Synthesis J. A. Cabezas et al. Feature

One-Pot Conversion of Aldehydes and Ketones into 1-Substituted and 1,4-Disubstituted 1,3-Enynes

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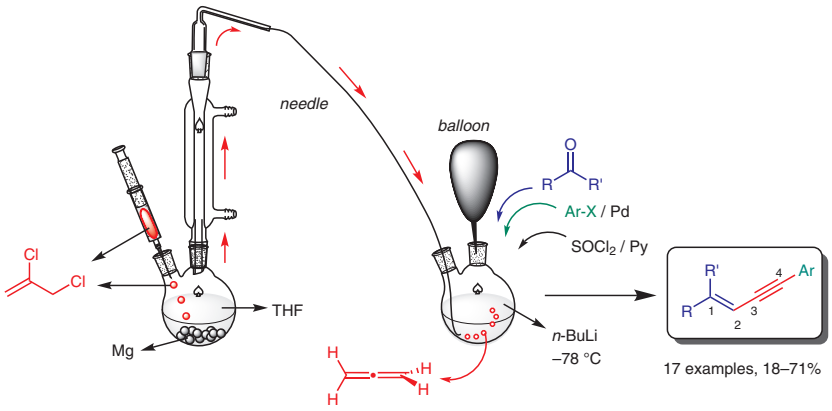
This article is dedicated to Professor Cam Oehlschlager, senior supervisor and friend



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Abstract Sequential treatment of 2,3-dichloropropene with magnesium and *n*-BuLi generates the operational equivalent of 1,3-dilithiopropyne, which upon treatment with aldehydes or ketones, produces the corresponding alkoxy lithium acetylide intermediates. Reaction of this alkoxide with tosyl chloride, and *t*-BuLi produces 1-substituted, or 1,1-disubstituted 1,3-enynes in a one-pot reaction. When this lithium acetylide intermediates, obtained by this procedure, were used to perform palladium-catalyzed cross-coupling reactions, followed by addition of thionyl chloride and pyridine, 1,4-disubstituted or 1,1,4-trisubstituted 1,3-enynes were obtained in a one-pot protocol.

Key words 1,3-dilithiopropyne, lithium acetylides, 1,3-enynes, palladium catalysis, cross-coupling, propargylation

Introduction

1,3-Enynes are found widely in many natural products and exhibit diverse biological activities. Some examples of these are the marine natural products phorbasides A (**1**) and B–E, highly cytotoxic macrolides isolated from the Western Australian marine sponge *Phorbas* sp.,[1] and the structurally related (–)-callipeltosides A, B (**2**), and C (Figure 1). These are active against human bronchopulmonary non-small-cell lung carcinoma (NSCLC-N6 and P388 cell lines),[2] and were first isolated in 1996 from the New Caledonian lithistida sponge *Callipelta* sp.[3] Additionally, the 1,3-enyne pyrrhoxanthin (**3**) has been isolated from the chloroplasts of dinoflagellates *Gyrodinium resplendens*,[4] *Gymnodinium nelsoni*,[5] and a natural bloom of *Ceratium* spp.[6] Other examples of natural products containing the 1,3-enyne moiety are the enediynes: neocarzinostatin (**4**) is the first enediyne antitumor antibiotic, isolated in 1965 from a culture of *Streptomyces carzinostaticus*,[7,8] whose antitumor activity[9] is due to the cleavage of DNA in cells,[10] provoked by this chromophoric moiety (its protein component is essential in transporting and stabilizing the drug).[10c] Kedarcidin chromophore (**5**) is a chromoprotein isolated from the fermentation broth of an actinomycete;[11,12] the potent antitumor agent dynemicin A (**6**)[13] was isolated from the bacteria *Micromonospora chersina*;[14] and the potent antitumor agent calicheamicin γ_1[15] (**7**) is derived from the bacterium *Micromonospora echinospora*, which has been marketed as targeted therapy against non-solid tumors of acute myeloid leukemia. Other interesting examples are histrionicotoxins (**8**),[16] gephyrotoxin (**9**),[17] and *N*-methyldecahydroquinoline alkaloids,[18] found in the skin of poison frogs from the family Dendrobatidae (*Dendrobates histrionicus*), as well as xerulin (**10**), an inhibitor of cholesterol biosynthesis, isolated from cultures of *Xerula melanotricha* Dörfelt.[19]

The 1,3-enyne framework is also present in some important pharmaceutical compounds. Terbinafine (**11**), commercially known as lamisil, was the first pharmaceutical agent to contain an (*E*)-1,3-enyne in its chemical structure.[20] It was discovered in 1984,[21] as a synthetic modification of naftifine (Exoderil), and it has been used commercially since 1996, in oral and topical treatment of skin and toenail infections (onychomycosis) caused by dermatophytes such as *Trichophyton rubrum*[22] and *Trichopyton mentagrophytes*.[22] Another important example is oxamflatin (**12**), a growth inhibitor of various cancer cells.[23] It has been found that oxamflatin has *in vitro* antiproliferative activity against various mouse and human tumor cell lines, and *in vivo* antitumor activity against B16 melanoma.

1,3-Enynes are also used as important building blocks in organic synthesis.[24] Numerous methods for the preparation of 1,3-enynes have been developed,[25] and, among those, palladium-catalyzed Sonogashira cross-coupling[26] of termi-

nal acetylenes with vinyl halides is widely used.[27] Other methods include palladium-catalyzed alkynylation[28] and the direct transition-metal-catalyzed coupling of alkynes.[29]

We report herein a new method for the efficient, one-pot conversion of aldehydes and ketones into 1,3-enynes.

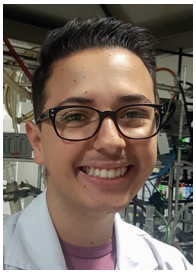
Results and Discussion

We previously reported that treatment of allene **13** with two equivalents of *n*-BuLi produced the operational equivalent of 1,3-dilithiopropyne (**14**; Scheme 1, method A).[30] This dianion **14** added regiospecifically to aromatic aldehydes and ketones **15** to produce, after protonolysis, homopropargyl alcohols **17** in very good yields. Since the high cost of allene **13** considerably restricts the use of this methodology, we later developed a procedure to prepare the above dianion **14** by treatment of propargyl bromide (**18**) with *n*-BuLi, in the presence of TMEDA (method B).[31] The organometallic intermediate **14** thus generated reacts with aldehydes and ketones, producing the corresponding homopropargyl alcohols **17** in excellent yields.[31] Recently we showed that this dianion **14** (or its equivalent) could be prepared in the absence of TMEDA, by sequential treatment of 2,3-dichloropropene (**19**) with magnesium and *n*-BuLi, and it also reacted with aldehydes and ketones in similar yields (method C).[32]

Biographical Sketches

Jorge A. Cabezas was born in San José, Costa Rica, and studied chemistry at the University of Costa Rica, where he obtained B.Sc. and Licentiate degrees in chemistry. He obtained his Ph.D. in chemistry (1990–1994) at Simon Fraser University (SFU), British Columbia, Canada, under the supervision of Professor Cam Oehlschlager, where he worked on mechanistic, spectroscopic, and synthetic aspects of the stannylcupration of acetylenic ethers. After finishing his Ph.D., he spent one more year (1994–1995) at SFU as a postdoctoral fellow working on the synthesis of pheromones. He returned to the University of Costa Rica and in 1996 was promoted to Associate Professor and became Full Professor in 1999. He is the recipient of several awards: 'TWAS-CONICIT for Young Scientists' (1998) from the National Council of Scientific and Technological Research, 'Contributions to Creativity and Excellence' (2002) from the Florida Ice & Farm, 'National Prize in Science Clodomiro Picado Twight' (2006) from the Ministry of Science and Technology and the Ministry of Culture of the Government of Costa Rica, and 'Chemist of the Year' (2007) from the National Association of Chemists of Costa Rica. Also, he has been frequently recognized for excellence in teaching. His research interests involve the development of new synthetic methodologies, organometallic chemistry, and the synthesis of pheromones. His hobbies include nature photography, arts, drawing, music, high-end audio, home-studio acoustics design, literature, and long walks with his Rottweilers.

Rebeca Poveda was born in Cartago, Costa Rica. She is finishing her undergraduate studies at the School of Chemistry, University of Costa Rica, where she has worked as a teaching assistant in analytical and organic chemistry lab courses. Currently, she works as a research assistant, under the supervision of Professor Cabezas, on new synthetic methodologies using organometallics and its application to the synthesis of enynes and antitumor compounds.



José Á. Brenes was born in Cartago, Costa Rica, in 1993. He obtained his B.Sc. degree at the University of Costa Rica. He carried out his M.Sc. thesis research under the guidance of Prof. Cabezas on new methodologies for the organometallic synthesis of enynes and their application in total synthesis of antifungal molecules. Also during this period he worked as an instructor at the UCR. Recently, he joined Chem-Tica International, where he works on the synthesis of insect pheromones for the biological control of plagues. He likes cooking, hiking, club culture, dancing, Japanese culture, ufology, reading, and traveling to new places.

