

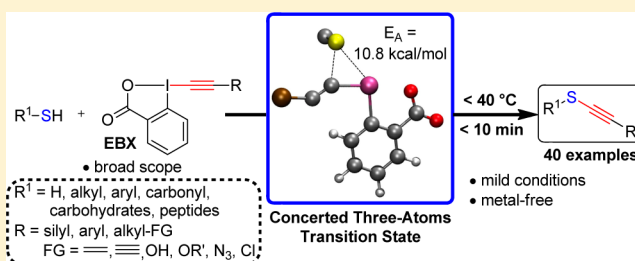
Fast and Highly Chemoselective Alkynylation of Thiols with Hypervalent Iodine Reagents Enabled through a Low Energy Barrier Concerted Mechanism

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S Supporting Information

ABSTRACT: Among all functional groups, alkynes occupy a privileged position in synthetic and medicinal chemistry, chemical biology, and materials science. Thioalkynes, in particular, are highly useful, as they combine the enhanced reactivity of the triple bond with a sulfur atom frequently encountered in bioactive compounds and materials. Nevertheless, general methods to access these compounds are lacking. In this article, we describe the mechanism and full scope of the alkynylation of thiols using ethynyl benziodoxolone (EBX) hypervalent iodine reagents. Computations led to the discovery of a new, three-atom concerted transition state with a very low energy barrier, which rationalizes the high reaction rate. On the basis of this result, the scope of the reaction was extended to the synthesis of aryl- and alkyl-substituted alkynes containing a broad range of functional groups. New sulfur nucleophiles such as thioglycosides, thioacids, and sodium hydrogen sulfide were also alkynylated successfully to lead to the most general and practical method yet reported for the synthesis of thioalkynes.



INTRODUCTION

One of the most important tasks of organic chemistry is discovering practical and general methods for introducing functional groups into molecules to modify their properties and to serve as a platform for further modifications. At a time when research in neighboring fields such as medicine, biology, or materials science is becoming increasingly molecular, easy-to-perform transformative reactions that do not require highly specialized synthetic skills have a particularly broad impact. Among all functional groups in organic chemistry, alkynes occupy a privileged position in this respect.¹ Despite being one of the simplest functional groups with only two carbon atoms, the reactivity of the triple bond makes alkynes exceptionally useful in organic chemistry. They have found applications in bulk chemical synthesis based on acetylene gas² as well as in fine chemistry for the stereoselective construction of the carbon backbone of complex natural products³ and in a myriad of complexity-enhancing metal-catalyzed cyclization reactions to access carbo- and heterocycles.⁴ Most importantly, the utility of alkynes has now crossed the boundaries of organic chemistry: their electronic properties have led to widespread applications in organic materials and dyes⁵ and the [3 + 2] cycloaddition with azides is now recognized as one of the best biorthogonal conjugation method to modify biomolecules and polymers.⁶ The latter transformation is particularly representative of how discoveries in fundamental organic reactivity can strongly

impact neighboring research areas. When considering the importance of alkynes for progress in numerous fields of molecular sciences, the development of new methods to access them efficiently under user-friendly conditions is highly desirable.

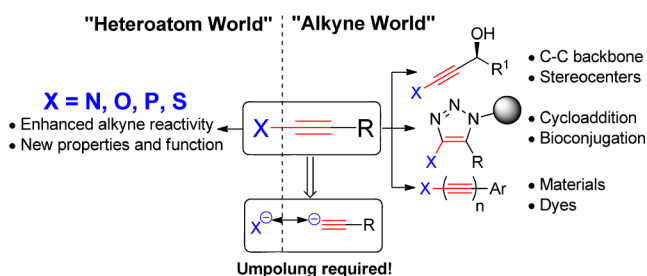
Among the different classes of alkynes, those directly substituted by a heteroatom are especially interesting for two reasons:⁷ (1) the electron-rich heteroatom makes the triple bond more reactive, allowing new chemical transformations and (2) they constitute value-added building blocks, as heteroatoms are essential for the physical and biological properties of small molecules. In short, they bring together the new properties conferred by heteroatoms with the exceptionally rich chemistry of alkynes (Scheme 1). Nevertheless, the synthetic potential of heteroatom-substituted alkynes has long remained underdeveloped due to the absence of convenient methods to access these often sensitive compounds. The coupling of heteroatoms with acetylides is indeed not favorable, as both fragments are inherently nucleophilic and an Umpolung of the reactivity is required.

