 Different approaches for the synthesis of alkynes.

Consequently, the reaction of alkynyl iodonium salts and, more recently, ethynylbenziodoxol(on)e reagents with soft carbon nucleophiles and heterocycles allows the synthesis of alkynes in good yields (eqn (b), Scheme 1).[14] However, the alkynylation with versatile organolithium or organomagnesium reagents is not possible due to decomposition processes.

Recently, our group has published the anti-Michael addition of organolithium reagents to arylsulfonylacetylenes, which are commercially available or easily prepared in one step from alkynes,[15] giving access to a large variety of alkynes in a very easy manner (bottom, Scheme 1).[16,17] Therefore, we

[a]*Departamento de Química Orgánica (módulo 01). Universidad Autónoma de Madrid. Calle Francisco Tomás y Valiente, 7, Cantoblanco, 28049 Madrid, Spain. E-mail: jose.aleman@uam.es*
[b]*Institute for Advanced Research in Chemical Sciences (IAdChem), Universidad Autónoma de Madrid, 28049 Madrid, Spain*

†Electronic supplementary information (ESI) available: Copies of ^{1}H NMR spectra of all final compounds. See DOI: 10.1039/c7ob00783c



Scheme 2 Initial considerations for the present work.

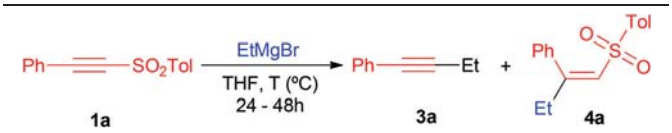
have applied this methodology for the synthesis of aryl–aryl-alkynes (Ar–≡–Ar), aryl–alkyl-alkynes (Ar–≡–Alk) or alkyl–alkyl-alkynes (Alk–≡–Alk) by addition of the corresponding aryl and alkyl organolithium derivatives to aryl- or alkyl-sulfonylacetylenes at −78 °C (left-bottom, Scheme 1). Moreover, this methodology also allowed the addition of vinyl-lithiums, leading to important enynes. However, we found that the addition of the alkynyl-lithiums was not possible (see below). Very recently, we have also applied this methodology for the synthesis of alkynyl heterocycles[17a] and the alkynylation of metallocenes.[17b]

Despite these good results, these organolithium reagents present some limitations such as the functional group tolerance (*e.g.* not compatible with carbonyl groups), their sensitivity to moisture (require extremely dried conditions), and the need for low temperatures (usually −78 °C) (top, Scheme 2). In addition, the synthesis of diynes was not possible with alkynyl-lithium derivatives. For these reasons, we thought that the use of organomagnesium reagents could be the solution for a new approach for the synthesis of disubstituted acetylenes (bottom, Scheme 2). Taking into account that Grignard reagents are less reactive and, in some cases, more selective than organolithium compounds, we studied the applicability of Grignard reagents to synthesize different alkynyl derivatives. In this work, we present our results in the addition of Grignard reagents to arylsulfonylacetylenes as a general method for obtaining disubstituted alkynes.

Results and discussion

With these initial ideas on mind, we started the screening of reaction conditions by the addition of EtMgBr to the alkynyl sulfone **1a** in THF as the solvent (Table 1). At 0 °C and 2.5 equivalents of EtMgBr, we could observe a complex mixture in which the product **3a** was identified along with different unidentified by-products (entry 1), while the use of 2.0 equiv. of the Grignard reagents gave a mixture (89 : 11) of products **3a** (anti-Michael addition) and **4a** (Michael addition) (entry 2). Interestingly, a decrease in the number of equivalents of the EtMgBr increases the ratio **3a** : **4a** (entries 3 and 4) up to 92 : 8, that was found to be optimal when 1.0 equivalent of the Grignard reagent was used (**3a** : **4a**, >98 : 2, entry 5). In order to reduce the reaction time, we carried out the reaction at room temperature (entry 6), but a 90 : 10 ratio of alkyne **3a** and