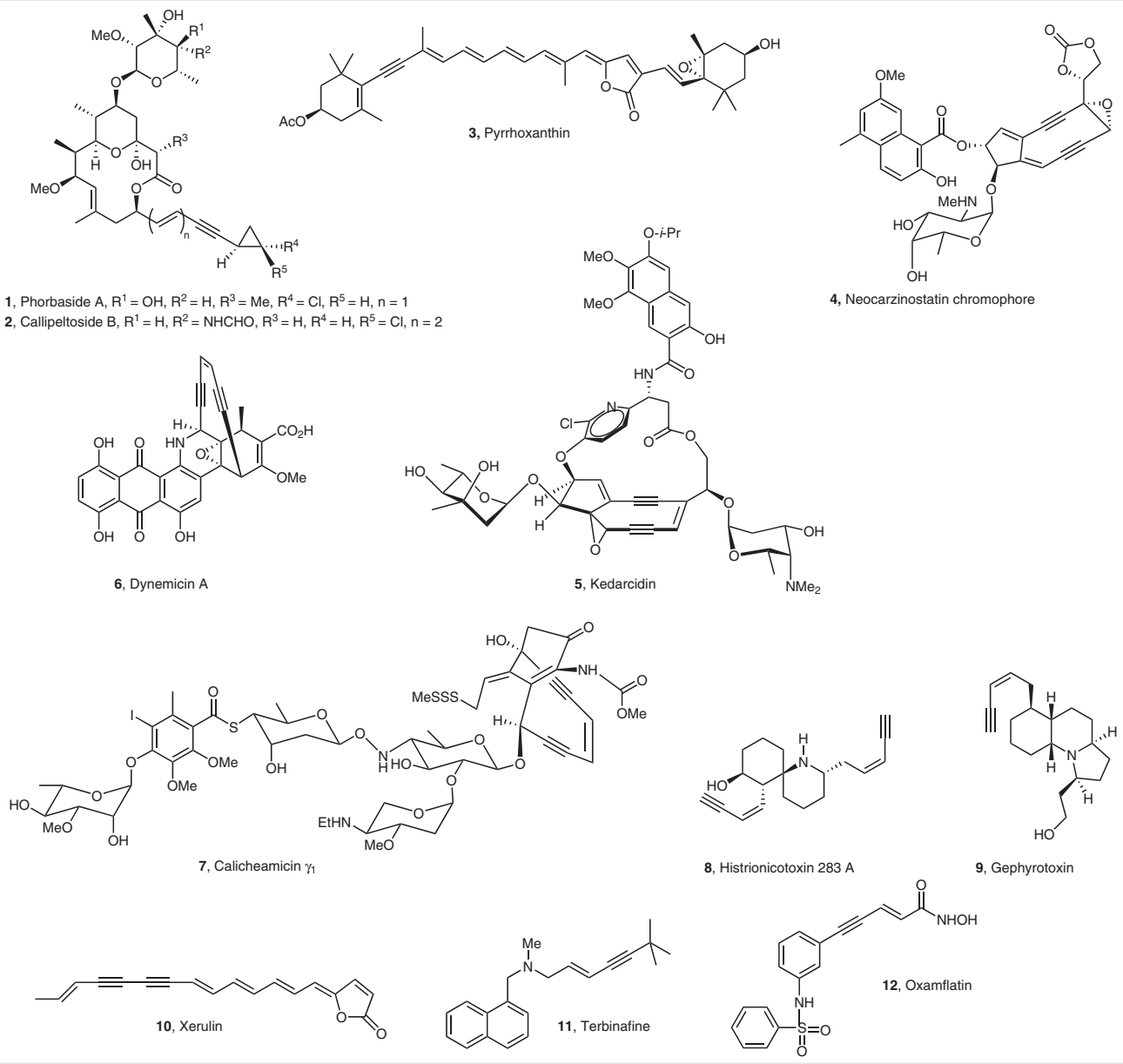
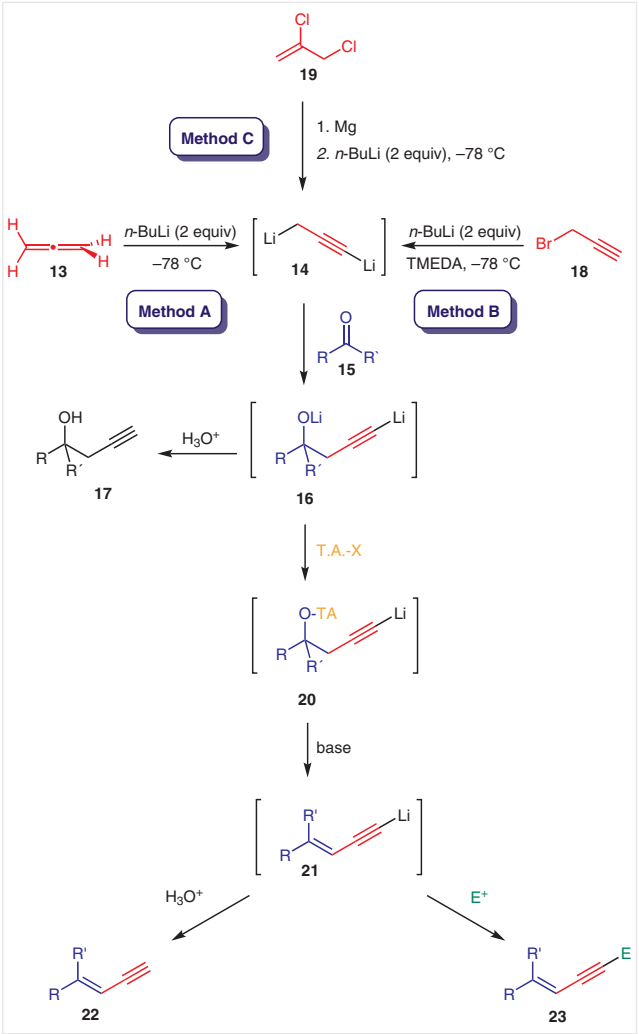


Figure 1 Examples of some biologically active compounds containing the 1,3-enyne framework

We envisioned that the lithium alkoxide intermediate **16** formed in the above protocols could be selectively reacted with a trapping agent (T.A.) at the alkoxide over the acetylide terminus, to convert it into a good leaving group, as in **20**, to obtain, after basic treatment and protonolysis, the corresponding 1,3-enyne **22** (Scheme 1). An additional advantage of this methodology is that the lithium acetylide intermediate **21** obtained through this methodology could be reacted with an electrophile (E^+) to produce 4-substituted enynes **23** in a one-pot reaction.

Synthesis of 1,3-Enynes Type 22

Initial reactions involved treatment of propargyl bromide (**18**) with *n*-BuLi in the presence of TMEDA (Scheme 1, method B), followed by addition of benzophenone **24** to produce the corresponding lithium alkoxide intermediate **25** (Scheme 2). Subsequent reaction of intermediate **25** with ethyl chloroformate was not selective, resulting in

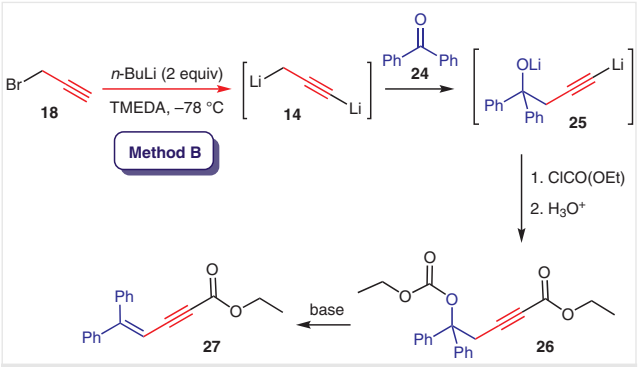


Scheme 1 Methods for preparation of dianion **14**, and its application to the synthesis of 1,3-enynes **22** and **23**

C- and O-carbonylation, forming acetylenic ester **26**. The presence of TMEDA probably enhances the nucleophilicity of the acetylide in **25**, favoring C-carbonylation.

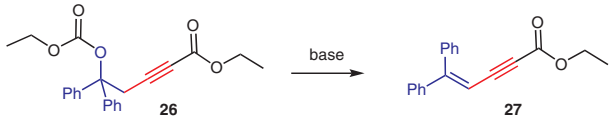
Acetylenic ester **26** was isolated, dissolved in THF, and treated with LDA to obtain the corresponding substituted enyne **27** in only 10% yield (Table 1, entry 1). Using KOH in MeOH improved the yield to 42% (entry 2). The use of *t*-BuLi, as a base for this elimination step, improved the yield of **27** to 87 % (entry 3). Surprisingly, several attempts to perform this transformation on benzophenone **24** to give enyne **27** in a one-pot reaction resulted in very poor yields. Perhaps the presence of TMEDA interferes in the elimination.

