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Very Important Publication

Redox-Neutral Arylations of Vinyl Cation Intermediates

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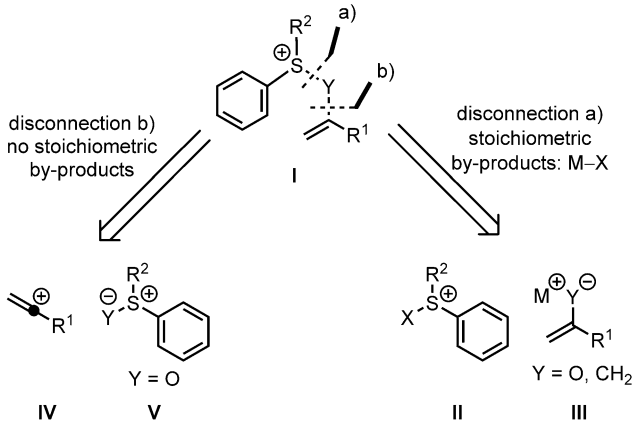
Abstract: Herein we present a new unified concept for C–C bond formation under redox-neutral conditions. Our strategy hinges upon interception of a vinyl cation with a sulfoxide resulting in simultaneous C–C and C–O bond formation and arylation. A range of structurally diverse vinyl cations are generated *in situ* in the presence of a sulfoxide, resulting in hydrative arylation, direct arylation of enol triflates and interrupted Meyer–Schuster rearrangement. Mechanistic investigations showcase the crucial role played by the fleeting vinyl cation intermediate and structural features that lead to its stabilization. Applications of the reaction products to synthesis are also presented.

Keywords: arylation; Meyer–Schuster rearrangement; sigmatropic rearrangement; sulfoxides; vinyl cations

Introduction

The Claisen rearrangement is ideally suited for creation of molecular complexity from simple precursors, achieving this through skeletal reorganization.[1] In the context of α-arylation chemistry, our group[2] and others[3] have exploited the opportunities presented by [3,3]-sigmatropic Claisen-type rearrangements of intermediates of the general formula **I** (Scheme 1). Conventional analysis (a) of **I** suggests a disconnection along the Y–S bond, leading to electrophilic (**II**, sulfonium-like) and nucleophilic (**III**, enolate-like) precursors. While highly successful in the past,[2b,3d,e] this approach pays a price in atom-economy given the generation of wasteful by-products.

An alternative analysis (b) of the same intermediate **I** would suggest the possibility of adding a neutral sulfoxide **V** to a vinyl cation species **IV**. Given the instability and fleeting nature of vinyl cations, this appears to be a pathway fraught with pitfalls; can vinyl cations be generated under conditions that enable capture by a weak nucleophile and, if so, can redox-neutral sequences be developed? In this article, we report our endeavours in this field and the deployment of a family of redox-neutral arylations of vinyl cation intermediates.[2f]



Scheme 1. Approaches to the generation of crucial vinylsulfonium intermediate **I**.

Results and Discussion

Hydrative Arylation of Alkynes

Initial attempts at intercepting intermittently generated vinyl cations were met with moderate success. Treating a solution of phenylacetylene **1a** and diphenyl sulfoxide **2a** with various Brønsted acids resulted only in trace amounts of the desired α-arylated ketone **3a** (TfOH, Table 1, entries 1–3), or failed to deliver any product at all (AcOH, TFA). Due to a high degree of apparent decomposition of the start-

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Table 1. Optimization of conditions for hydrative arylation of alkyne **1a**.

Entry	Acid (equiv.)	**2a** (equiv.)	Solvent	*T*/*t*	Yield [%][a]
1	TfOH (0.5)	2.0	CH_2Cl_2	25 °C/21 h	trace
2	TfOH (0.5)	2.0	MeCN	25 °C/16 h	13
3	TfOH (0.1)	2.0	MeCN	25 °C/16 h	2
4	TfOH (1.0)	4.0	neat	80 °C/2 h	79
5	Tf_2NH (0.5)	4.0	neat	80 °C/2 h	80
6	TfOH (1.0)	2.0	neat	80 °C/2 h	69
7	**TfOH (0.5)**	**4.0**	**neat**	**80 °C/2 h**	**96**[b]

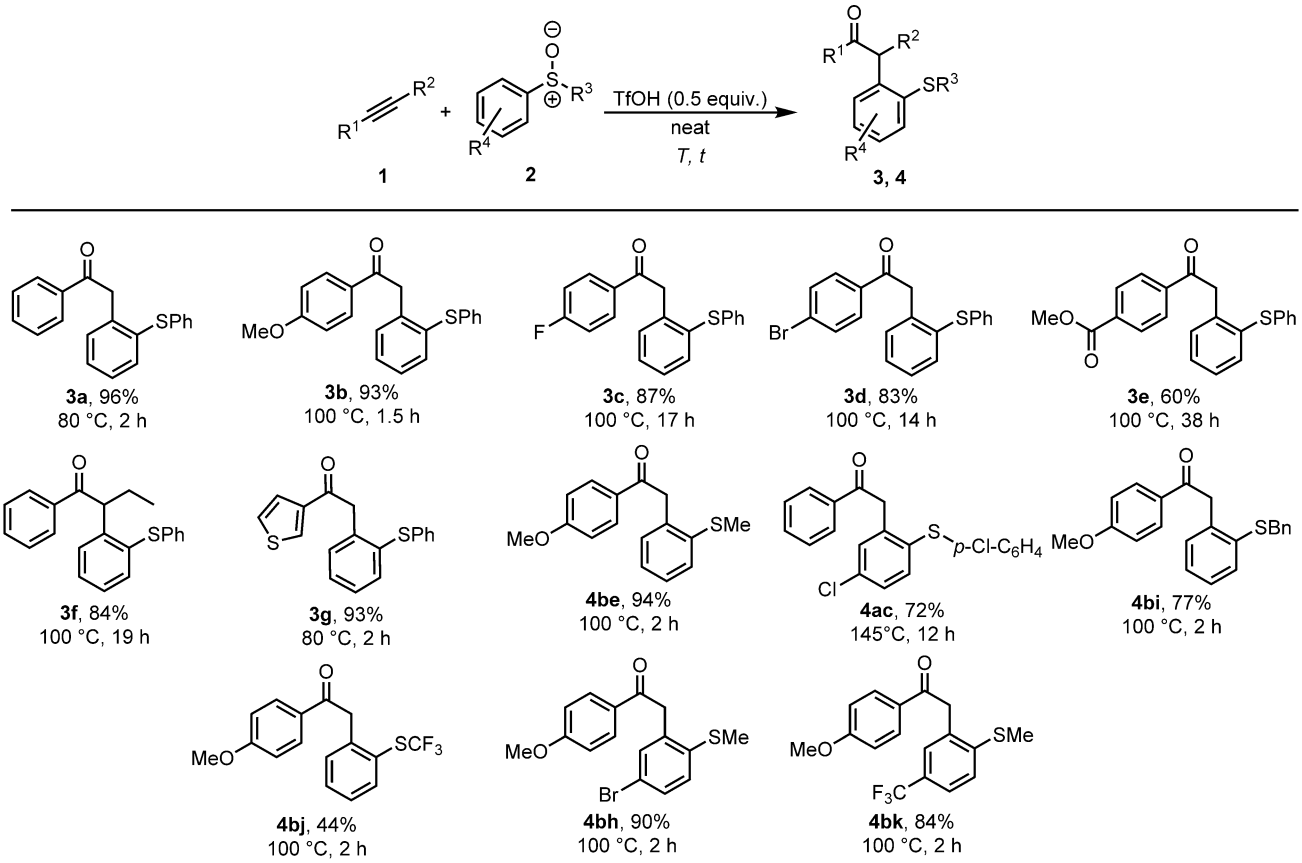
[a] NMR yield using 1,3,5-trimethoxybenzene as internal standard.
[b] Isolated yield. 2.97 equiv. (99%) unreacted diphenyl sulfoxide (**2a**) recovered.

ing material, we suspected that failure to rapidly trap the high-energy protonation adduct with an appropriate nucleophile (sulfoxide oxygen) opened up other reaction pathways, including oligomerization, polymerization and hydration. Therefore we opted to perform the reaction under solvent-free conditions, employing 4 equivalents of diphenyl sulfoxide as both the nucleophile and the solvent. Satisfyingly, this increase in nucleophile concentration enabled the formation of α-arylated ketone **3a** in a high yield with either triflic acid (entry 4) or bis(trifluoromethane)-sulfonimide (entry 5). While, once again, lowering the apparent concentration of the nucleophile led to diminished product formation (entry 6), the use of substoichiometric amounts of triflic acid at 80 °C afforded **3a** in 96% yield (Table 1, entry 7).