Table 1 Screening reaction conditions for the addition of EtMgBr to **1a**



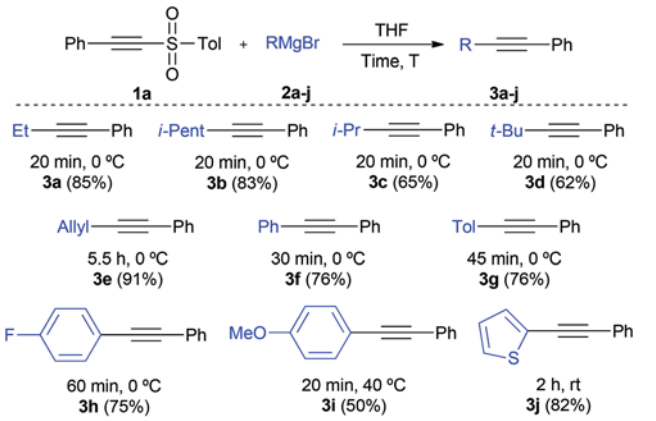
1a **3a** **4a**

Entry[a]	Equiv. EtMgBr	*T*	Time (h)	Conv.[b]	Ratio (**3a** : **4a**)
1	2.5	24	0 °C	—	Complex mixture
2	2.0	24	0 °C	99	89 : 11
3	1.5	24	0 °C	96	92 : 8
4	1.2	24	0 °C	99	92 : 8
5	**1.0**	**48**	**0 °C**	>**99**	>**98 : 2**
6	1.0	24	rt	97	90 : 10

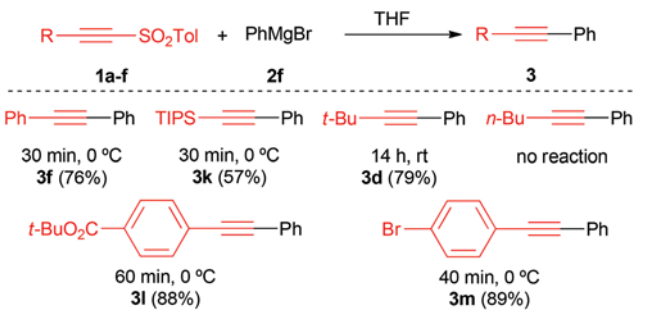
[a] Reactions were performed on a 0.2 mmol scale of **1a** in 0.5 mL of THF. [b] Determined by ^{1}H NMR.

Michael adduct **4a** was obtained (entry 6, Table 1). Therefore, the reaction conditions in entry 5 were applied for the use of different Grignard reagents (Scheme 3) and different sulfones (Scheme 4) and for the synthesis of diynes (Scheme 6).

The reactions of primary, secondary and tertiary alkyl derivatives (EtMgBr, i-PentMgBr, i-PrMgBr, *t*-BuMgBr) afforded, in only 20 min at 0 °C, the alkynes **3a–d** in high to



Scheme 3 Reactions of 2-*p*-tolylsulfonylphenylacetylene (**1a**) with alkyl- and aryl-magnesium derivatives.



Scheme 4 Reactions of PhMgBr **2f** with different acetylenes **1**.

good yields without further purification by column chromatography (Scheme 3).

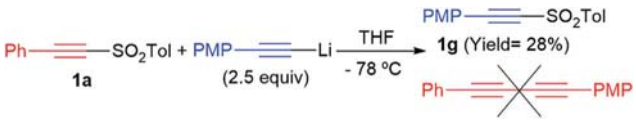
The short reaction times, even for the bulkier *tert*-butyl derivative, are remarkable. This latter result is particularly attractive because the synthesis of acetylene derivatives bearing tertiary and quaternary centers is not an easy task (the addition of metal-acetylenic derivatives to secondary or tertiary halides mainly gave rise to elimination products).[18] It is also remarkable that the reaction with the less reactive allylic derivative afforded the corresponding alkyne **3e** in very high yield (91%) after 5.5 h at 0 °C.