We decided to prepare dianion **14** from 2,3-dichloropropene (**19**) and then treat it with benzophenone (**24**), followed by sequential addition of ethyl chloroformate and



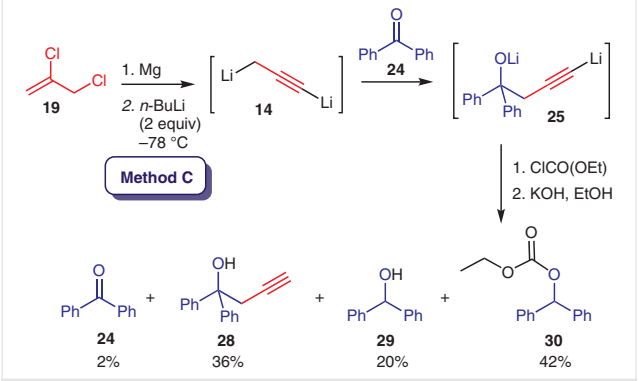
Scheme 2 Initial synthesis of enyne **27** from benzophenone **24** and dianion **14**

Table 1 Effect of Base on the Synthesis of **27** from **26**



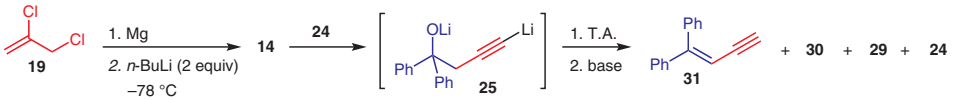
Entry	Base	Yield (%) of **27**
1	LDA	10
2	KOH/MeOH	42
3	*t*-BuLi	87

treatment with KOH in ethanol (Scheme 3). In this case, the expected enyne **27** was not obtained. Instead, a mixture of the corresponding homopropargyl alcohol **28**, benzhydrol (**29**), carbonate **30**, and unreacted benzophenone (**24**) was obtained (Scheme 3; Table 2, entry 1). Benzhydrol **29** is obtained from reduction of benzophenone **24** and its reaction with ethyl chloroformate produces carbonate **30**. We have previously observed this type of reduction in this reaction system.[32]



Scheme 3 Initial reactions of benzophenone **24** with dianion **14**, generated from 2,3-dichloropropene **19**

Table 2 Effect of Reaction Conditions on Synthesis of Enyne **31**



Entry	Trapping agent (T.A.)	Base	Yield (%)[a]				
			31	**30**	**29**	**28**	**24**
1	ClC(O)(OEt)	KOH/EtOH	–	42	20	36	2
2	ClC(O)(OEt)	*t*-BuLi	–	47	5	35	13
3	$ClP(O)(OEt)_2$	*t*-BuLi	46		4	16	4
4	TsCl/HMPA	KOH/MeOH	40		30	14	
5	TsCl/HMPA	*t*-BuLi	66			34	–

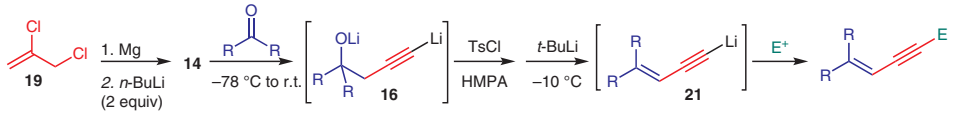
[a] Yields were determined by GC.

To determine the best reaction conditions for performing this transformation in a one-pot process, we studied different alkoxide trapping reagents and different bases. As described above, when ethyl chloroformate was used as a trapping reagent, and KOH/EtOH as the base for the elimination step, no enyne **31** was obtained (Table 2, entry 1). Furthermore, the use of *t*-BuLi, for the elimination step, did not produce the desired product (entry 2). When intermediate **25** was reacted with diethyl chlorophosphate, followed by elimination with *t*-BuLi, terminal enyne **31** was obtained in 46% yield (entry 3). Use of tosyl chloride, as the alkoxide trapping agent, and KOH in methanol, as base, afforded the desired enyne **31** in 40% yield (entry 4). When this reaction was repeated using the stronger base *t*-BuLi, enyne **31** was obtained in 66% isolated yield (entry 5).

Apparently, the reaction of intermediate **25** (prepared from **19**) with diethyl chlorophosphate or tosyl chloride was regioselective, and only reaction at the oxygen occurred. This was corroborated by the formation of only the non-substituted enyne **31** (Table 2, entries 3–5). This behavior contrast with the preliminary results obtained when dianion **14** was prepared from propargyl bromide (**18**) in TMEDA (Scheme 2, Table 1). One advantage of the latter methodology is that the corresponding lithium acetylide intermediate **21** could be derivatized *in situ*, producing 4-substituted enynes **23**.

To demonstrate the reproducibility of this methodology under the best reaction conditions developed (Table 2, entry 5), several 1,3-enynes were prepared from diverse aldehydes and ketones (Table 3). When aldehydes **32**, **36**, and **38** were used as the carbonyl component, mixtures of *trans*- and *cis*-enynes, largely favoring the *trans* isomer, were obtained (entries 2, 4, and 5). The use of acetophenone (**34**) and cyclopropyl phenyl ketone (**40**) produced mixtures of *E* and *Z* isomers. In both cases, the *E* isomers were obtained as the major isomers (entries 3 and 6).

Table 3 Conversion of Aldehydes and Ketones into 1,3-Enynes



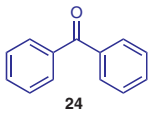
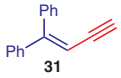
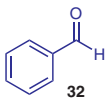
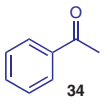
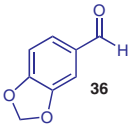
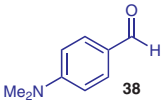
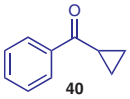
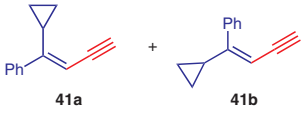
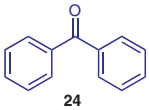
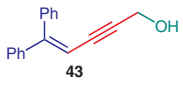
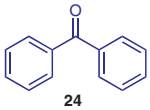
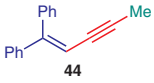
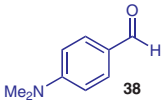
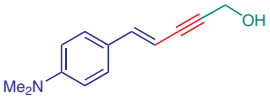
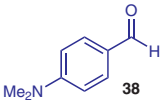
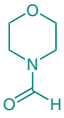
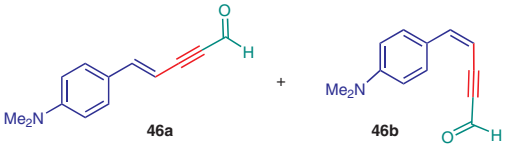
Entry	Aldehyde or Ketone	Electrophile (E^+)	Product(s)	Yield (%)[a]
1	 **24**	H_3O^+	 **31**	66
2	 **32**	H_3O^+	 **33a** + **33b** (*trans*/*cis* 78:22)	68

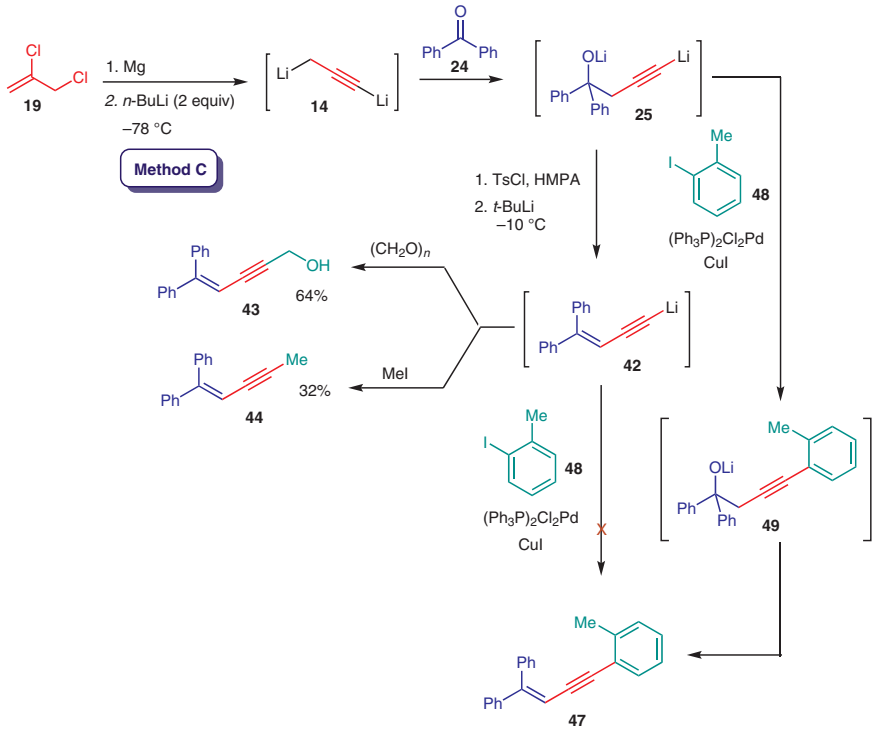
Table 3 (continued)