It is important to note that the high conversion and pronounced polarity difference between product **3a** and sulfoxide **2a** enabled an easy and quantitative (99%) recovery of excess sulfoxide by chromatography.[4]

Exploration of the generality and functional group tolerance of this transformation included the investigation of various alkynes and sulfoxides, with generally good results obtained (selected results are shown in Scheme 2; see ref.[2f] for the full scope).

The chemoselectivity and connectivity of the final product is governed by the stability of the intermittently formed vinyl cation. As shown by Hanack,[5] both aryl substituents and cyclopropyl moieties (as the ideal alkyl substituents) allow for high degrees of vinyl cation stabilization. In this context, while compound **3h** (Scheme 3) was isolated in moderate yield – owing to reduced ability of vinyl cation stabilization – hydrative arylation of cyclopropyl(pentyl)acetylene **1i**



Scheme 2. Selected scope of alkynes and sulfoxides for the hydrative arylation of alkynes.[2f]

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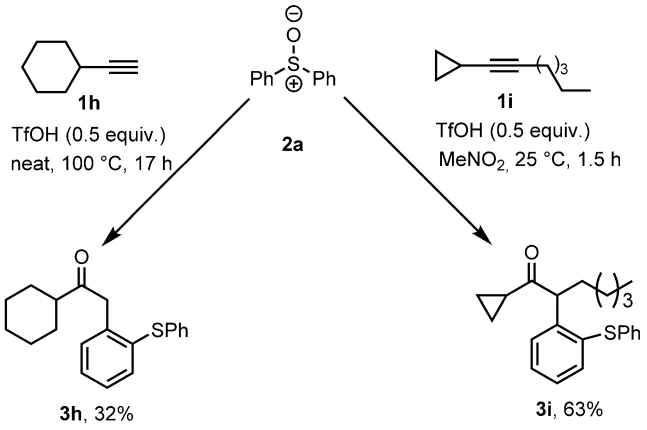
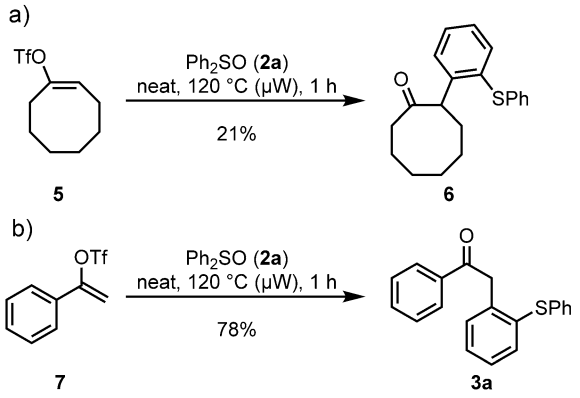


Scheme 3. Hydrative arylation of alkyl-substituted alkynes.[6]

leads to the exclusive formation of cyclopropyl ketone **3i** in good yield and with complete regiospecificity.[6]

Encouraged by these results, in support of the reaction manifold laid forth in our original mechanistic proposal (see Scheme 1), i.e., the successful nucleophilic attack of a sulfoxide (**V**) on a vinyl cation (**IV**), we carried out additional experiments (Scheme 4).



Scheme 4. Trapping solvolytically-generated vinyl cations.

Since thermal solvolysis of vinyl triflates and nonaflates is possible in highly polar solvents,[5] the formation of **6** and **3a**, from **5** and **7**, respectively, by this method provides further experimental evidence for the intermediacy of vinyl cations. From a synthetic viewpoint, the implicit retrosynthetic disconnection of an α-aryl ketone being formed from a vinyl triflate is interesting and non-obvious.

Intercepted Meyer–Schuster Rearrangement

Intrigued by the possibility of expanding this transformation beyond classical alkynes, the reaction of propargyl alcohols with triflic acid in the presence of aryl sulfoxides was investigated. Herein, protonation of the alcohol (and departure of water) leads to the intermittent generation of a propargyl cation, in resonance with the corresponding allenic vinyl cation – the classical pathway of the well-known Meyer–Schuster rearrangement.[7] Ensuing nucleophilic attack of the aryl sulfoxide, followed by [3,3]-sigmatropic rearrangement, was expected to afford α,β-unsaturated, α-aryl carbonyl compounds. Nonetheless, a more stringent limitation than in the prior study was at play here: not only was the fleeting vinyl cation intermediate to be intercepted by a sulfoxide, but this was to occur in the presence of water as a competing nucleophile.

Initial experiments were conducted with propargyl alcohol **8a** and diphenyl sulfoxide **2a** under solvent-free reaction conditions, but led only to the formation of low amounts of the desired product (not shown). Anticipating a pronounced effect of the solvent and reaction conditions on the feasibility of the desired reaction and the crucial suppression of the undesired classical Meyer–Schuster pathway, our efforts focused on finding the best conditions for a variety of diversely substituted substrates (**8a**, **12a**, Table 2, see the Supporting Information for further details). Polar aprotic solvents (entry 4) showed to be optimal, while weaker acids than TfOH showed a deleterious effect (entry 5). It was found that a catalytic amount of triflic acid and mild heating provided the best results. In the event, a 96% yield of the desired α-arylated, α,β-unsaturated carbonyl compound, alongside 98% of recovered excess diphenyl sulfoxide were obtained (entry 8).

With suitable reaction conditions in hand (see the Supporting Information for a full optimization table), the scope of propargyl alcohols was explored. Varia-

Table 2. Optimization of conditions for the interrupted Meyer–Schuster rearrangement of propargyl alcohols **8a** and **12a**.

Entry	R^1	Acid (equiv.)	Solvent (1 M)	T [°C]	t [h]	Yield [%][a]
1	H	TfOH (0.2)	DCE	80	3	38, **13aa**
2	H	TfOH (0.2)	PhMe	80	3	43, **13aa**
3	H	TfOH (0.2)	MeCN	80	3	61, **13aa**
4	H	TfOH (0.2)	$MeNO_2$	80	3	75, **13aa**
5	Ph	TFA (1.0)	$MeNO_2$	80	18	trace, **9aa**
6	Ph	TfOH (0.5)	$MeNO_2$	80	4	86, **9aa**
7	Ph	TfOH (0.1)	$MeNO_2$	50	4	86, **9aa**
8	**Ph**	**TfOH (0.2)**	**$MeNO_2$**	**50**	**4**	**96**,[b] **9aa**

[a] NMR yield using 1,3,5-trimethoxybenzene as internal standard.
[b] Isolated yield. 2.94 equiv. (98%) unreacted diphenyl sulfoxide (**2a**) recovered. TfOH = trifluoromethanesulfonic acid. TFA = trifluoroacetic acid.