In the specific case of nitrogen-substituted alkynes (ynamines and ynamides), however, the situation has changed dramatically in the last two decades, when new synthetic methods for the

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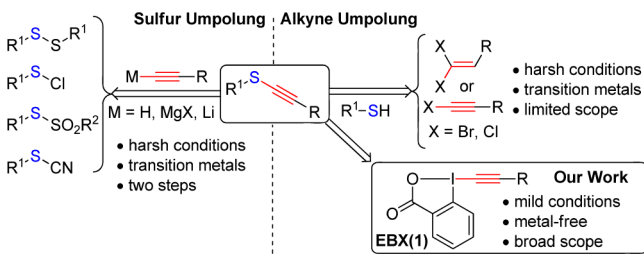
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Scheme 1. Heteroatoms-Substituted Alkynes: The Best of Two Worlds, but How To Access Them?



alkynylation of nitrogen with either hypervalent iodine reagents or terminal and halogeno alkynes in the presence of copper catalysts were developed.⁸ Ynamides in particular are now intensively used in modern synthetic chemistry.^{7c,d} In contrast, the chemistry of thioalkynes is still underdeveloped. This is surprising considering the importance of sulfur in drugs, materials and biomolecules.⁹ In fact, the high nucleophilicity of thiols has led to the development of very efficient methods for the formation of S–S (oxidative disulfide formation), S–C(sp³) (alkylation, thiol–ene) and S–C(sp²) (thiol–yne) bonds.¹⁰ All of these reactions are routinely used for important transformations in chemical biology and materials science. Until very recently, the direct synthesis of thioalkynes from thiols, on the other hand, has been limited to addition–elimination reactions on alkynyl or alkenyl halides under strongly basic conditions (Scheme 2).¹¹ The most commonly used methods permitting

Scheme 2. Method To Access Thioalkynes Based on Umpolung of Sulfur or Alkyne



access have been based on the reaction of terminal alkynes with activated sulfur derivatives bearing a leaving group, such as chloride, tosyl or cyano, or disulfides.¹² This lack of efficient synthetic methods under mild conditions has clearly limited the applications of potentially very useful thioalkynes in synthetic and medicinal chemistry.

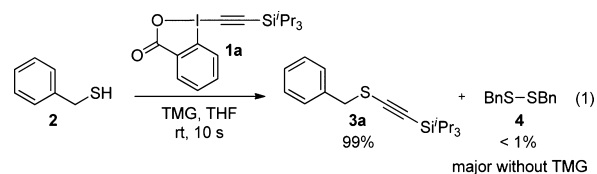
In 2013, the first efficient metal-catalyzed examples of alkynylation of thiols appeared using copper, palladium or nickel catalysts.¹³ Nevertheless, these transformations still required the use of a transition metal catalyst, and the scope of thiols described in these works remained limited to very simple thiophenols and aliphatic thiols^{13a} or to thioglycosides,^{13b,c} respectively. The same year, our group reported the first method for the alkynylation of thiols using 1-[(triisopropylsilyl)ethynyl]-1,2-benzodioxol-3(1H)-one (TIPS-EBX, **1a**, R = SiⁱPr₃).¹⁴ In contrast to previously published methods, the reaction was efficient and user-friendly, leading to the complete alkynylation of aromatic and aliphatic thiols in less than 1 min at room temperature in an open flask. Furthermore, selective alkynylation of thiols was possible in the presence of numerous functional groups such as halogens,

alcohols, carboxylic acids, electron-rich aromatic groups or free amines. Nevertheless, two aspects of the developed methodology were not fully satisfying: (1) The mechanistic basis of the extreme efficiency of the reaction could not be rationalized. An in-depth understanding of the alkylation would be highly useful for further development. (2) The reaction was limited to the transfer of silyl acetylenes on thiols as nucleophiles. Although we demonstrated that the obtained products could easily be deprotected and functionalized, this made our approach less convergent and attractive if the introduction of functionalized alkyne groups is desired. Furthermore, the alkynylation of other sulfur nucleophiles such as thioacetals, thioacids or sulfides salts would also be important in extending the range of accessible thioalkynes.

In this article, we address both issues. On the basis of the isolated side products and computational studies, we propose a mechanism for the reaction. In particular, computations showed that a concerted transition state between the deprotonated thiol and the iodine reagent was possible, leading to an exceptionally low (10.8 kcal/mol) activation energy for the alkynylation using silylated EBX reagents. This type of mechanism has never been proposed for the alkynylation of nucleophiles using hypervalent iodine reagents and is expected to change the way many researchers think about these transformations. We then report an extension of the alkynylation reaction to the use of aryl and functionalized alkyl acetylenes and further extend the scope of thiols to thioglycosides, thioacids and sulfide salts, resulting in the most general and practical thiol alkynylation method reported to date.