Entry	Aldehyde or Ketone	Electrophile (E^+)	Product(s)	Yield (%)[a]
3	 **34**	H_3O^+	 **35a** + **35b** (*E*/*Z* 84:16)	61
4	 **36**	H_3O^+	 **37a** + **37b** (*trans*/*cis* 73:27)	58
5	 **38**	H_3O^+	 **39a** + **39b** (*trans*/*cis* 88:12)	53
6	 **40**	H_3O^+	 **41a** + **41b** (*E*/*Z* 90:10)	40
7	 **24**	$(CH_2O)_n$	 **43**	64
8	 **24**	MeI	 **44**	32
9	 **38**	$(CH_2O)_n$	 **45a** (*trans*/*cis* 99:1)	20
10	 **38**		 **46a** + **46b** (*trans*/*cis* 87 : 13)	18

[a] Yields are of isolated products, purified by column chromatography.

Synthesis of 4-Substituted 1,3-Enynes

As stated before, one of the advantages of this methodology is that the lithium acetylide intermediate **21**, obtained after addition of dianion **14** to aldehydes or ketones, and elimination reaction, can be derivatized, by addition of an electrophile, to obtain a 1,3-enyne substituted at position 4, in a one-pot reaction (Scheme 1). When reaction of benzophenone (**24**) with dianion **14** under the above reaction conditions was repeated and the final intermediate **42** was quenched with paraformaldehyde, instead of NH_4Cl, acetylenic alcohol **43** was obtained in 64% overall yield in a one-pot reaction (Scheme 4, Table 3, entry 7). When same intermediate **42** was quenched with methyl iodide, enyne **44** was obtained in 32% overall yield (Scheme 4, Table 3, entry 8).



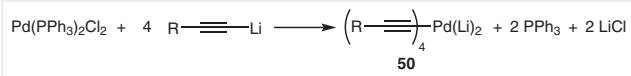
Scheme 4 Synthesis of 1,4-disubstituted 1,3-enynes in a one-pot reaction

Particularly important are the reactions where *p*-(dimethylamino)benzaldehyde **38** was reacted with dianion **14** and, after the elimination reaction, paraformaldehyde or *N*-formylmorpholine was added as a second electrophile. In these cases, highly functionalized *trans*-enynes **45** and **46** were obtained, respectively, which are not easily accessible by other methodologies (Table 3, entries 9 and 10). Although formylation with *N*-formylmorpholine gives a low yield, the highly functionalized aldehyde **46** is obtained in a one-pot reaction.

Palladium-Catalyzed Cross-Coupling Reactions of Acetylenic Intermediates. Synthesis of 1,4-Disubstituted and 1,1,4-Trisubstituted 1,3-Enynes

Our final objective was to perform *in situ* palladium-catalyzed cross-coupling reactions on lithiated acetylenic intermediates such as **42** (Scheme 4), to obtain 1,3-enynes substituted at the terminal acetylenic carbon with an aromatic group (e.g., **47**). Initial reactions of intermediate **42**, prepared as outlined in Scheme 4, with *o*-iodotoluene (**48**) in the presence of catalytic amounts of $[PdCl_2(PPh_3)_2]$ and CuI failed to produce enyne **47**.

We considered that a highly coordinating solvent such HMPA, used in the tosylation of intermediate **25**, might strongly coordinate with palladium, interfering with its catalytic function. We have previously observed this type of behavior with TMEDA.[32] On the other hand, it has been reported that the palladium-catalyzed cross-coupling reaction between lithium acetylides and aromatic halides, in the presence of catalytic amounts of the palladium complex (without CuI), produces only very low yields of the desired alkynylation products.[28] Thus, the desired reaction is difficult to achieve, probably because the highly nucleophilic alkynyllithiums act as catalyst poisons by displacing the ligands (i.e., PPh_3, Cl) from the palladium complex, forming lithium palladates **50** that do not exhibit catalytic activity (Scheme 5).[33] This coupling reaction can be achieved if a stoichiometric amount of Pd complex is used.[28,33] This probably explains why palladium-catalyzed couplings between lithium acetylide **42** and *o*-iodotoluene (**48**) were unsuccessful under these conditions. We reacted acetylide **25** with *o*-iodotoluene (**48**) in the presence of $[PdCl_2(PPh_3)_2]$, but without CuI, and no product was obtained. This result is in agreement with Negishi's results (Scheme 5).[33]

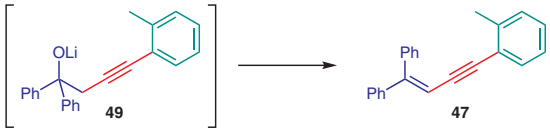


Scheme 5 Poisoning of palladium complex by an excess of lithium acetylide

To overcome these difficulties, we decided to perform first the palladium cross coupling, on the lithium acetylide intermediate **25** to obtain lithium alkoxide **49** (Scheme 4).

In this way, the palladium cross coupling would be performed without HMPA. Thus, when acetylide **25** was reacted with *o*-iodotoluene (**48**) in the presence of catalytic amounts of [$PdCl_2(PPh_3)_2$] and CuI, conditions used in the Sonogashira reaction, the alkoxide intermediate **49** was successfully obtained, as verified by GC-MS analysis of a quenched aliquot of the reaction mixture. Surprisingly, addition of tosyl chloride and HMPA to this mixture, followed by reaction with *t*-BuLi, failed to produce the desired enyne **47** (Table 4, entry 1).

Table 4 Conversion of Alkoxide Intermediate **49** into Enyne **47**



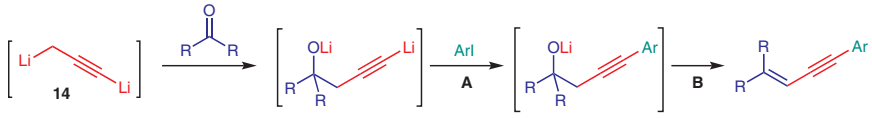
Entry	Reaction conditions	Yield (%)[a]
1	TsCl/HMPA, −78 °C to r.t., then *t*-BuLi, −10 °C	0
2	Me_3SiCl, then *t*-BuLi	0
3	$ClP(O)(OEt)_2$, then *t*-BuLi	0
4	DEAD, Ph_3P	0
5	pyridine, then $SOCl_2$	75

[a] Yield based on total conversion from benzophenone.

We decided to treat alkoxide **49** with trimethylsilyl chloride, to prepare the corresponding silyl ether, followed by treatment with *t*-BuLi (Table 4, entry 2). We envisioned the removal of a propargylic proton and generation of conditions similar to the Peterson olefination.[34] In this case, enyne **47** was not obtained. Reaction of intermediate **49** with diethyl chlorophosphate, followed by treatment with *t*-BuLi, also failed to produce enyne **47** (entry 3). We attempted reaction of **49** with DEAD and Ph_3P (Mitsunobu conditions),[35] trying to produce triphenylphosphine oxide as driving force for the elimination reaction, but also in this case enyne **47** was not produced (entry 4). Finally, treatment of intermediate **49** with pyridine, followed by addition of thionyl choride, afforded the desired enyne **47** in very good overall yield (entry 5).

Treatment of intermediate **25** with 4-iodo-1-nitrobenzene (**51**) and *o*-iodoanisole (**52**) under the above developed reaction conditions produced enynes **53** and **54** respectively (Table 5, entries 2 and 3). It is unclear why, under our reaction conditions (catalytic amounts of Pd and Cu),[32] the coupling reaction of acetylide intermediates (i.e., **25**) with aromatic iodides was very successful (entries 1–3) when compared with the conditions described in Scheme 5. Perhaps the presence of catalytic amounts of CuI (5–10%) account for this success. A possible explanation is that transmetalation of lithium intermediates (i.e., **25**) with CuI and the subsequent palladium catalytic cycle is much faster than the poisoning of the palladium complex.