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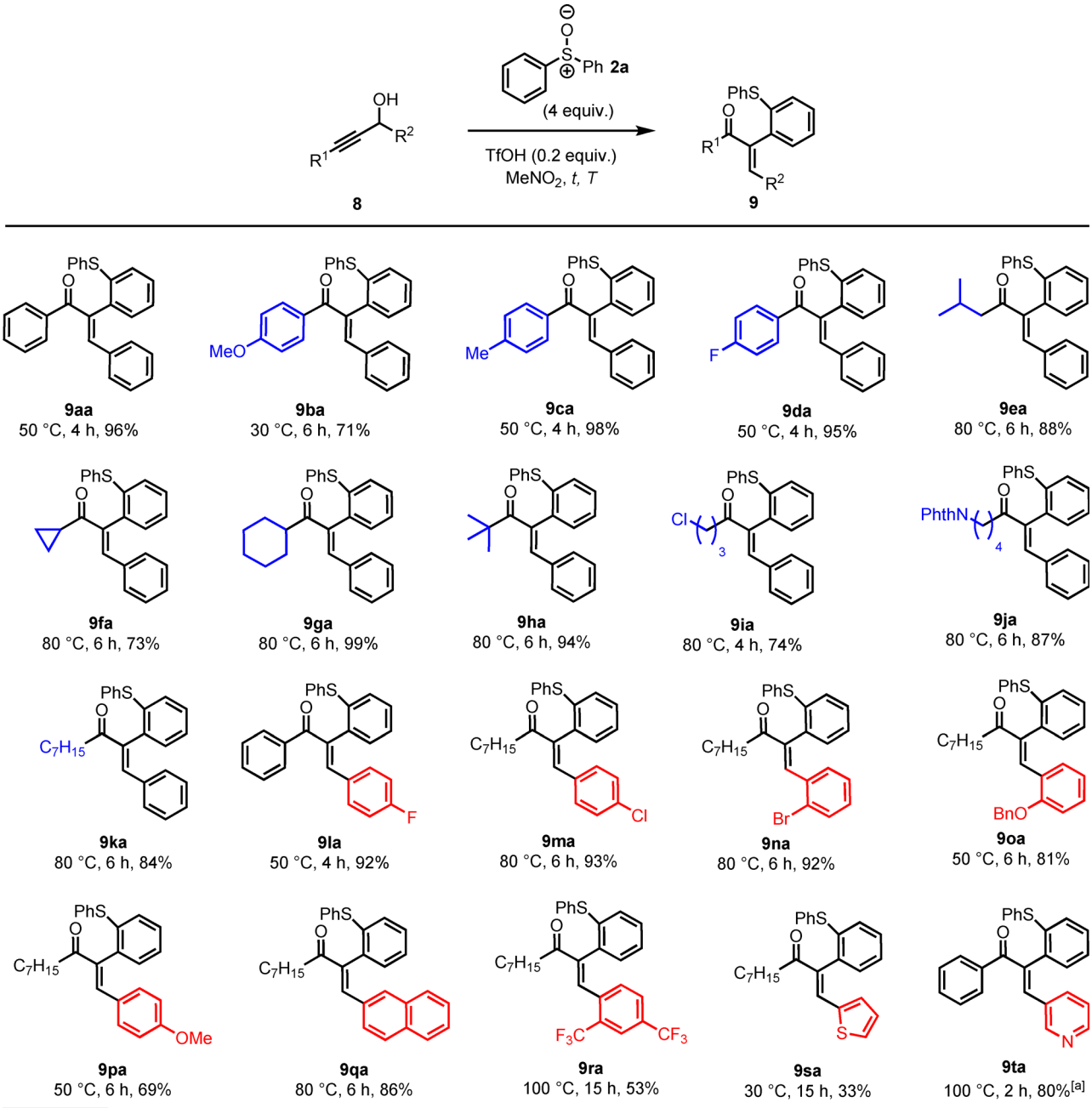

[a] 2 equiv. of TfOH were employed

Scheme 5. Interrupted Meyer–Schuster rearrangement of various propargyl alcohols **8**.

tions on the acetylenic moiety were well tolerated in all cases (Scheme 5), giving high yields for a variety of aromatic and aliphatic substituents (**9aa–9ka**). Similarly, varying substitution on the fragment of the substrate containing the benzyl alcohol moiety gave excellent yields (**9la–9ta**), with the exception of the moderate yield of **9ra**, reflecting the reduced stabilization of the intermittent carbocation, and the highly electron-rich product **9sa**. As shown in Scheme 5, the optimum reaction temperature varied considerably, depending on the nature of the substrate. While the electron-rich substrate **8b**, additionally containing two aryl substituents stabilizing the cationic intermediate, afforded **9ba** under mild heating (30 °C), the electron-poor substrate **8r** required a higher temperature (100 °C) in order for the reaction to proceed and yield **9ra**. Analogously, substrates with a decreased capability of cation-stabilization, such as **8e** (leading to **9ea**) and **8t** (the nitrogen being protonated under the reaction conditions, leading to **9ta**) also required elevated reaction temperatures.

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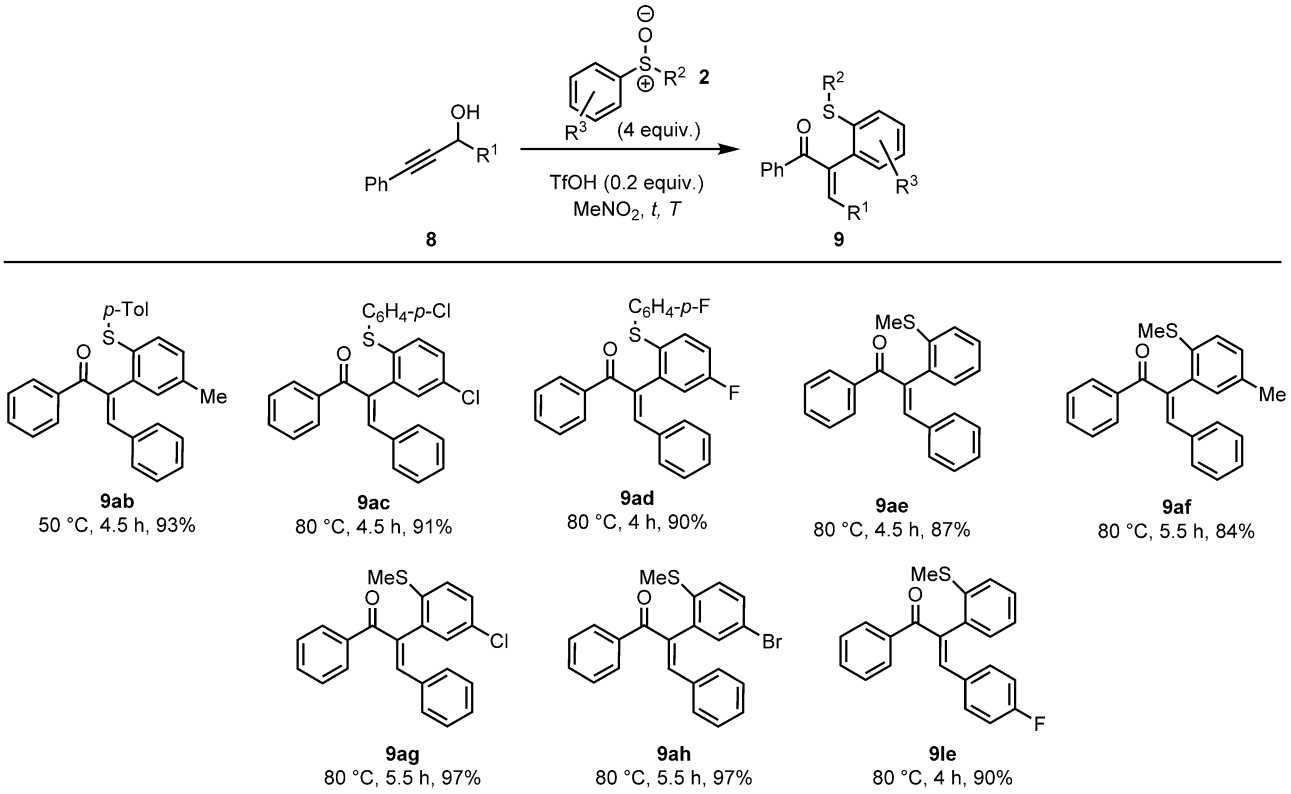


Scheme 6. Scope of products formed by interrupted rearrangement of various sulfoxides **2**.

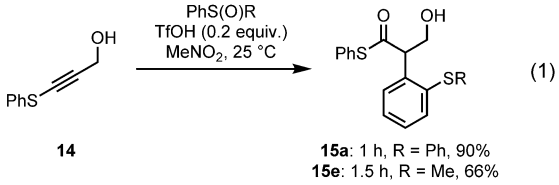
The use of a variety of aryl sulfoxides (Scheme 6) led to the desired products in consistently high yields.

In addition to internal alkynes **8a–t**, derivatives containing either a primary propargyl alcohol (**10**) (Scheme 7) or a terminal alkyne (**12**) (Scheme 8) were also employed. The products of these transformations are, respectively, enones containing a terminal olefin (**11aa–11be**) or (*E*)-configured enals (**13aa–13ae**). Substrates containing protons in the β-position to the alcohol afforded low yields due to competing elimination (as observed by crude NMR analysis) and conceivable side reactions, such as Rupe rearrangement (see the Supporting Information for further details).[8]

To the best of our knowledge, this method constitutes the first instance in which an arylative Meyer–Schuster rearrangement is capable of yielding the corresponding aldehydes.