We then explored the reactivity of different aryl Grignard derivatives with the phenylethynylsulfone **1a** (Scheme 3). The reactions with phenylmagnesium bromide allowed the synthesis of **3f** in good yield in only 30 min (reaction followed by TLC). The reaction proceeded in a similar manner when the *p*-fluoro-phenyl derivative was used (**3h**). However, a lower conversion was found when the *p*-methoxy group was used. It was necessary to increase the temperature up to 40 °C to obtain **3i** with moderate yield, probably due to the decomposition of the starting sulfone **1a** or final product **3i** in the reaction media. The reaction time with these aryl Grignard reagents was longer than that with the alkyl ones (20 min *vs.* 30–60 min), which is in accordance with the expected reactivity (higher nucleophilicity with alkyl derivatives). The reaction also worked with heterocycles like thiophene, giving the alkyne **3j** in good yield and with a longer reaction time (2 h).[19]

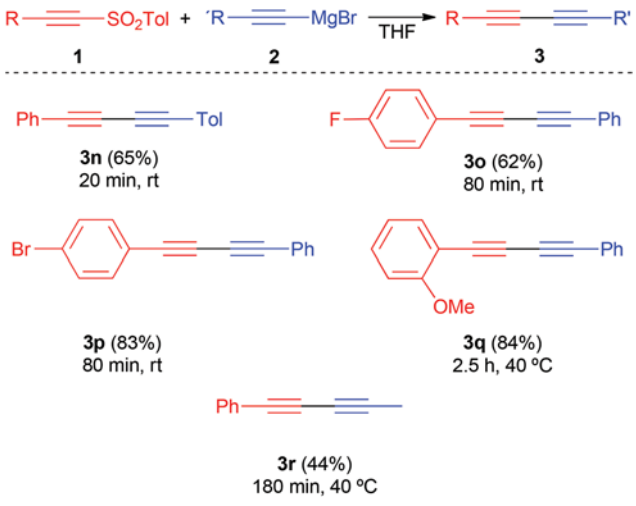
We then studied the reaction of different ethynylsulfones **1** with the phenylmagnesium bromide **2f** (Scheme 4). The reactions with sulfones **1a** and **1b** at 0 °C led to the corresponding alkynes **3f** and **3k**, respectively, in good yields and in short reaction times. It is noteworthy that alkyne **3k** is a very useful alkyne because the subsequent elimination of the TIPS group affords a terminal alkyne that could be used as a starting material to prepare other alkynes (*e.g.* alkyl-alkynes). We were also able to synthesize the *tert*-butyl derivative **3d** in 79% yield by reaction with the bulkier ethynylsulfone **1c**. In this case it was necessary to increase the reaction time to 14 h and the temperature up to rt, to achieve full conversion. We also attempted the reaction with the aliphatic alkynyl derivatives **1d** but the reaction did not take place, even when heating the reaction mixture up to 40 °C, due to the easy deprotonation of the propargylic position. In addition, we checked if the reaction tolerates the presence of sensitive substituents at the aromatic ring of the starting ethynylsulfone in the presence of Grignard reagents. Therefore, we carried out the addition of phenylmagnesium bromide **2f** to *p*-ester **1e** and *p*-bromo **1f** derivatives, obtaining in very good yields the corresponding alkynes **3l** and **3m**, respectively.

Conjugated diynes are unique structures because they are present in several natural products and they have been used like starting materials for a large number of transformations.[20] The most direct synthesis, the Cadiot–Chodkiewicz dimerization[20b] or Glaser–Hay coupling,[20c] only allows the synthesis of symmetric diynes or need a large excess of one of the alkyne units. However, the synthesis of unsymmetrical 1,3-diynes, from the required 1-bromo-alkyne, is more difficult due to the formation of homo-coupling by-products along with the desired product, which complicates its purification.[20d,e] Recently, the synthesis of unsymmetrical 1,3-diynes using a nickel-catalyzed cross coupling reaction from acetylenic sulfones **1** was reported.[20f] Therefore, during our studies using organolithium derivatives, we wanted to avoid the use of transition metal catalysed processes in the synthesis of diynes from the addition of alkynyl-lithiums to arylsulfonylacetylenes.[16] We found that the *ipso*-substitution of the sulfonyl moiety was not possible, causing the direct attack to the sulfur atom and elimination of the phenylacetylene as a leaving group to give sulfone **1g** in low yield (Scheme 5). The ability of the phenyl acetylene to stabilize the negative charge as a leaving group would be the reason for the observed behaviour.