Table 5 Synthesis of 1,4-Disubstituted and 1,1,4-Trisubstituted 1,3-Enynes



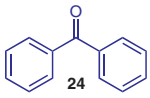
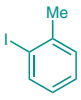
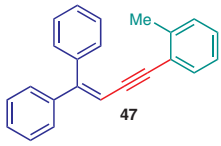
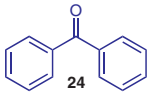
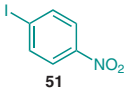
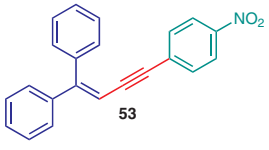
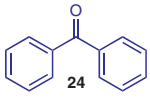
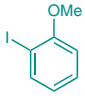
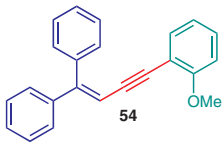
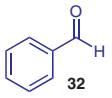
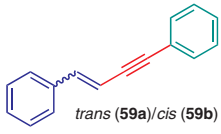
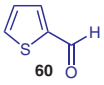
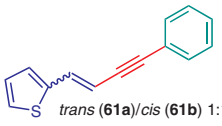
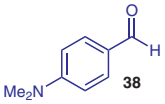
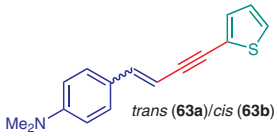
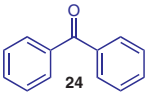
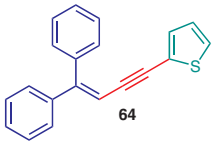
Entry	Carbonyl compound	ArI	Conditions	Product(s)	Yield (%)[a]
1	 24	 48	A. $Pd(PPh_3)_4$, CuI B. $SOCl_2$, py	 47	71
2	 24	 51	A. $Pd(PPh_3)_4$, CuI B. $SOCl_2$, py	 53	68
3	 24	 52	A. $Pd(PPh_3)_4$, CuI B. $SOCl_2$, py	 54	60

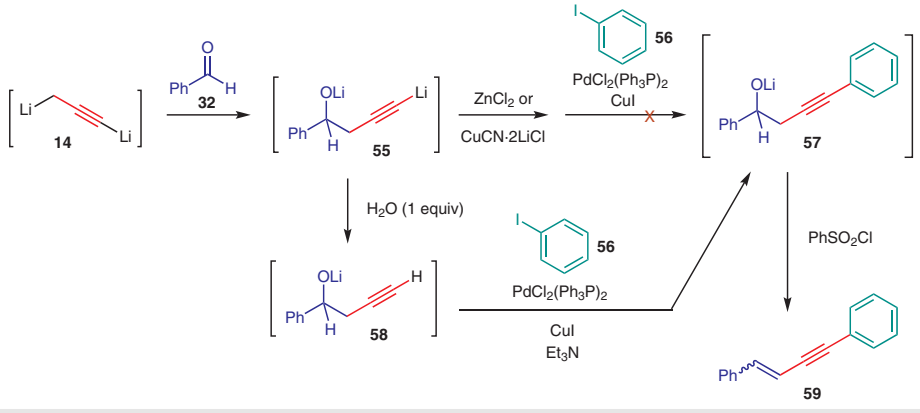
Table 5 (continued)

Entry	Carbonyl compound	ArI	Conditions	Product(s)	Yield (%)[a]
4	 32	 56	A. H_2O (1 equiv), Et_3N, $[PdCl_2(PPh_3)_2]$, CuI B. $PhSO_2Cl$	 *trans* (**59a**)/*cis* (**59b**) 1:1	53
5	 60	 56	A. H_2O (1 equiv), Et_3N, $[PdCl_2(PPh_3)_2]$, CuI B. $PhSO_2Cl$	 *trans* (**61a**)/*cis* (**61b**) 1:1	35
6	 38	 62	A. H_2O (1 equiv), Et_3N, $[PdCl_2(PPh_3)_2]$, CuI B. $PhSO_2Cl$	 *trans* (**63a**)/*cis* (**63b**) 7:3	25
7	 24	 62	A. H_2O (1 equiv), Et_3N, $[PdCl_2(PPh_3)_2]$, CuI B. $PhSO_2Cl$	 64	43

[a] Overall yields of isolated compounds, after purification by chromatography.

We decided to explore the palladium coupling reaction under different conditions, and thus transmetalation of lithium acetylide intermediate **55** was performed (Scheme 6). We attempted the palladium-catalyzed cross coupling step under Negishi conditions.[36] Thus, treatment of benzaldehyde **32** with dianion **14** (generated from 2,3-dichloropropene (**19**) according to Scheme 4) produced the corresponding alkoxyalkyne **55**, which was treated with an ethereal solution of $ZnCl_2$ (2 equiv). This was followed by addition of iodobenzene (**56**) and a catalytic amount of $Pd(PPh_3)_4$. Surprisingly, this reaction sequence failed to produce any coupling product. We attempted this reaction adding CuCN·2LiCl (1 and 2 equiv) to intermediate **55** instead of $ZnCl_2$, followed by addition of iodobenzene (**56**) and $Pd(PPh_3)_4$. In this case, no coupling product was observed either (Scheme 6). This reaction was repeated several times without any positive result.

In a typical Sonogashira reaction,[26] an acetylene is converted, by means of an amine, into a copper acetylide in catalytic amounts (~5% CuI). Under our reaction conditions, we were coupling an alkoxy lithium acetylide intermediate (i.e., **55**), presumably through a copper acetylide, under palladium catalysis, with an aromatic iodide. We envisioned that lithium acetylide intermediate in **55** could be selectively protonated over the lithium alkoxide moiety, because of the pK_a differences (pK_a RC≡CH ~25; pK_a ROH ~16) of the



Scheme 6 Transmetalation reactions of intermediate **55** and synthesis of enyne **59**

conjugated acids. Reaction of lithium acetylide with water (pK_a ~16) should be largely favored (K_{eq} ~10^9) over reaction of alkoxide with water (pK_a ~1). Thus, we intended to protonate lithium acetylide selectively to perform a palladium cross-coupling reaction under Sonogashira conditions.

Dianion **14** was prepared by reaction of allene **13** generated from excess of 2,3-dichloropropene **19** (20 mmol) with *n*-BuLi (1.70 mmol). Assuming a quantitative reaction, then 1,3-dilithiopropyne (**14**; 0.85 mmol) should react with benzaldehyde (**32**; 0.60 mmol) (Scheme 6). After this reaction, intermediate **55** (0.60 mmol) should be produced and a portion of dianion **14** (0.25 mmol) should remain unreacted. To protonate unreacted dianion **14** and the lithium acetylide part in **55**, water (1.10 mmol, 20 µL) should be used.

Benzaldehyde **32** was reacted with **14** at –78 °C and the mixture was warmed to room temperature over 3 hours; the addition of water (10–20 µL) in THF (5 mL) followed (Scheme 6). After stirring for 5 minutes, a THF solution (5 mL) of iodobenzene (**56**) and [$PdCl_2(PPh_3)_2$], triethylamine, and CuI were sequentially added. After stirring at room temperature overnight, intermediate **55** was consumed and cross-coupling product **57** was obtained. This was verified by GC-MS of a quenched aliquot of the reaction mixture. The mixture was treated with benzenesulfonyl chloride to obtain, after aqueous workup, a mixture of *cis*- and *trans*-enyne **59** (Table 5, entry 4). Treatment of thiophene-2-carboxaldehyde (**60**) under same reaction conditions produced an isomeric mixture of enyne **61** (entry 5). Also *p*-(dimethylamino)benzaldehyde (**38**) was sequentially reacted with dianion **14** and 2-iodothiophene (**62**) under identical conditions, to provide a *cis*/*trans* mixture of enyne **63** (entry 6). Finally, treatment of benzophenone (**24**) under the above reaction conditions and coupling with 2-iodothiophene (**62**) gave product **64** (entry 7). When aldehydes are used instead of ketones as starting materials, the final elimination step has to be performed using $PhSO_2Cl$ instead of $SOCl_2$/py. The latter gave the corresponding chlorides by a substitution reaction on the alkoxide carbon.

Conclusion

In summary, we have developed a protocol for the conversion of aldehydes and ketones into 1-substituted and 1,1-disubstituted enynes in a one-pot reaction in good yields. The advantage of this methodology is that the lithium acetylide intermediate formed in this procedure can be further functionalized, by the addition of an electrophile to obtain highly functionalized enynes. We have also developed experimental conditions to perform palladium-catalyzed cross-coupling reactions on lithium alkoxy acetylide intermediates to obtain 1,4-disubstituted and 1,1,4-trisubstituted enynes in one-pot reactions. Original conditions developed for the palladium cross coupling gave better yields than the conditions where a controlled protonolysis was intended. Probably in the latter case, a small excess of water can also protonate the alkoxide in intermediate **16**, lowering the yield of the subsequent elimination step. As far as we know, these are the first palladium cross couplings reported on these lithium alkoxy acetylide intermediates and their application in the synthesis of 1,3-enynes.