All reactions reported in this work furnished exclusively the (*E*)-isomer of the double bond (as proven by X-ray crystallographic analysis for **13ba**, Scheme 8. CCDC 1440462 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif).

The treatment of 3-(phenylthio)prop-2-yn-1-ol (**14**) with aryl sulfoxides **2a** and **2e** interestingly yields the corresponding hydrated products **15a** and **15e** [Eq. (1)].[9] This showcases the versatility of this method further, expanding from the formation of α,β-unsaturated, α-aryl carbonyl compounds to α-arylated functionalized carboxylic acid derivatives.



Mechanistic Considerations

Owing to the highly reactive nature of the vinyl cations at the centre of this transformation, as well as the pronounced influence of the electronic properties of the employed aryl sulfoxides on the efficiency of the arylation, our interest turned towards mechanistic investigations.

In order to probe the mechanism of the reaction, DFT calculations were undertaken, as previously reported.[2f,10] Herein, phenylacetylene (**1a**) and either diphenyl sulfoxide (**2a**) or methyl phenyl sulfoxide

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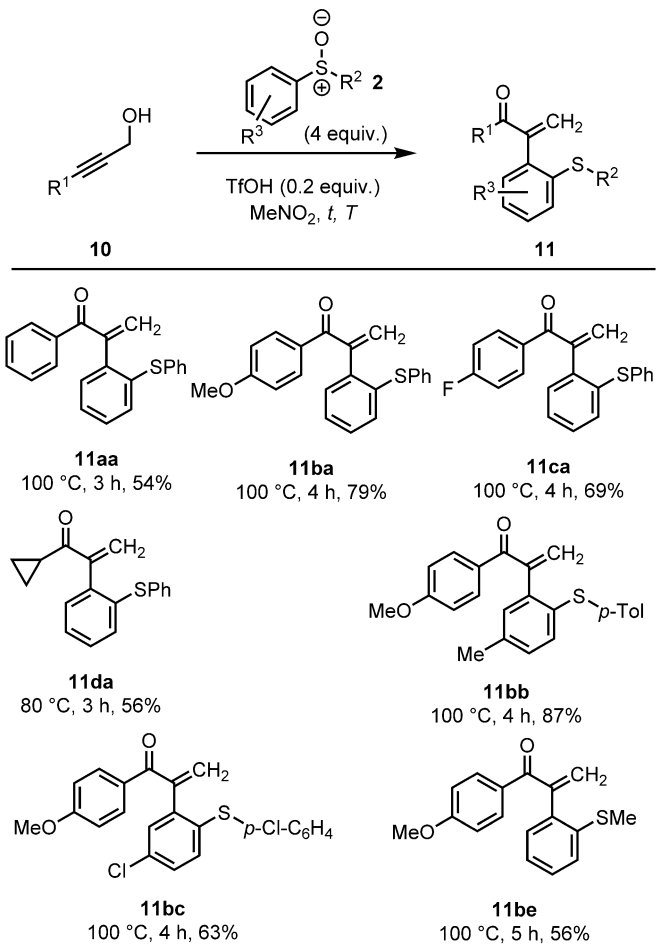

Scheme 7. Terminal α,β-unsaturated ketones formed *via* interrupted rearrangement of primary propargyl alcohols.

(**2e**) were considered as the reactants. Scheme 9 shows the free energy profile of the reaction of **1a** with **2a** (for the corresponding representation of the reaction with **2e**, see the Supporting Information).

Triflic acid-mediated protonation of phenylacetylene (**1a**), **A**→**B**, has a barrier of 10.1 kcal mol^{-1}. As can be easily rationalized with the well-established instability of the formed vinyl cation, this step is endergonic ($\Delta G = 5.6$ kcal mol^{-1}). Owing to this high reactivity, the following step, namely *O*-nucleophilic attack of the sulfoxide on the *sp*-hybridized carbocation, **B**→**D**, is exergonic ($\Delta G = -27.8$ kcal mol^{-1}) and possesses an energetic barrier of only 2.0 kcal mol^{-1}. The final steps, involving [3,3]-sigmatropic rearrangement and triflate-promoted rearomatization (**D**→**E**→**F**) appear to be facile in nature. The sigmatropic shift has a value of $\Delta G^{\neq} = 13.7$ kcal mol^{-1}, a barrier easily surpassed under the reaction conditions (*vide supra*). The overall process, being thermodynamically favoured, displays a free energy balance of $\Delta G = -65.0$ kcal mol^{-1}.

A similar reaction pathway can be observed for the reaction of **1a** with methyl phenyl sulfoxide (**2e**) (see Supporting Information, Figure S2). For both nucleophilic attack of the sulfoxide and rearomatization, barrier differences of less than 2 kcal mol^{-1} were found. The [3,3]-sigmatropic rearrangement, however, is 4.4 kcal mol^{-1} higher in energy than for the respective reaction with **2a**. This result is reflected in the experimental results shown above, requiring higher temperatures when alkyl aryl sulfoxides are employed (see Scheme 2 and Scheme 4).[11,12]

Turning to the protonation of propargyl alcohols and the ensuing interrupted Meyer–Schuster rearrangement, we were intrigued by the possibility of varying substitution – and with it stabilization of the intermittent cation. The ease of the protonation-dehydration step was further investigated. To this effect, an initial qualitative NMR study was performed, showcasing the differences of reactivity of substrates **8a**, **10a** and **12a** at 25 °C, forming **9aa**, **11aa** and **13aa**, respectively (Figure 1).

These qualitative curves confirm the assumption and experimental observation (*cf.* Scheme 6, Scheme 7 and Scheme 8) that the reactivities of substrates with varying substitution patterns differ greatly. While **8a** is converted to **9aa** smoothly, even at ambient temperature, the analogous reactions of **12a** (and, even more so, **10a**) are sluggish.

These observations were further substantiated by probing the stabilities of cations of type **VI** by DFT calculations (Scheme 10).[10]

The free energy balances shown in Scheme 10 indicate clearly that, under our conditions, the reaction outcome directly mirrors the stability of the carbocation. Thus, in the case of $R^1 = R^2 = Ph$, the increased extension of the π-conjugated system leads to a more effective delocalization of the positive charge, a more stable carbocation and a more effective reaction (product **9aa**). The reaction outcome is further reflected by the charge distribution along the cation and, particularly, in the two phenyl groups that accommodate more than 50% of the total charge with charges of $C_{Ph} = 0.21$ and $C_{Ph} = 0.32$ (NPA, see Figure 2).

Comparing the other two carbocations, for the case of $R^1 = H$ and $R^2 = Ph$ (**12a**, leading to **13aa**), cation **VI** shows greater stability, displaying a better charge distribution along the π-system with a charge of $C_{Ph} = 0.46$ in the phenyl moiety, compared to $C_{Ph} = 0.38$ in the case of the cation derived from **10a** ($R^1 = Ph$, $R^2 = H$). This is reflected in the reaction conditions necessary for the corresponding reactions, yielding **13aa** and **11aa**, respectively.

Following the activation step, forming **VI**, *O*-nucleophilic attack of the aryl sulfoxide leads to an intermediate of type **I**, as illustrated in Scheme 1. The progression of the reaction, including the aforementioned