With these preliminary reactions, we hypothesized that the change to the Grignard reagents could provoke a change in this reactivity. Therefore, the possibility of obtaining diynes, which were not able to be synthesized starting from alkynyl lithium was studied. For our delight, the reaction of the *p*-tolylethynylmagnesium bromide afforded the diyne **3i** in good yield after 20 minutes (Scheme 6) with a slightly excess of the Grignard compound. The reaction also tolerated electron-donating and electron-withdrawing groups, affording diynes **3o**, **3p** and **3q** with good yields. However, in the case of the prop-1-yn-1-ylmagnesium bromide (**3r**), the reaction proceeded with a slightly lower yield.



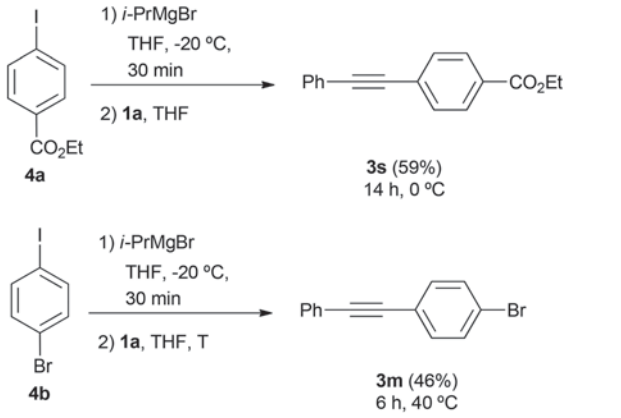
Scheme 5 Previous reaction of alkynyl-lithium derivative with **1a**. PMP = *p*-methoxyphenyl.



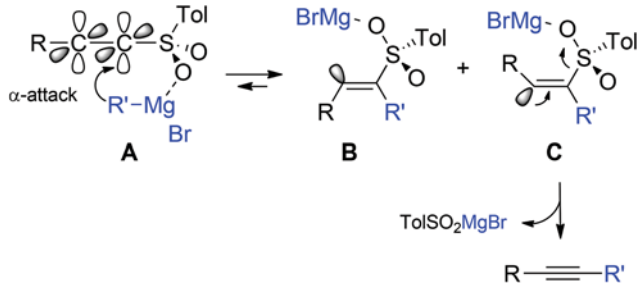
Scheme 6 Synthesis of diynes by addition of alkynylmagnesium to sulfones **1**.

In our previous studies,[16] we found that the alkynylation process was incompatible with esters (due to the higher reactivity of the carbonyl group than the *ipso* substitution of the alkyne moiety) and also incompatible with bromine atoms (due to the easy exchange process). Following the Knochel–Grignard exchange procedure,[21] the addition of a Grignard reagent, bearing an ester group at the aromatic ring to the phenylethynylsulfone **1a** provided the alkyne **3s** in a respectable yield (59%) (top, Scheme 7). Finally, we selectively carried out the synthesis of *p*-bromophenylmagnesium iodide, which was prepared from 4-bromo-1-iodobenzene (**4b**) and iso-propylmagnesium bromide (**2c**) that reacted with the phenylethynylsulfone **1a** to afford the alkyne **3m** after 6 h at 40 °C. The presence of a bromine in the alkyne **3m** would allow carrying out other transformations.

Based on our previous proposal on the reaction of organolithiums to alkynyl sulfones (supported by experimental evidence and DFT calculations),[16a] we assume a first coordination of the Grignard reagent to the sulfonyl moiety. To explain the regioselectivity obtained in the addition of Grignard reagents to sulfonylacetylenes, the attack of the R′ group at the α position, instead of the β position, is preferred (**A** Scheme 8), and an intramolecular transfer of the nucleophilic alkynyl group. Then, based on our previous observations on the substitution with alkoxy derivatives for the synthesis of ynol-ethers,[16d] we assumed that the formation of *E* (**B**) and *Z* (**C**) isomers could take place (Scheme 8). However, only **C** can evolve to the final alkyne by elimination of the magnesium salt. Therefore, the easy equilibration from **B** to **A** should be responsible to explain a good conversion into the final obtained alkyne.