All glassware and syringes were dried in an oven overnight at 140 °C, assembled while hot, flamed and flushed and cooled under N_2 immediately prior to use. Transfers of reagents were performed with syringes equipped with stainless-steel needles. All reactions were carried out under a positive pressure of N_2. N_2 was passed through a Drierite gas drying unit prior to use. Et_2O and THF were refluxed and freshly distilled from sodium and potassium/benzophenone ketyl respectively, under a N_2 atmosphere. Hexane was distilled from sodium and collected and kept over activated molecular sieves. $Pd(PPh_3)_4$, [$PdCl_2(PPh_3)_2$], and CuI were weighed in a glovebox under N_2. *n*-BuLi was titrated according to the method of Watson and Eastham.[37] ^1H NMR and ^{13}C NMR spectra were recorded on a 400 MHz NMR Bruker spectrometer. Low-resolution mass spectra were obtained on an Agilent Technologies 7820A GC coupled to a mass spectrometer 5977E unit using electron impact at 70 eV. High resolution mass spectra were measured on a Waters Synapt HMDS G1, Q-TOF. IR spectra were recorded on a Perkin Elmer FT-IR Spectrum 1000.

1,3-Dilithiopropyne (14)

An oven-dried, 100 mL, three-necked, round-bottomed flask was equipped with a magnetic stirring bar and a Liebig condenser bearing a glycerin bubbler at the top (Figure 2). The exit of the bubbler, bearing a septum, was punctured with a double-tipped needle, whose other end was inserted, through a rubber septum, into a two-necked flask equipped with a magnetic stirring bar, and capped by a rubber septum bearing a needle attached to a balloon. All joints were greased and secured with Parafilm. The three-necked flask was charged with Mg turnings (1.55 g, 64 mmol), a small crystal of I_2 and THF (25 mL). A small amount (~0.5 mL) of a THF solution (5 mL) of 2,3-dichloropropene (**19**; 2.22 g, 20 mmol) was added to the Mg and the mixture was stirred for about 10 min; a very exothermic reaction ensued after slight warming of the reaction flask. The allene gas, generated, was

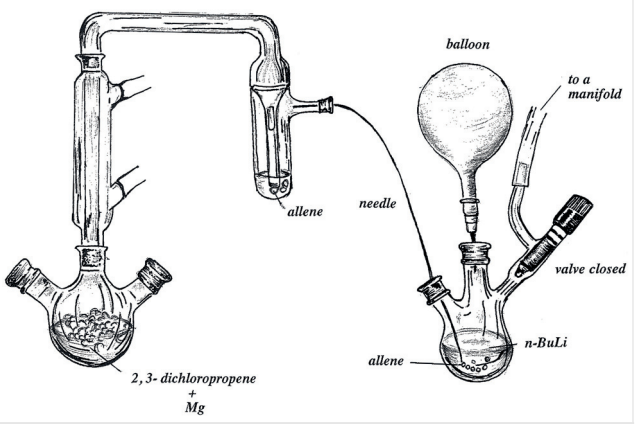


Figure 2 Glassware used for the generation of allene **13** and its conversion into dianion **14**

bubbled into a solution of *n*-BuLi in hexane (2.6 M, 0.65 mL, 1.70 mmol) in anhyd Et_2O (5 mL) and anhyd hexanes (4.35 mL),[38] at –78 °C, in a two-necked flask, under a N_2 atmosphere. The remaining THF solution of 2,3-dichloropropene was added in small portions, in order to maintain a vigorous generation of allene. It is important to keep a positive pressure of allene during the whole process, otherwise a drop in pressure in the three-necked flask would produce a vacuum in the second flask. To avoid loss of material, during the process of generation of allene, the valve connected to the manifold, in the second flask containing the *n*-BuLi, was kept closed, and the allene was collected in a balloon. After generation of allene stopped, the cannula was removed from the flask, and the *n*-BuLi/allene solution was stirred at –78 °C for 1 h.

1,1-Diphenylbut-1-en-3-yne (31); Typical Procedure

An Et_2O solution (3 mL) of benzophenone (**24**; 0.109 g, 0.60 mmol) was added to a cold (–78 °C) solution of 1,3-dilithiopropyne (**14**; prepared as described above, presumably 0.85 mmol; prepared from 1.70 mmol *n*-BuLi). The mixture was slowly warmed to r.t over 3 h, and a THF solution (2 mL) of TsCl (0.270 g, 1.4 mmol) and HMPA (0.8 mL, 4.6 mmol) was added and the solution was stirred at r.t. overnight. After this time, the temperature was lowered to 0 °C and a 1.7 M pentane solution of *t*-BuLi (2.0 mL, 3.4 mmol) was added dropwise. At this point a color change to dark green was observed and, due to the exothermic reaction, the mixture spontaneously refluxed. The reaction was allowed to reach r.t. in 2 h and a sat. aq NH_4Cl solution (3–5 mL) was added. The crude reaction mixture was extracted with Et_2O (3 × 5 mL) and the organic phase was washed several times with H_2O. The ethereal phase was dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography (Et_2O–hexanes) to give **31**.

Yield: 0.081 g (66%).

1,1-Diphenyl-4-(2-tolyl)but-1-en-3-yne (47); Typical Procedure

An Et_2O solution (3 mL) of benzophenone (**24**; 0.109 g, 0.60 mmol) was added to a cold (–78 °C) 1,3-dilithiopropyne (**14**; prepared as described above, presumably 0.85 mmol; prepared from 1.70 mmol *n*-BuLi). The mixture was slowly warmed to r.t. over 3 h and a THF solution (5 mL) of 2-iodotoluene (**48**; 0.196 g, 0.9 mmol) and $Pd(PPh_3)_4$ (0.070 g, 0.06 mmol) was added, followed by addition of a suspension of CuI (0.006 g) in THF (4 mL); then the resulting mixture was stirred overnight. The reaction was quenched by the addition of a sat. aq NH_4Cl solution (4 mL) and extracted with Et_2O (2 × 20 mL). The organic phase was dried over MgSO4 and concentrated *in vacuo*. The residue was purified by column chromatography (hexane, then 5% Et_2O–hexane) to give **47**.

Yield: 0.125 g (71%); pale-yellow solid; mp 78.1–80.5 °C.

The product was obtained as a mixture of *cis* and *trans* (and *E* and *Z*) isomers; we did not separate them.

1,1-Diphenylbut-1-en-3-yne (31)

Yield: 0.081 g (66%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (dd, *J* = 2.0, 7.9 Hz, 2 H), 7.35 (m, 4 H), 7.29 (m, 4 H), 6.02 (d, *J* = 2.6 Hz, 1 H), 3.00 (d, *J* = 2.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.64, 141.26, 139.01, 130.06, 128.44, 128.11, 128.08, 106.13, 82.58, 81.60.

MS (EI, 70 eV): *m*/*z* (%) = 51 (6), 76 (8), 101 (21), 126 (8), 176 (6), 202 (85), 203 (100), 204 (67).

HRMS (ESI, V$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}$: 205.1017; found: 204.1014.

***trans*-1-Phenylbut-1-en-3-yne (33a)**

Yield: 0.052 g of mixture of isomers (68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (m, 2 H), 7.33 (m, 3 H), 7.05 (d, *J* = 16.5 Hz, 1 H), 6.13 (dd, *J* = 2.35, 16.5 Hz, 1 H), 3.05 (d, *J* = 2.35 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.29, 136.00, 129.06, 128.88, 126.48, 107.15, 79.33, 81.04.

MS (EI, 70 eV): *m*/*z* (%) = 51 (10), 78 (8), 102 (21), 127 (26), 128 (100).

HRMS (ESI, V$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_9$: 129.0704; found: 129.0702.

***cis*-1-Phenylbut-1-en-3-yne (33b)**

Yield: 0.052 g of mixture of isomers (68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (m, 5 H), 6.72 (d, *J* = 12.0 Hz, 1 H), 5.69 (dd, *J* = 2.7, 12.1 Hz, 1 H), 3.35 (d, *J* = 2.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.73, 136.21, 128.88, 128.55, 128.42, 106.45, 84.24, 82.15.

MS (EI, 70 eV): *m*/*z* (%) = 51 (10), 78 (8), 102 (21), 127 (26), 128 (100).

HRMS (ESI, V$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_9$: 129.0704; found: 129.0702.

(*E*)-2-Phenylpent-2-en-4-yne (35a)

Yield: 0.052 g, of mixture of isomers (61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (m, 2 H), 7.35 (m, 3 H), 5.88 (dq, *J* = 1.0, 2.4 Hz, 1 H), 3.28 (d, *J* = 2.4 Hz, 1 H), 2.35 (d, *J* = 1.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.52, 140.72, 128.57, 128.45, 125.60, 106.66, 82.89, 82.31, 18.76.

MS (EI, 70 eV): *m*/*z* (%) = 77 (11), 89 (5), 115 (47), 126 (5), 141 (100), 142 (62).

HRMS (ESI, V$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{11}$: 143.0861; found: 143.0866.