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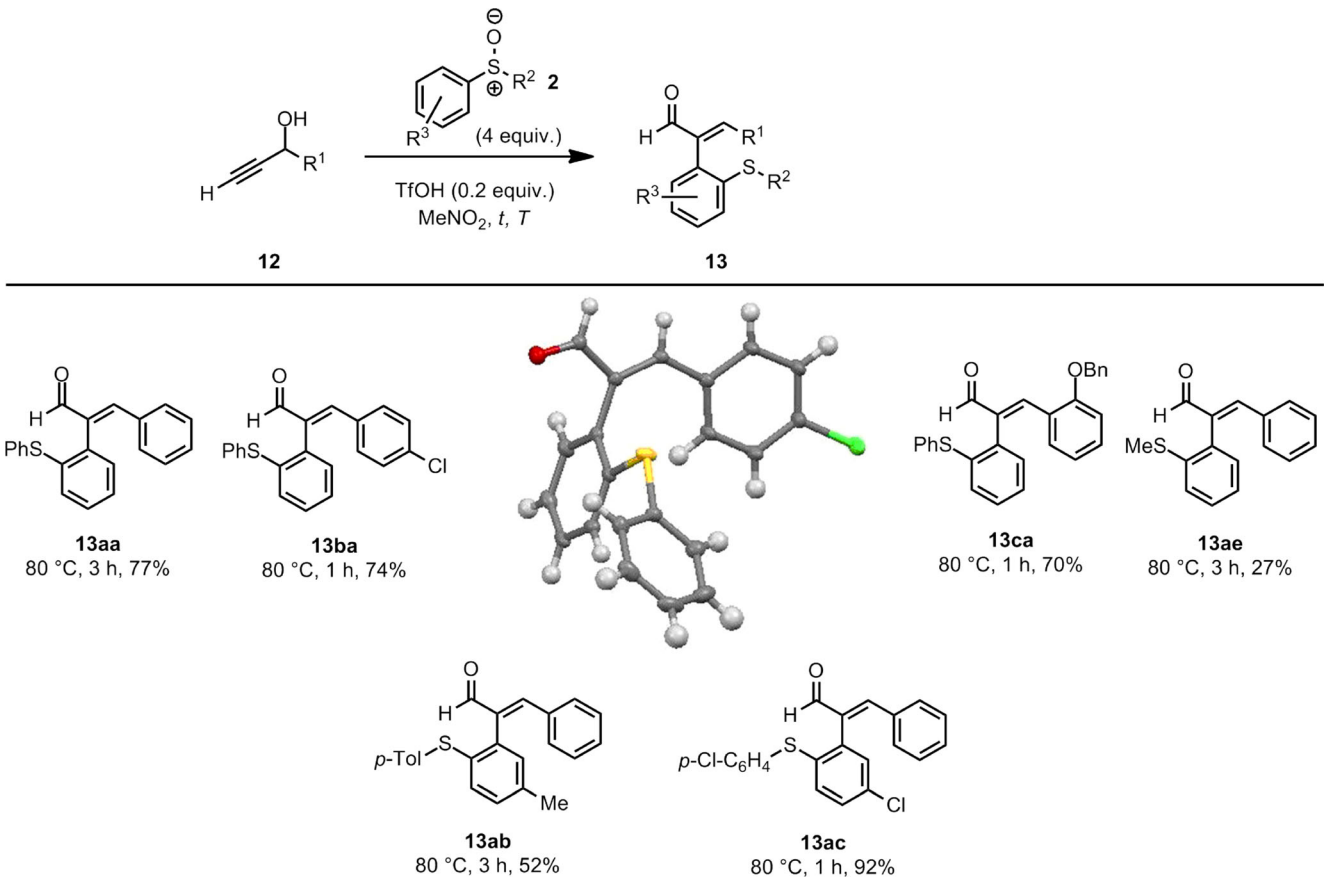

Scheme 8. α,β-Unsaturated aldehydes *via* rearrangements of terminal propargyl alcohols.

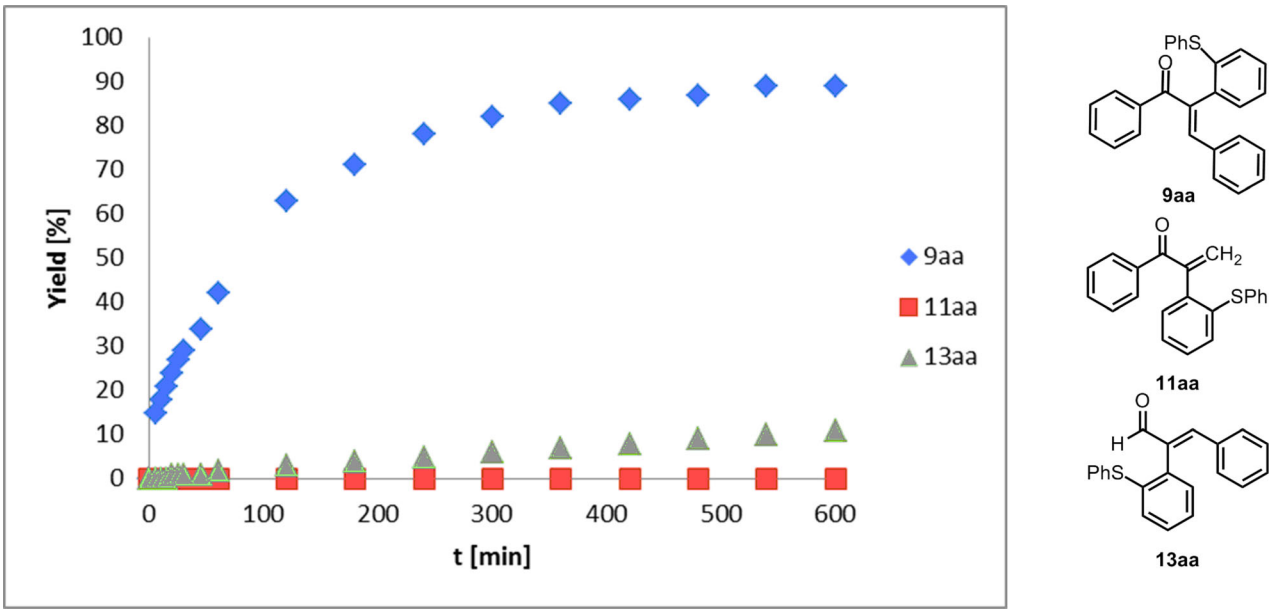

Figure 1. Reaction monitoring for the formation of **9aa**, **11aa** and **13aa** at 25 °C. The reactions were performed in $MeNO_2$-d_3 (1 M), using 4 equiv. of **2a** and 0.2 equiv. of TfOH. Product formation was monitored by NMR, using 1,2-dibromoethane as an internal standard.

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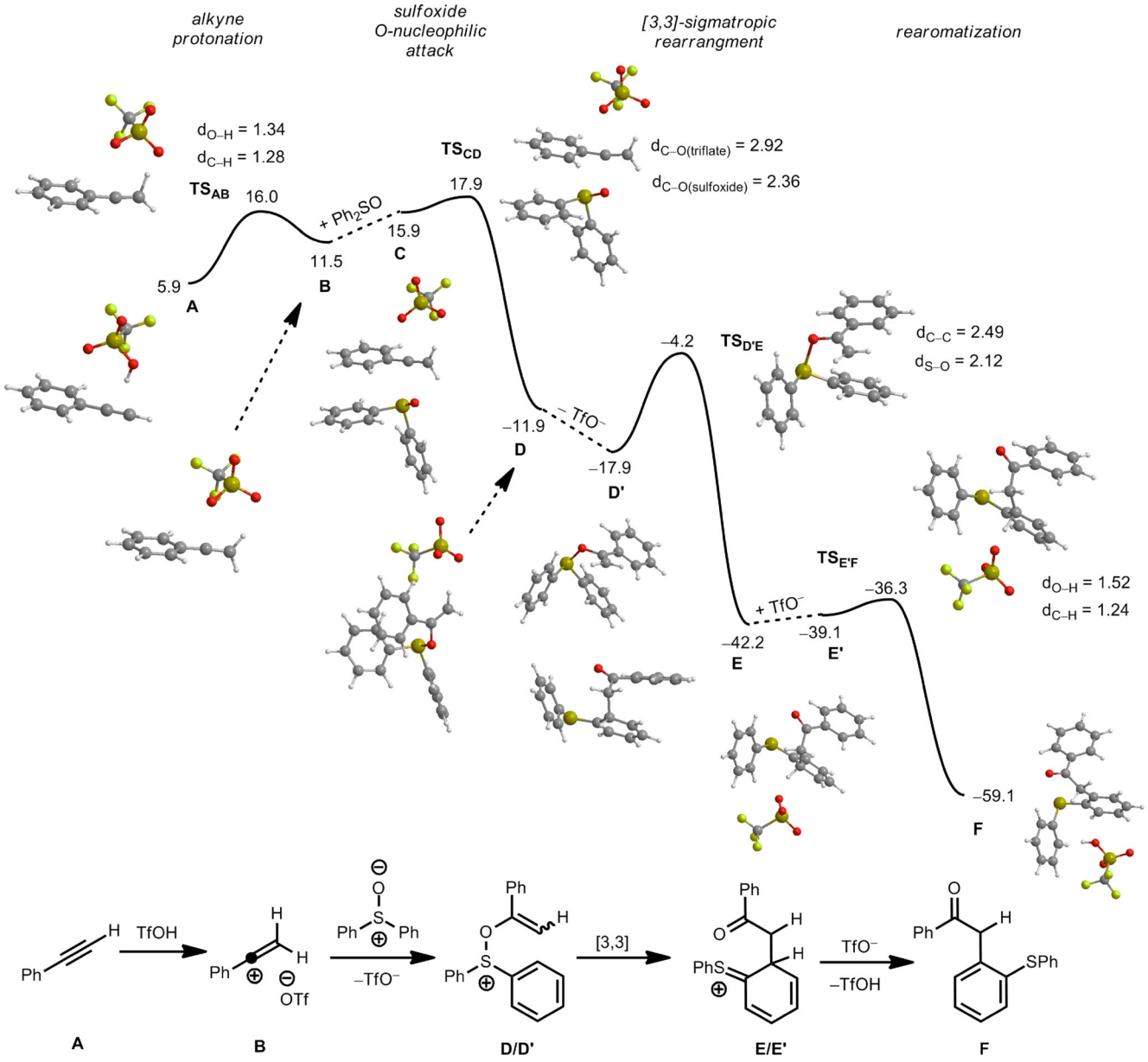
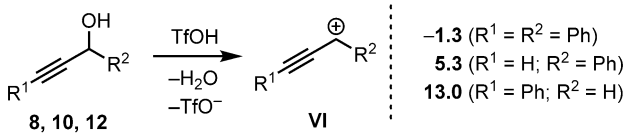