Scheme 7 Functional group tolerance in the anti-Michael reaction.



Scheme 8 Mechanistic proposal for the reaction of organomagnesium reagents to sulfonylacetylenes **1**.

Experimental

Materials and methods

Tetrahydrofuran was purified by passing through a Pure Solv™ column drying system from Innovative Technology, Inc. Grignard reagents are commercially available (except in indicated cases) and were used as received. Sulfonyl acetylenes **1a** (R = Ph),[15a] **1b** (R = TIPS),[15a] **1c** (R = *t*-Bu),[22] **1d** (R = *n*-Bu),[23] **1e** (R = 4-*t*-$BuO_2CC_6H_4$),[15a] **1f** (R = 4-BrC_6H_4),[15b] **1h** (R = 4-FC_6H_4)[15b] and **1i** (R = 2-$MeOC_6H_4$)[15b] were synthesized following the reported procedures. NMR spectra were acquired on a Bruker AVANCE-II 300 spectrometer, running at 300 and 75 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to the residual solvent signals ($CDCl_3$, 7.26 ppm for ^{1}H NMR). Analytical thin layer chromatography (TLC) was performed using pre-coated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or by phosphomolybdic acid or potassium permanganate stain. Purification of reaction products was carried out by flash chromatography (FC) using silica gel Merck-60.

General procedure A for the synthesis of alkynes

To a solution of **1** (0.2 mmol) in THF (1 ml) under an argon atmosphere and at 0 °C was added a solution of the corresponding magnesium compound (equivalents are indicated in each case). The reaction mixture was stirred, at temperature indicated in each case, until the total consumption of sulfone (monitored by TLC 6 : 1, cHex : AcOEt). The reaction mixture was treated with a saturated solution of NH_4Cl and extracted with Et_2O. The resulting residue was purified by silica gel flash chromatography (solvents indicated in each case).

General procedure B for the synthesis of alkynes

To a solution of **1** (0.2 mmol) in THF (1 ml) under an argon atmosphere and at 0 °C was added phenylmagnesium bromide (3.0 M in THF) (equivalents are indicated in each final product). The reaction mixture was stirred, at temperature indicated in each case, until the total consumption of sulfone (monitored by TLC 6 : 1, chex : AcOEt). The reaction mixture was treated with a saturated solution of NH_4Cl and extracted with Et_2O. The resulting residue was purified by silica gel flash chromatography (solvents indicated in each case).

General procedure C for the synthesis of alkynes

To a solution of **4** (0.48 mmol) in THF (2 ml) under an argon atmosphere and at −20 °C was added i-PrMgBr (1.0 M in THF) (0.4 mmol). The mixture was stirred at −20 °C for 30 min. Then, a solution of sulfone **1a** (0.2 mmol) in THF (0.5 ml) was added and the reaction mixture was stirred, at temperature

indicated in each case, until the total consumption of sulfone (monitored by TLC 6 : 1, chex : AcOEt). The reaction mixture was treated with a saturated solution of NH_4Cl and extracted with Et_2O. The resulting residue was purified by silica gel flash chromatography (solvents indicated in each case).

Characterisation data for synthesised alkynes

But-1-yn-1-ylbenzene (3a). Following the general procedure A from 1-methyl-4-((phenylethynyl)sulfonyl)benzene (**1a**) and 1.0 equivalent of EtMgBr (3.0 M in THF). The product was obtained after 20 min at 0 °C, as a colorless liquid without purification with a yield of 85%. Data for **3a** are in agreement with those described in the literature.[24]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.35 (m, 2H), 7.30–7.23 (m, 3H), 2.42 (q, J = 7.5 Hz, 2H), 1.23 (t, J = 7.5 Hz, 3H).