(*Z*)-2-Phenylpent-2-en-4-yne (35b)

Yield: 0.052 g, of mixture of isomers (61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (m, 2 H), 7.35 (m, 3 H), 5.63 (dq, *J* = 1.1, 2.6 Hz, 1 H), 2.90 (d, *J* = 2.6 Hz, 1 H), 2.19 (d, *J* = 1.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.35, 139.86, 128.25, 128.09, 127.64, 106.35, 79.45, 77.36,15.42.

MS (EI, 70 eV): *m*/*z* (%) = 77 (11), 89 (5), 115 (47), 126 (5), 141 (100), 142 (62).

HRMS (ESI, V$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{11}$: 143.0861; found: 143.0866.

***trans*-1-(3,4-Dioxymethylenephenyl)but-1-en-3-yne (37a)**

Yield: 0.060 g of mixture of isomers (58%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (d, *J* = 16.42 Hz, 1 H), 6.91 (d, *J* = 1.69 Hz, 1 H), 6.83 (dd, *J* = 1.70, 8.04 Hz, 1 H), 6.76 (d, *J* = 8.06 Hz, 1 H), 5.99 (s, 2 H), 5.95 (dd, *J* = 2.30, 16.40 Hz, 1 H), 3.02 (d, *J* = 2.36 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.53, 148.33, 142.87, 130.53, 121.95, 108.55, 106.33, 106.15, 101.45, 83.18, 78.90.

MS (EI, 70 eV): *m*/*z* (%) = 88 (26), 102 (4), 114 (100), 127 (5), 142 (5), 171 (78), 172 (83).

HRMS (ESI, V⁺): *m*/*z* [M + H]⁺ calcd for $C_{11}H_9O_2$: 173.0603; found: 173.0602.

(*cis*-1-(3,4-Dioxymethylenephenyl)but-1-en-3-yne (37b)

Yield: 0.060 g of mixture of isomers (58%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 1.7 Hz, 1 H), 7.17 (dd, *J* = 1.7, 8.0 Hz, 1 H), 6.79 (d, *J* = 8.0 Hz, 1 H), 6.60 (d, *J* = 12.1 Hz, 1 H), 5.98 (s, 2 H), 5.56 (dd, *J* = 2.7, 12.05 Hz, 1 H), 3.37 (d, *J* = 2.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.06, 147.67, 140.17, 130.79, 124.30, 108.21, 108.18, 104.33, 101.35, 84.36, 82.17.

MS (EI, 70 eV): *m*/*z* (%) = 88 (26), 102 (4), 114 (100), 127 (5), 142 (5), 171 (78), 172 (83).

HRMS (ESI, V⁺): *m*/*z* [M + H]⁺ calcd for $C_{11}H_9O_2$ 173.0603; found: 173.0602.

4-(*trans*-But-1-en-3-ynyl)-*N*,*N*-dimethylaniline (39a)

Yield: 0.054 g of mixture of isomers (53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.9 Hz, 2 H), 6.97 (d, *J* = 16.3 Hz, 1 H), 6.65 (d, *J* = 8.9 Hz, 2 H), 5.93 (dd, *J* = 2.3, 16.3 Hz, 1 H), 2.99 (s, 1 H), 2.98 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.02, 143.51, 127.72, 124.29, 112.20, 101.80, 84.21, 77.69, 40.43.

MS (EI, 70 eV): *m*/*z* (%) = 77 (12), 115 (8), 127 (37), 128 (8), 141 (3), 155 (15), 171 (100).

HRMS (ESI, V⁺): *m*/*z* [M + H]⁺ calcd for $C_{12}H_{14}N$: 172.1126; found: 172.1124.

4-(*cis*-But-1-en-3-ynyl)-*N*,*N*-dimethylaniline (39b)

Yield: 0.054 g of mixture of isomers (53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 8.8 Hz, 2 H), 6.68 (d, *J* = 8.8 Hz, 2 H), 6.59 (d, *J* = 11.9 Hz, 1 H), 5.42 (dd, *J* = 2.62, 11.9 Hz, 1 H), 3.32 (dd, *J* = 0.89, 2.8 Hz, 1 H), 2.98 (s, 6 H),.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.43, 77.36, 83.01, 101.12, 111.67, 130.26, 140.80.

MS (EI, 70 eV): *m*/*z* (%) = 77 (12), 115 (8), 127 (37), 128 (8), 141 (3), 155 (15), 171 (100).

HRMS (ESI, V⁺): *m*/*z* [M + H]⁺ calcd for $C_{12}H_{14}N$: 172.1126; found: 172.1124.

(*E*)-1-Cyclopropyl-1-phenylbut-1-en-3-yne (41a)

Yield: 0.040 g of mixture of isomers (40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (m, 2 H), 7.36 (m, 2 H), 7.30 (m, 1 H), 5.47 (dd, *J* = 0.98, 2.48 Hz, 1 H), 2.85 (d, *J* = 2.48 Hz, 1 H), 1.70 (m, 1 H), 0.84 (m, 2 H), 0.61 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.65, 139.41, 128.25, 128.07, 128.00, 102.54, 82.23, 80.10, 18.26, 7.30.

MS (EI, 70 eV): *m*/*z* (%) = 77 (14), 91 (12), 115 (23), 128 (29), 139 (28), 152 (90), 165 (57), 167 (100), 168 (53).

HRMS (ESI, V⁺): *m*/*z* [M + H]⁺ calcd for $C_{13}H_{12}$: 168.0939; found: 168.0938.

(*Z*)-1-Cyclopropyl-1-phenylbut-1-en-3-yne (41b)

Yield: 0.040 g of mixture of isomers (40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (m, 5 H), 5.61 (dd, *J* = 0.70, 2.51 Hz, 1 H), 3.25 (d, *J* = 2.50 Hz, 1 H), 2.16 (m, 1 H), 0.90 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.63, 127.89, 127.60, 106.72, 82.53, 77.36, 14.19, 6.69.

MS (EI, 70 eV): *m*/*z* (%) = 77 (14), 91 (12), 115 (23), 128 (29), 139 (28), 152 (90), 165 (57), 167 (100), 168 (53).

HRMS (ESI, V⁺): *m*/*z* [M + H]⁺ calcd for $C_{13}H_{12}$: 168.0939; found: 168.0938.

5,5-Diphenylpent-4-en-2-yn-1-ol (43)

Yield: 0.090 g (64%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (m, 2 H), 7.34 (m, 4 H), 7.27 (m, 4 H), 6.03 (t, *J* = 2.2 Hz, 1 H), 4.29 (d, *J* = 2.2 Hz, 2 H), 1.62 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.23, 141.33, 139.16, 130.06, 128.54, 128.42, 128.35, 128.10, 128.04, 106.52, 91.47, 84.84, 51.91.

MS (EI, 70 eV): *m*/*z* (%) = 77 (28), 128 (45), 165 (39), 178 (25), 190 (34), 203 (81), 215 (100), 234 (92).

HRMS (ESI, V⁺): *m*/*z* [M + H]⁺ calcd for $C_{17}H_{15}O$: 235.1123; found: 235.1123.

1,1-Diphenylpent-1-en-3-yne (44)

Yield: 0.042 g (32%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (dd, *J* = 1.8, 7.9 Hz, 2 H), 7.32 (m, 4 H), 7.24 (m, 4 H), 5.97 (q, *J* = 2.6 Hz, 1 H), 1.89 (d, *J* = 2.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.20, 141.93, 139.47, 130.10, 128.32, 128.07, 127.96, 127.93, 108.03, 90.66, 78.73, 4.84.

MS (EI, 70 eV): *m*/*z* (%) = 63 (8), 101 (13), 176 (5), 202 (100), 203 (80), 215 (45), 216 (19), 217 (48), 218 (95).

HRMS (ESI, V⁺): *m*/*z* [M + H]⁺ calcd for $C_{17}H_{15}$: 219.1174; found: 219.1172.

***trans*-5-[4-(*N*,*N*-Dimethylamino)phenyl]pent-4-en-2-yn-1-ol (45a)**

Yield: 0.015 g (20%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.8 Hz, 2 H), 6.91 (d, *J* = 16.2 Hz, 1 H), 6.65 (d, *J* = 8.8 Hz, 2 H), 5.97 (dt, *J* = 2.21, 16.2 Hz, 1 H), 4.46 (dd, *J* = 2.1, 6.1 Hz, 2 H), 3.00 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.44, 140.95, 127.69, 124.47, 112.23, 87.88, 86.17, 52.06, 40.44.

MS (EI, 70 eV): *m*/*z* (%) = 77 (5), 115 (11), 128 (26), 157 (17), 170 (16), 184 (15), 201 (100).

HRMS (ESI, V⁺): *m*/*z* [M + H]⁺ calcd for $C_{13}H_{16}NO$: 202.1232; found: 202.1230.

***trans*-5-[4-(*N*,*N*-Dimethylamino)phenyl]pent-4-en-2-ynal (46a)**

Yield: 0.021 g of mixture of isomers (18%).