Scheme 9. Schematic profile calculated for the reaction of **1a** with **2a** (distances in Å). Free energy values (kcal mol^{-1}) relative to the separated reactants. See the Supporting Information for details.



Scheme 10. Free energy balance (kcal mol^{-1}) calculated for the formation of carbocation **VI**.

nucleophilic attack, [3,3]-sigmatropic rearrangement and rearomatization, proceeds analogously to the previously described formation of product **3a** (Scheme 9).

Product Elaboration

The products shown above can be easily functionalized due to the large number of synthetic handles they contain.

Alkyl aryl sulfides can be chemoselectively coupled with arylzinc reagents, affording biaryl-compounds, even in the presence of carbonyls (Scheme 11).[13] Treating alkyl aryl sulfides **4ce/ae/cf** with arylzinc-lithium chloride complexes and a palladium catalyst (Pd-PEPPSI-SIPr) afforded biphenyls **16a–d** in high yields.[2f]

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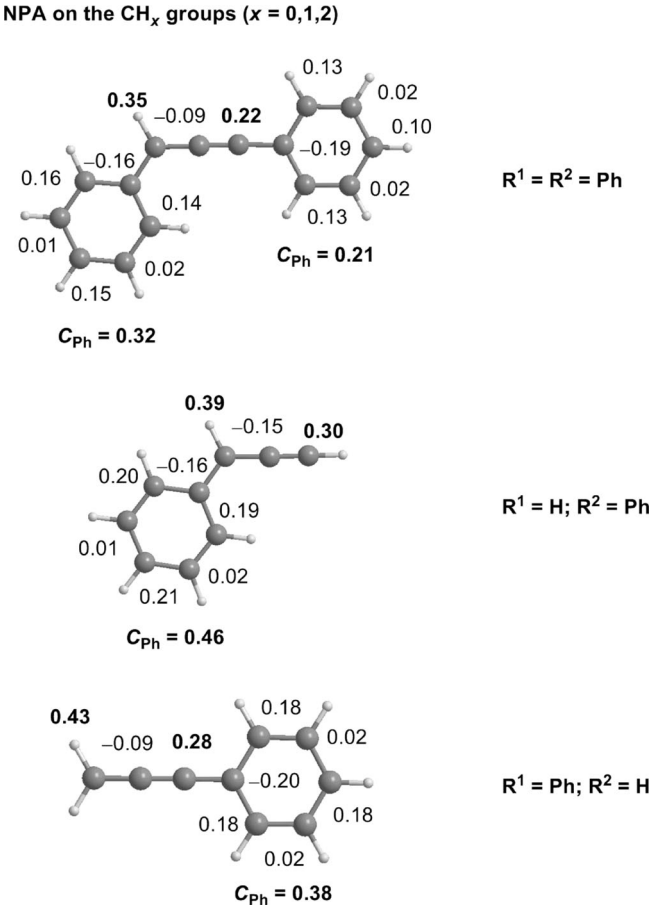


Figure 2. Charge distributions (NPA) along the C-atoms of the carbocations **VI**.

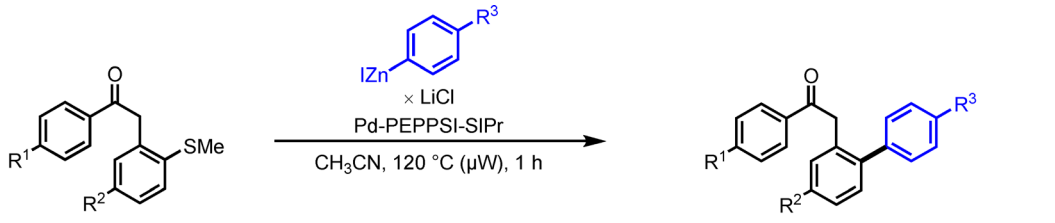
The newly formed carbonyl moieties lend themselves to several forms of derivatization.[2f] Amongst these, heterocycle formation plays a prominent role and enables the facile formation of aryl-substituted heterocycles (Scheme 12a). The oxidation of **3a** to diketone **17** can be achieved by copper-catalyzed oxidation.[14] This diketone, in turn, can be readily condensed with a variety of nucleophiles, as exemplified by the formation of imidazole **18** and diaryl-thioxo-imidazolidinone **19**.[15,16] The formation of quinoxaline **20** can be achieved even more conveniently by combined aerobic oxidation and condensation of **3a** with phenylenediamine.[17] It is noteworthy that **20** is formed in only two steps from phenylacetylene, diphenyl sulfoxide and *o*-phenylenediamine, employing only air and catalytic amounts of triflic acid and DABCO as promoters. Quinoxaline cores related to **20** have been described in DNA-cleaving agents or electroluminescent materials.[18]

Similarly, enones can be condensed to afford drug-like heterocycles, as shown in Scheme 12b and c. Heterocycle formation was achieved by treatment of **9ae** with either guanidinium chloride, to afford pyrimidine-amine **21** in moderate yield (Scheme 12b), or methylhydrazine, which led to the formation of a mixture of pyrazoline **22a** and pyrazole **22b** (Scheme 12c).[19]

While reduction of the arylsulfanyl moiety has been previously reported for similar substrates,[2d] the high degree of functionalization of the arylated enones renders reduction difficult to control (Scheme 13a). Whereas treatment of **9le** with Raney nickel and hydrogen in acetone led merely to hydrogenation of the α,β-unsaturation (product **24**), omitting hydrogen and changing the solvent to ethanol afforded **23** as the main product.[20] Additionally, chloride **9ia** could be converted to vinyltetrahydrofuran **25** in two simple steps, involving Luche reduction and silver-mediated S_N2 ring closure (Scheme 13b).[21]

Methyl thioether **9ae** could be selectively converted to benzothiophene **26** by treatment with *N*-bromosuccinimide (Scheme 14). The resulting structure constitutes the core motif of the potent selective estrogen-receptor modulator (SERM) raloxifene.[22]

The inherent, albeit low, nucleophilicity of alkynes enables the use of electrophiles other than protons. Preliminary studies show the possibility of activation of **1a** with *N*-bromosuccinimide, followed by trapping with diphenyl sulfoxide (**2a**). Subsequent rearrange-



[a] Yield based on recovered starting material.

Scheme 11. Palladium-catalyzed cross coupling of **4ce/ae/cf** with an arylzinc reagent.