(5-Methylhex-1-yn-1-yl)benzene (3b). Following the general procedure A from 1-methyl-4-((phenylethynyl)sulfonyl)benzene (**1a**) and 1.0 equivalent of iso-pentylmagnesium bromide (2.0 M in Et_2O). The product was obtained after 20 min at 0 °C, as a colorless oil after purification by column chromatography (pentane) with a yield of 83%. Data for **3b** are in agreement with those described in the literature.[25]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.35 (m, 2H), 7.35–7.24 (m, 3H), 2.42 (t, J = 7.4 Hz, 2H), 1.86–1.70 (m, 1H), 1.52 (td, J = 7.2, 6.0 Hz, 2H), 0.95 (d, J = 6.6 Hz, 6H).

(3-Methylbut-1-yn-1-yl)benzene (3c). Following the general procedure A from 1-methyl-4-((phenylethynyl)sulfonyl)benzene (**1a**) and 1.0 equivalent of i-PrMgCl (1.0 M in THF). The product was obtained after 20 min at 0 °C, as a colorless liquid without purification with a yield of 65%. Data for **3c** are in agreement with those described in the literature.[26]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.35 (m, 2H), 7.31–7.20 (m, 3H), 2.78 (hept, J = 7.0 Hz, 1H), 1.21 (t, J = 7.0 Hz, 6H).

(3,3-Dimethylbut-1-yn-1-yl)benzene (3d). Following the general procedure A from 1-methyl-4-((phenylethynyl)sulfonyl) benzene (**1a**) and 1.0 equivalent of *t*-BuMgBr (1.0 M in THF). The product was obtained after 20 min at 0 °C, as a colorless liquid without purification with a yield of 62%.

Following the general procedure B from 1-((3,3-dimethylbut-1-yn-1-yl)sulfonyl)-4-methylbenzene (**1c**) with 2.0 equivalents of PhMgBr (3.0 M in THF). The product was obtained after 14 h at room temperature, as a colorless liquid after purification by column chromatography (gradient pentane/AcOEt from 1 : 0 to 6 : 1) with a yield of 79%. Data for **3d** are in agreement with those described in the literature.[27]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.35 (m, 2H), 7.30–7.23 (m, 3H), 1.33 (s, 9H).

Pent-4-en-1-yn-1-ylbenzene (3e). Following the general procedure A from 1-methyl-4-((phenylethynyl)sulfonyl)benzene (**1a**) and 1.0 equivalent of allylmagnesium bromide (1.0 M in Et_2O). The product was obtained after 5.5 h at 0 °C, as a colorless oil after purification by column chromatography (pentane) with a yield of 91%. Data for **3e** are in agreement with those described in the literature.[28]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 5.0 Hz, 2H), 7.34–7.27 (m, 3H), 6.00–5.82 (m, 1H), 5.42 (brd, J = 17.0 Hz, 1H), 5.17 (brd, J = 9.9 Hz, 1H), 3.20 (brd, J = 5.1 Hz, 2H).

1,2-Diphenylethyne (3f). Following the general procedure A from 1-methyl-4-((phenylethynyl)sulfonyl)benzene (**1a**) and 1.0 equivalent of PhMgBr (3.0 M in THF). The product was obtained after 30 min at 0 °C, as a white amorphous solid after purification by column chromatography (pentane) with a yield of 67%. Data for **3f** are in agreement with those described in the literature.[29]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.41 (m, 4H), 7.31–7.22 (m, 6H).

1-Methyl-4-(phenylethynyl)benzene (3g). Following the general procedure A from 1-methyl-4-((phenylethynyl)sulfonyl) benzene (**1a**) and 1.0 equivalent of TolMgBr (0.5 M in Et_2O). The product was obtained after 45 min at 0 °C, as a white amorphous solid after purification by column chromatography (pentane) with a yield of 76%. Data for **3g** are in agreement with those described in the literature.[29]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.45 (m, 2H), 7.38 (d, J = 8.1 Hz, 2H), 7.32–7.24 (m, 3H), 7.10 (d, J = 8.1 Hz, 2H), 2.32 (s, 3H).

1-Fluoro-4-(phenylethynyl)benzene (3h). Following the general procedure A from 1-methyl-4-((phenylethynyl)sulfonyl) benzene (**1a**) and 1.0 equivalent of *p*-FC_6H_4MgCl (1.0 M in THF). The product was obtained after 60 min at 0 °C, as a white amorphous solid after purification by column chromatography (pentane) with a yield of 75%. Data for **3h** are in agreement with those described in the literature.[29]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.47 (m, 4H), 7.39–7.31 (m, 3H), 7.05 (t, J = 8.7 Hz, 2H).