(^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.31 (d, *J* = 1.2 Hz, 1 H), 7.35 (d, *J* = 9.0 Hz, 2 H), 7.25 (d, *J* = 16.1 Hz, 1 H), 6.65 (d, *J* = 9.0 Hz, 2 H), 6.03 (dd, *J* = 1.2, 16.1 Hz, 1 H), 3.03 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.58, 170.65, 150.32, 147.24, 129.10, 123.15, 111.95, 98.58, 91.09, 40.26.

MS (EI, 70 eV): *m*/*z* (%) = 77 (9), 115 (7), 127 (26), 128 (26), 140 (4), 155 (18), 170 (38), 198 (30), 199 (100).

HRMS (ESI, V⁺): *m*/*z* [M + H]⁺ calcd for $C_{13}H_{13}NO$: 200.1075; found: 200.1076.

cis-5-[4-(*N*,*N*-Dimethylamino)phenyl]pent-4-en-2-ynal (46b)

Yield: 0.021 g of mixture of isomers (18%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.40 (d, *J* = 1.4 Hz, 1 H), 7.79 (d, *J* = 9.0 Hz, 2 H), 6.87 (d, *J* = 12.0 Hz, 1 H), 6.69 (d, *J* = 8.9 Hz, 2 H), 5.53 (dd, *J* = 1.4, 12.0 Hz, 1 H), 2.94 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.24, 171.46, 152.01, 131.39, 111.58, 98.77, 97.68, 40.26.

MS (EI, 70 eV): *m*/*z* (%) = 77 (9), 115 (7), 127 (26), 128 (26), 140 (4), 155 (18), 170 (38), 198 (30), 199 (100).

HRMS (ESI, V$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{13}NO$: 200.1075; found: 200.1076.

1,1-Diphenyl-4-*o*-tolylbut-1-en-3-yne (47)

Yield: 0.125 g (71%); pale-yellow solid; mp 78.1–80.5 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (m, 2 H), 7.43–7.27 (m, 9 H), 7.20–7.05 (m, 3 H), 6.33 (s, 1 H), 2.20 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.2, 141.3, 140.1, 139.4, 131.9, 130.1, 129.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 125.4, 123.4, 107.4, 92.9, 92.7, 20.5.

MS (EI, 70 eV): *m*/*z* (%) = 294 (100), 279 (24), 265 (10), 252 (8), 203 (17), 202 (25), 179 (2), 217 (21), 215 (60), 115 (7), 91 (9).

HRMS (ESI, V$^+$): *m*/*z* [M – 1]$^+$ calcd for $C_{23}H_{17}$: 293.1330; found: 293.1330.

4-(*p*-Nitrophenyl)-1,1-diphenylbut-1-en-3-yne (53)

Yield: 0.133 g (68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17–8.09 (m, 2 H), 7.54–7.48 (m, 2 H), 7.47–7.40 (m, 3 H), 7.39–7.31 (m, 7 H), 6.26 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.4, 147.7, 140.8, 139.1, 131.9, 130.6, 130.1, 129.9, 128.9, 128.6, 128.4, 128.3, 128.1, 128.0, 127.9, 123.6, 106.0, 94.9, 91.6.

MS (EI, 70 eV): *m*/*z* (%) = 325 (1), 293 (2), 281 (20), 207 (37), 167 (40), 141 (86), 125 (28), 106 (19), 90 (11), 77 (100).

HRMS (ESI, V$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{16}NO_2$: 326.1181; found: 326.1183.

4-(*o*-Methoxyphenyl)-1,1-diphenylbut-1-en-3-yne (54)

Yield: 0.112 g (60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.56 (m, 2 H), 7.44–7.36 (m, 3 H), 7.34–7.32 (m, 5 H), 7.25–7.18 (m, 2 H), 6.89–6.80 (m, 2 H), 6.30 (s, 1 H), 3.83 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 151.7, 141.5, 139.0, 133.4, 133.2, 130.1, 129.3, 128.7, 128.1, 128.0, 127.9, 127.8, 127.5, 120.3, 112.7, 110.4, 107.4, 93.0, 90.1, 55.5.

MS (EI, 70 eV): *m*/*z* (%) = 310 (100), 295 (8), 294 (10), 233 (7), 204 (27), 203 (25), 178 (7), 119 (58), 91 (40).

HRMS (ESI, V$^+$): *m*/*z* [M – 1]$^+$ calcd for $C_{23}H_{17}O$: 309.1279; found: 309.1274.

1,4-Diphenylbut-1-en-3-yne (59)

Yield: 0.065 g (53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97–7.90 (m, 2 H), 7.54–7.27 (m, 18 H), 7.05 (d, *J* = 16.1 Hz, 1 H), 6.71 (d, *J* = 12.0, 1 H), 6.40 (d, *J* = 16.1 Hz, 1 H), 5.93 (d, *J* = 12.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.4, 138.8, 136.7, 136.5, 131.7, 131.6, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 126.4, 123.6, 123.5, 108.3, 107.5, 96.0, 91.9, 89.0, 88.3.

MS (EI, 70 eV): *m*/*z* (%) = 204 (100), 126 (7), 103 (1), 102 (9), 101 (17), 77 (3).

HRMS (ESI, V$^+$): *m*/*z* [M – 1]$^+$ calcd for $C_{16}H_{11}$: 203.0861; found: 203.0855.

4-Phenyl-1-(2-thienyl)but-1-en-3-yne (61)

Yield: 0.0044 g (35%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.57 (m, 2 H), 7.49–7.44 (m, 2 H), 7.41–7.27 (m, 8 H), 7.22 (d, *J* = 4.9 Hz, 1 H), 7.15 (d, *J* = 15.8 Hz, 1 H), 7.08–6.94 (m, 4 H), 6.21 (d, *J* = 15.8 Hz, 1 H), 5.78 (d, *J* = 10.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.3, 140.6, 133.8, 132.0, 131.3, 131.2, 129.5, 128.2, 128.1, 128.0, 127.6, 126.9, 126.8, 126.2, 125.3, 123.3, 123.2, 107.1, 104.5, 98.5, 91.9, 88.5, 88.3, 65.7.

MS (EI, 70 eV): *m*/*z* (%) = 210 (100), 178 (7), 165 (54), 153 (3), 152 (2), 126 (5), 83 (1).

HRMS (ESI, V$^+$): *m*/*z* [M – 1]$^+$ calcd for $C_{14}H_9S$: 209.0425; found: 209.0418.

***N*,*N*-Dimethyl-4-[4-(2-thienyl)but-1-en-3-ynyl]aniline (63)**

Yield: 0.038 g (25%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.80 (m, 1 H), 7.32 (m, 2 H), 7.25–7.17 (m, 2 H), 7.03–6.94 (m, 1 H), 6.74–6.64 (m, 3 H), 6.15 (d, *J* = 16.0, 1 H), 5.66 (d, *J* = 12.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.2, 142.1, 139.4, 131.6, 131.5, 130.6, 128.1, 127.6, 127.5, 127.4, 127.0, 125.6, 125.0, 124.6, 112.5, 112.0, 102.8, 102.0, 94.4, 93.9, 88.5, 83.7, 40.7.

MS (EI, 70 eV): *m*/*z* (%) = 253 (100), 237 (12), 223 (10), 209 (25), 165 (12), 152 (4), 139 (2), 126 (9), 104 (10), 77 (1).

HRMS (ESI, V$^+$): *m*/*z* [M – 1]$^+$ calcd for $C_{16}H_{14}NS$: 252.0847; found: 252.0842.

1,1-Diphenyl-4-(2-thienyl)but-1-en-3-yne (64)

Yield: 0.074 g (43%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.51 (m, 2 H), 7.44–7.37 (m, 3 H), 7.35–7.33 (s, 5 H), 7.23 (dd, *J* = 5.1, 1.1 Hz, 1 H), 7.07 (dd, *J* = 3.6, 1.1 Hz, 1 H), 6.95 (dd, *J* = 5.1, 3.6 Hz, 1 H), 6.23 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.3, 141.1, 138.9, 131.3, 129.9, 128.2, 128.1, 128.0, 127.9, 127.7, 127.1, 126.9, 123.6, 106.5, 93.0, 86.7.

MS (EI, 70 eV): *m*/*z* (%) = 286 (100), 271 (7), 252 (49), 239 (17), 226 (11), 209 (7), 202 (14), 184 (8), 163 (7), 77 (2).

HRMS (ESI, V$^+$): *m*/*z* [M – 1]$^+$ calcd for $C_{20}H_{13}S$: 285.0738; found: 285.0733.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610197. Copies of ^{1}H NMR and ^{13}C NMR spectra of all compounds prepared and shown in Tables 3 and 5 are provided.

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(38) In the current procedure a solvent ration (v/v) of Et_2O/hexanes of 1:1 was used, as previously reported.[30]