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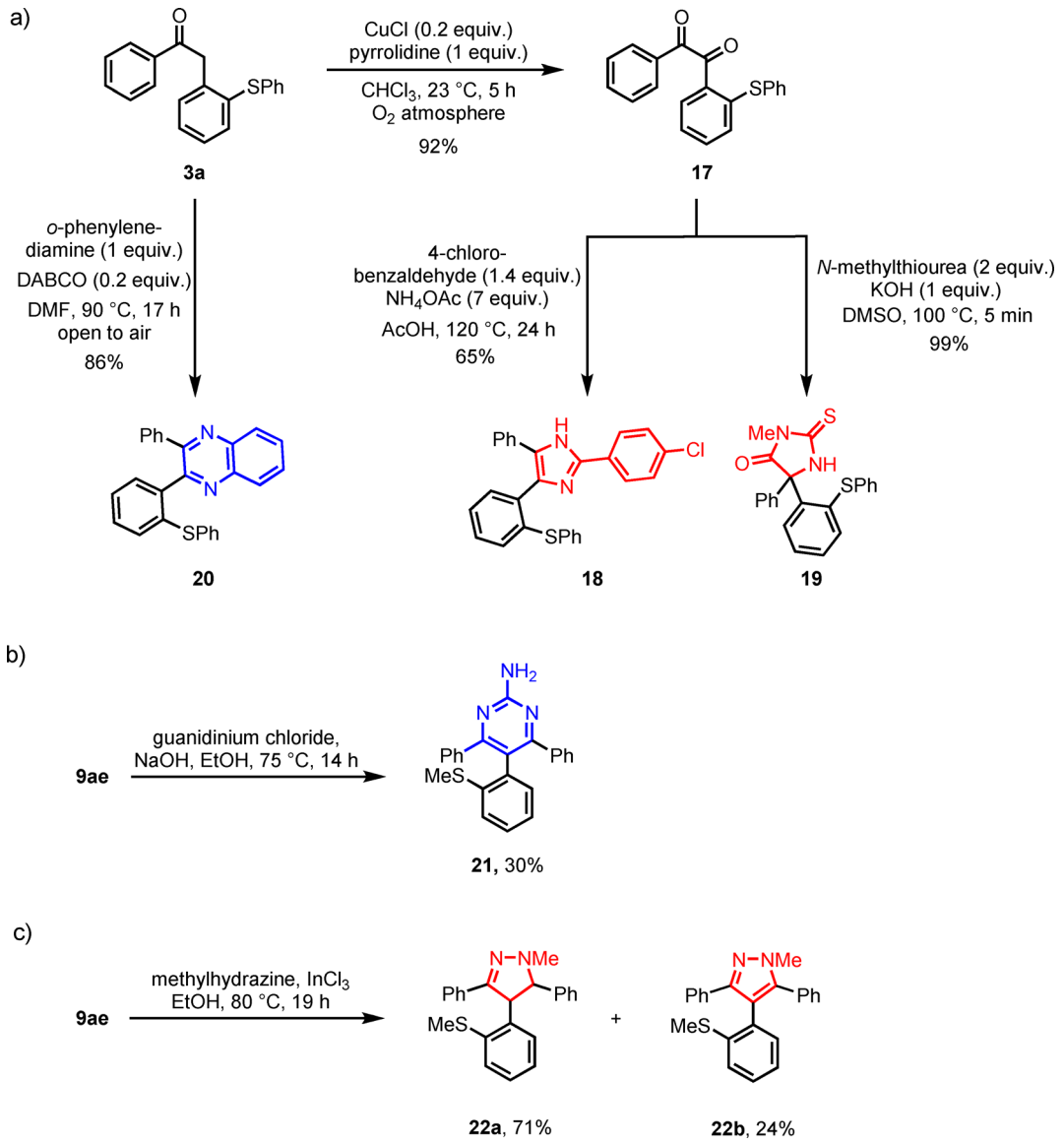
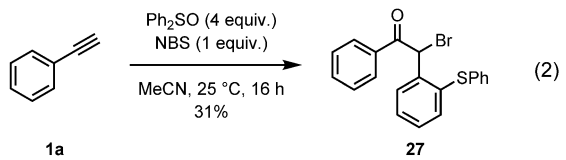


Scheme 12. Facile oxidation and subsequent condensation of the products, leading to heterocycles.

ment and rearomatization leads to the formation of the α-bromo ketone **27** [Eq. (2)].



(2)

Conclusions

In summary, we have developed a novel concept for carbon-carbon bond formation *via* the interception of highly reactive vinyl cations with sulfoxides. The latter species function as both the nucleophile and arylating agent. These reactions lead to the formation of α-aryl ketones or *E*-configured α-aryl enones and enals at will, and show a tolerance for a wide range of functionality. The *ortho*- or *ortho/meta*-substitution patterns on the aryl moiety, arising from [3,3]-sigmatropic rearrangement, are unprecedented in the 1,2-difunctionalization of alkynes and propargyl alcohols,[3g–i] and offer handles for further elaboration by palladium-catalyzed cross-coupling and conjugate additions. The procedures detailed herein benefit from the use of highly stable and, in most cases, commercially available starting materials, as well as operational simplicity (atmospheric conditions, "wet" solvents, facile purification) and the atom-economical nature of the reactions, including quantitative recovery of excess reagents. DFT calculations and mechanistic experiments highlight the crucial role of the intermittent

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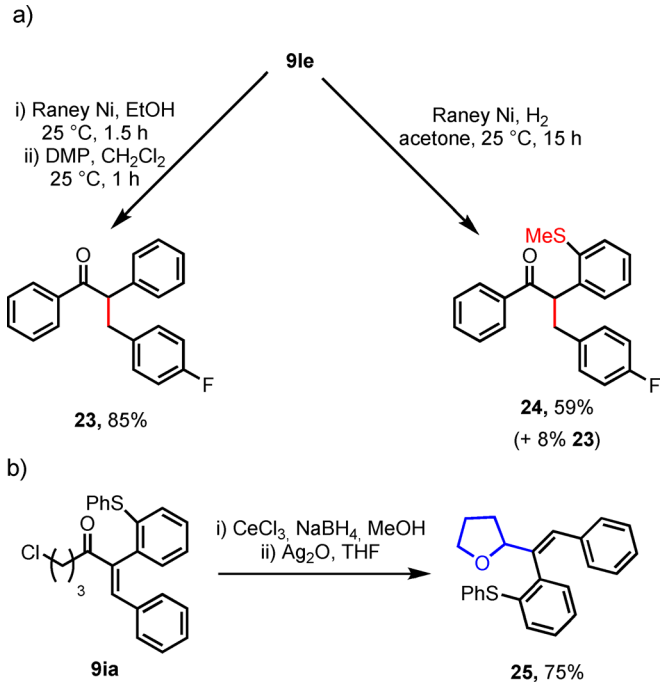
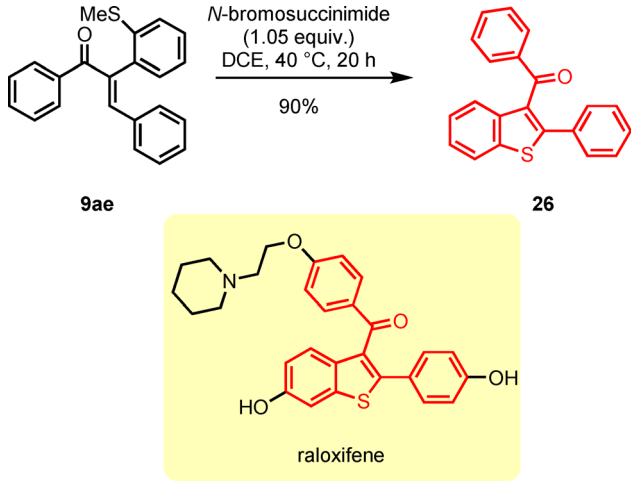


Scheme 13. a) Raney-Ni catalyzed reduction of **9le** and b) synthesis of a *cis*-stilbene-substituted furan.



Scheme 14. Synthesis of the core motif **26** of the potent pharmaceutical raloxifene.

vinyl cation and the subsequent arylative [3,3]-sigmatropic rearrangement of the pivotal sulfonium intermediate.

Experimental Section

General Procedure for Interrupted Meyer–Schuster Rearrangement of Propargyl Alcohols

Under atmospheric conditions, the propargyl alcohol (1.00 equiv.) and the corresponding sulfoxide (4.00 equiv.) were dissolved in nitromethane (1 M). Trifluoromethanesulfonic acid (0.20 equiv.) was added in one portion and the reaction mixture was stirred at the indicated temperature until TLC analysis showed full consumption of the starting material. Heating was ceased and the reaction was terminated by addition of a saturated aqueous solution of sodium bicarbonate, followed by ethyl acetate. The phases were separated, the organic phase was dried over anhydrous sodium sulfate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Flash column chromatography purification afforded the corresponding α-arylated α,β-unsaturated carbonyl compound.