1-Methoxy-4-(phenylethynyl)benzene (3i). Following the general procedure A from 1-methyl-4-((phenylethynyl)sulfonyl) benzene (**1a**) and 1.0 equivalent of *p*-$MeOC_6H_4MgBr$ (0.5 M in THF). The product was obtained after 20 min at 40 °C, as a white amorphous solid after purification by column chromatography (pentane) with a yield of 50%. Data for **3i** are in agreement with those described in the literature.[29]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61–7.49 (m, 4H), 7.38–7.30 (m, 3H), 6.89 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H).

2-(Phenylethynyl)thiophene (3j). Following the general procedure A from 1-methyl-4-((phenylethynyl)sulfonyl)benzene (**1a**) and 1.0 equivalent of 2-thienylmagnesium bromide (1.0 M in THF). The product was obtained after 120 min at rt, as a yellow amorphous solid after purification by column chromatography (hexane/AcOEt, 15 : 1) with a yield of 82%. Data for **3j** are in agreement with those described in the literature.[30]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54–7.50 (m, 2H), 7.35–7.33 (m, 3H), 7.30–7.28 (m, 2H), 7.01 (dd, J = 4.9, 3.9 Hz, 1H).

Triisopropyl(phenylethynyl)silane (3k). Following the general procedure B from trimethyl(tosylethynyl)silane (**1b**) and 1.0 equivalent of PhMgBr (3.0 M in THF). The product was obtained after 30 min at 0 °C, as a white amorphous solid after purification by column chromatography (pentane/AcOEt, 95 : 5) with a yield of 57%. Data for **3k** are in agreement with those described in the literature.[31]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.33 (m, 2H), 7.28–7.18 (m, 3H), 1.14–1.08 (m, 21H).

***tert*-Butyl 4-(phenylethynyl)benzoate (3l).** Following the general procedure B from *tert*-butyl 4-(tosylethynyl)benzoate (**1e**) and 1.0 equivalent of PhMgBr (3.0 M in THF). The product was obtained after 60 min at 0 °C, as a white amorphous solid after purification by column chromatography (gradient: pentane to pentane/AcOEt, 9 : 1) with a yield of 88%.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.48–7.45 (m, 2H), 7.35–7.24 (m, 3H), 1.53 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 132.1, 131.8, 131.7, 129.7, 129.0, 128.8, 127.8, 123.2, 92.3, 89.2, 81.6, 28.6.

HRMS (ESI+): m/z calculated for $C_{19}H_{19}O_2$ [M + H^+]: 279.1385, found: 279.1380 [M + H^+].

1-Bromo-4-(phenylethynyl)benzene (3m). Following the general procedure A from 1-bromo-4-(phenylethynyl)benzene (**1f**) and 1.0 equivalent of PhMgBr (3.0 M in THF). The product was obtained after 60 min at 0 °C, as a white amorphous solid after purification by column chromatography (pentane) with a yield of 89%.

The product was also obtained from **4b** and **1a** following the general procedure C, after 6 h at 40 °C, as a white amorphous solid after purification by column chromatography (gradient pentane/AcOEt from 19 : 1 to 6 : 1) with a yield of 46%. Data for **3m** are in agreement with those described in the literature.[32]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.34 (m, 4H), 7.34–7.21 (m, 3H), 7.19–7.08 (m, 2H).

1-Methyl-4-(phenylbuta-1,3-diyn-1-yl)benzene (3n). To a solution of Tol-C≡CH (0.13 mmol) in THF (0.4 ml) under an argon atmosphere and at rt was added EtMgBr (3.0 M in THF) (0.13 mmol). The mixture was stirred at rt for 30 min. Then, a solution of sulfone **1a** (0.2 mmol) was added and the reaction mixture was stirred for another 20 min at rt. The reaction mixture was treated with a saturated solution of NH_4Cl and extracted with Et_2O. The resulting residue was purified by silica gel flash chromatography (pentane) obtaining the diyne **3n** as a white amorphous solid with a yield of 65%. Data for **3n** are in agreement with those described in the literature.[33]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.48 (m, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.39–7.31 (m, 3H), 7.15 (d, J = 8.0 Hz, 2H), 2.37 (s, 3H).