Phenyl(2-phenylbenzo[*b*]thiophen-3-yl)methanone (26)

To a solution of (*E*)-2-[2-(methylthio)phenyl]-1,3-diphenylprop-2-en-1-one (**9ae**, 19.9 mg, 0.0602 mmol, 1.00 equiv.) in 1,2-dichloroethane (3.00 mL, 0.02 M), *N*-bromosuccinimide (11.3 mg, 0.0632 mmol, 1.05 equiv.) was added and the reaction mixture was heated at 40 °C. After 20 h, 1 M hydrochloric acid (2 mL) was added and the resulting biphasic mixture was extracted with dichloromethane (2×5 mL). The combined organic phases were dried over anhydrous sodium sulfate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (heptane/ethyl acetate 9/1) to afford of the title compound as a light yellow oil; yield: 17 mg (90%).

3-(4-Fluorophenyl)-2-[2-(methylthio)phenyl]-1-phenylpropan-1-one (24)

An aqueous suspension of an excess of activated Raney nickel was washed with anhydrous acetone (3×5 mL) under an argon atmosphere and ultimately covered in acetone (2.00 mL, 0.05 M). To this suspension, (*E*)-3-(4-fluorophenyl)-2-[2-(methylthio)phenyl]-1-phenylprop-2-en-1-one (**9le**, 34.8 mg, 0.100 mmol, 1.00 equiv.) was added. The reaction vessel was evacuated and back-filled with hydrogen gas three times, after which the reaction mixture was stirred vigorously at 25 °C under a hydrogen atmosphere. After 15 h, when TLC analysis indicated full consumption of the starting material, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (heptane/ethyl acetate 6/1) to afford an inseparable colourless oil (yield: 23 mg), containing a mixture of the title compound (59%) and 3-(4-fluorophenyl)-1,2-diphenylpropan-1-one (**23**, 8%).

(*E*)-2-{2-Phenyl-1-[2-(phenylthio)phenyl]vinyl}-tetrahydrofuran (25)

To a solution of (*E*)-6-chloro-1-phenyl-2-[2-(phenylthio)phenyl]hex-1-en-3-one (**9ia**, 30.0 mg, 0.0763 mmol, 1.00 equiv.) in methanol (760 μL, 0.1 M), cerium(III) chloride heptahydrate (28.4 mg, 0.0763 mmol, 1.00 equiv.) was added and the reaction mixture was stirred at 25 °C. After 15 min, sodium borohydride (3.03 mg, 0.0802 mmol, 1.05 equiv.) was added and stirring was continued at 25 °C. After 2 h, when TLC analysis showed no remaining starting material, a saturated aqueous solution of ammonium chloride (2 mL) was added

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and the resulting mixture was extracted with diethyl ether (2×5 mL). The combined organic phases were dried over anhydrous sodium sulfate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. The crude residue was subsequently dissolved in tetrahydrofuran (760 μL, 0.1 M) and the solution was cooled to 0 °C. At this temperature, silver(I) oxide (19.5 mg, 0.0839 mmol, 1.10 equiv.) and silver(I) trifluoromethanesulfonate (4.90 mg, 0.0191 mmol, 0.250 equiv.) were added and the resulting suspension was warmed to 50 °C. After 24 h, the reaction mixture was filtered through a pad of diatomaceous earth with ethyl acetate. The filtrate was washed with a saturated aqueous solution of sodium bicarbonate (10 mL) and the washed solution was dried over anhydrous sodium sulfate, before being filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (heptane/ethyl acetate 7/1) to afford the title compound as a yellow oil; yield: 20 mg (75%).

3-(4-Fluorophenyl)-1,2-diphenylpropan-1-one (23)

An aqueous suspension of an excess of activated Raney nickel was washed with anhydrous ethanol (3×5 mL) under an argon atmosphere and ultimately covered in ethanol (1.50 mL, 0.07 M). To this suspension, (*E*)-3-(4-fluorophenyl)-2-[2-(methylthio)phenyl]-1-phenylprop-2-en-1-one (**9le**, 34.8 mg, 0.100 mmol, 1.00 equiv.) was added and the reaction mixture was stirred vigorously at 25 °C. After 1 h, when TLC analysis indicated full consumption of the starting material, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was dissolved in dichloromethane (1.00 mL, 0.1 M) and to the resulting solution, Dess–Martin periodinane (DMP, 48.8 mg, 0.115 mmol, 1.15 equiv.) was added. After stirring at 25 °C for 1 h, excess oxidant was quenched by the addition of a saturated aqueous solution of sodium sulfite (1 mL) and the reaction mixture was neutralized by the addition of a saturated aqueous solution of sodium bicarbonate (2 mL). The mixture was extracted with dichloromethane (2×5 mL) and the combined organic phases were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (heptane/ethyl acetate 6/1) to afford the title compound as a colourless solid; yield: 26 mg (85%).

1-Methyl-4-[2-(methylthio)phenyl]-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole (22a) and 1-Methyl-4-[2-(methylthio)phenyl]-3,5-diphenyl-1*H*-pyrazole (22b)

To a solution of (*E*)-2-[2-(methylthio)phenyl]-1,3-diphenylprop-2-en-1-one (**9ae**, 80.0 mg, 0.242 mmol, 1.00 equiv.), and methylhydrazine (63.7 μL, 1.21 mmol, 5.00 equiv.) in ethanol (2.40 mL, 0.1 M), indium(III) chloride (21.4 mg, 0.0968 mmol, 0.400 equiv.) was added and the resulting mixture was heated at 80 °C for 19 h. After TLC analysis showed full consumption of the starting material, a saturated aqueous solution of ammonium chloride (10 mL) was added and the resulting mixture was extracted with ethyl acetate (2×7 mL). The combined organic phases were washed with a saturated aqueous solution of sodium chloride (5 mL) and subsequently dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (heptane/ethyl acetate 3/1) to afford **22a** as an off-white solid (yield: 62 mg, 71%) and **22b** as an off-white solid (yield: 20.5 mg, 24%).

5-[2-(Methylthio)phenyl]-4,6-diphenylpyrimidin-2-amine (21)

Under an atmosphere of air, a solution of (*E*)-2-[2-(methylthio)phenyl]-1,3-diphenylprop-2-en-1-one (**9ae**, 30.0 mg, 0.0908 mmol, 1.00 equiv.), guanidinium chloride (17.3 mg, 0.182 mmol, 2.00 equiv.) and sodium hydroxide (18.2 mg, 0.454 mmol, 5.00 equiv.) in ethanol (454 μL, 0.2 M) was heated at 75 °C for 14 h. After this time, the base was quenched by the addition of a saturated aqueous solution of ammonium chloride (10 mL) and the resulting mixture was extracted with ethyl acetate (2×7 mL). The combined organic phases were washed with a saturated aqueous solution of sodium bicarbonate (5 mL) and subsequently dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (heptane/ethyl acetate 1/1) to afford the title compound as a yellow solid; yield: 10 mg (30%).

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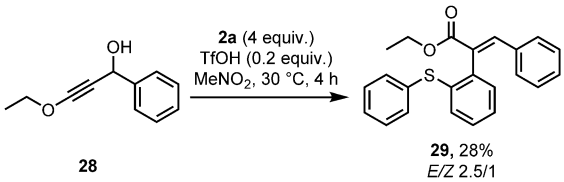

28 **29**, 28%, *E*/*Z* 2.5/1

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[11] Differences in the energy barriers of the [3,3]-sigmatropic shift are also reflected in the geometries of the corresponding transition states. Thus, in the case of reaction with PhS(O)Me, the reactants have to move further along the reaction coordinate in order to attain the transition state, corroborating a more difficult reaction in this case. See the Supporting Information for details.

[12] See the Supporting Information and ref.[2f] for details on control competition experiments; In further attempts at elucidation of the reaction mechanism, electrospray ionization mass spectrometry was employed in order to monitor ionic intermediates or other species generated from the fragmentation of such transiently

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Redox-Neutral Arylations of Vinyl Cation Intermediates

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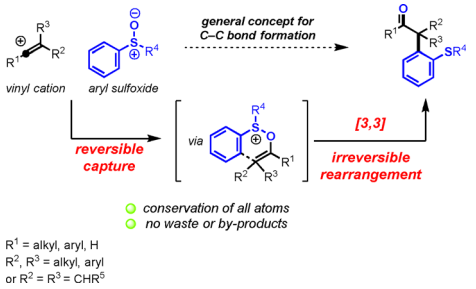

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