1-Fluoro-4-(phenylbuta-1,3-diyn-1-yl)benzene (3o). Following the general procedure A from 1.0 equivalent of 1-fluoro-4-(tosylethynyl)benzene (**1h**) and 5.0 equivalents of PhC≡CMgBr (1.0 M in THF). The product was obtained after 80 minutes at rt, as a white amorphous solid after purification by column chromatography (pentane) with a yield of 62%. Data for **3o** are in agreement with those described in the literature.[20f]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–7.49 (m, 4H), 7.40–7.30 (m, 3H), 7.04 (t, J = 8.7 Hz, 2H).

1-Bromo-4-(phenylbuta-1,3-diyn-1-yl)benzene (3p). Following the general procedure A from 1.0 equivalent of 1-bromo-4-(tosylethynyl)benzene (**1f**) and 5.0 equivalents of PhC≡CMgBr (1.0 M in THF). The product was obtained after 80 minutes at rt, as a white amorphous solid after purification by column chromatography (pentane) with a yield of 83%. Data for **3p** are in agreement with those described in the literature.[34]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 7.6 Hz, 2H), 7.48 (d, J = 8.7 Hz, 2H), 7.41–7.31 (m, 5H).

1-Methoxy-4-(phenylbuta-1,3-diyn-1-yl)benzene (3q). Following the general procedure A from 1.0 equivalent of 1-methoxy-4-(tosylethynyl)benzene (**1i**) and 5.0 equivalents of PhC≡CMgBr (1.0 M in THF). The product was obtained after 2.5 h at 40 °C, as a colourless oil after purification by column chromatography (gradient pentane/AcOEt from 1 : 0 to 9 : 1) with a yield of 84%. Data for **3q** are in agreement with those described in the literature.[35]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.48 (m, 3H), 7.40–7.30 (m, 4H), 6.97–6.86 (m, 2H), 3.91 (s, 3H).

Penta-1,3-diyn-1-ylbenzene (3r). Following the general procedure A from 1.0 equivalent of **1a** and 1.5 equivalents of MeC≡CMgBr (0.5 M in THF). The product was obtained after 180 min at 40 °C, as a white amorphous solid after purification by column chromatography (pentane) with a yield of 44%. Data for **3r** are in agreement with those described in the literature.[36]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (dd, J = 7.6, 1.8 Hz, 2H), 7.35–7.27 (m, 3H), 2.02 (s, 3H).

Ethyl 4-(phenylethynyl)benzoate (3s). The product was obtained from **4a** and **1a** following the general procedure C, after 14 h at 0 °C, as a white amorphous solid after purification by column chromatography (pentane) with a yield of 59%. Data for **3s** are in agreement with those described in the literature.[37]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 8.2 Hz, 2H), 7.54–7.40 (m, 4H), 7.30–7.22 (m, 3H), 4.36–4.20 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H).

Conclusions

In conclusion, we have demonstrated that the anti-Michael addition of Grignard reagents to sulfonylacetylenes constitutes an efficient methodology to obtain different alkynes under mild reaction conditions, easy procedures, without using low temperatures and an extremely dried atmosphere. In addition, we have proved that alkynyl-Grignard derivatives are appropriate derivatives for the synthesis of asymmetric diynes, which are difficult to obtain by other methodologies. Moreover, the use of Grignard reagents allows obtaining alkynes with substituents sensitive to organolithium reagents like halogens, or ester groups.

Acknowledgements

Financial support from the Spanish Government CTQ2012-35957 (MINECO) and CTQ2015-64561-R (MINECO/FEDER) is gratefully acknowledged. F. E. is thankful to the Spanish

government for a FPI fellowship, and L. B. is thankful to the Université Badji Mokhtar Annaba for a predoctoral stay grant.

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