RESULTS AND DISCUSSION

Mechanism and Computational Studies. Investigating the reaction mechanism of the alkynylation with TIPS-EBX (**1a**) is particularly challenging because of the fast rate: even 10 s after addition of the reagent, full conversion of thiol **2** was already observed when using 1,1,3,3-tetramethyl guanidine (TMG) as a base (eq 1). Furthermore, low-temperature

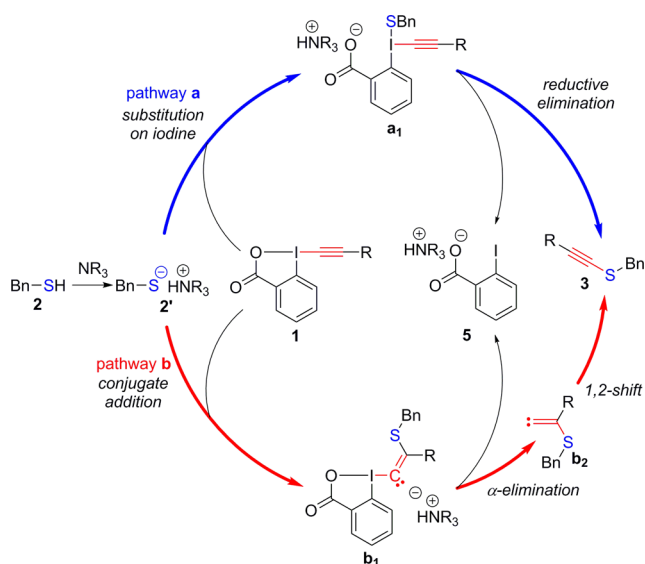


experiments are difficult because of low solubility of the hypervalent iodine reagent below 0 °C. Nevertheless, control experiments showed that no or very little alkynylation was observed in the absence of a base. In this case, oxidative dimerization to form disulfide **4** was the major process. In addition, no reaction or interaction was observed by NMR between reagent **1a** and TMG. These results permit the reasonable assumption that deprotonation of thiol **2** to form thiolate **2'** is required for the reaction to occur (Scheme 3).

From this point forward, a first possible mechanism would be substitution on iodine to give intermediate **a**₁, followed by reductive elimination (pathway **a**, blue in Scheme 3). This mechanism is well-established in hypervalent iodine chemistry, especially with aryliodonium salts.¹⁵

Alternatively, a single electron transfer mechanism (SET) has also been proposed.¹⁶ Nevertheless, in the case of the alkynylation reaction, no radical intermediate could be trapped when using TEMPO as a reagent and the reaction occurred

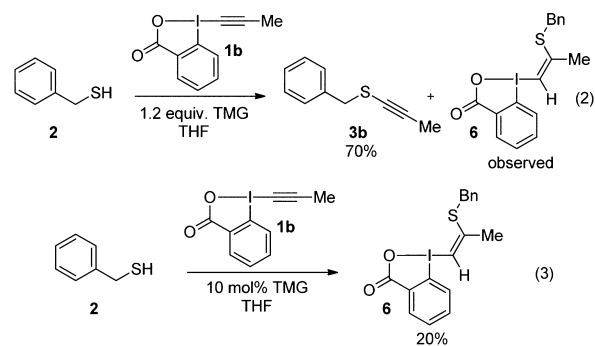
Scheme 3. Initial Speculative Mechanism for the Alkynylation Reaction



with the same yield and reaction time. Although this experiment is naturally not sufficient to exclude a SET pathway, it is also important to note that most reactions of hypervalent iodine reagents occurring via a SET pathway require activation of the reagent by a Lewis or Brønsted acid to accelerate electron transfer,¹⁶ and the alkynylation reaction occurs only under basic conditions.

Nevertheless, alkynyliodonium salts constitute a unique class of hypervalent iodine reagents, as the β -carbon of the alkyne has very strong electrophilic character.¹⁷ In this case, an alternative mechanism is possible: conjugate addition of the thiolate 2' on EBX 1 to give a vinyl benziodoxolone intermediate **b**₁ (pathway b, red in Scheme 3). From **b**₁, α -elimination of iodobenzoate 5 followed by a 1,2-shift of either the sulfur or silyl substituent gave thioalkyne 3. In fact, this type of mechanism was proposed by Ochiai and co-workers in the case of carbon nucleophiles based on the isolation of C–H insertion products originating from carbene intermediate **b**₂.¹⁸ Importantly, such insertion products could be observed only when carbon-substituted alkynyliodonium salts were used in the reaction, as the 1,2-shift of silyl groups was faster than insertion reactions.

To establish if Ochiai's mechanism was also correct in the case of sulfur nucleophiles, we decided to investigate Me-EBX (1b) as a reagent, as the methyl group was expected to have a very low migrating aptitude. This reagent was easily synthesized using the one-step protocol recently developed by Olofsson and co-workers.¹⁹ Surprisingly, the desired alkynylation product 3b could still be isolated in 70% yield, although the reaction was less clean than usual (eq 2). In particular, a polar side product with NMR signals in accordance with vinyl benziodoxolone 6 could be observed, although the small quantities of 6 formed did not allow us to isolate this product in pure form at this stage. Compound 6 most likely originated from protonation of intermediate **b**₁. Consequently, we hypothesized that its formation could be favored if only a catalytic amount of base was used. Indeed, this was the case and we were pleased to see that 6 precipitated directly from the reaction mixture in 20% yield as a single *Z* isomer when only 10 mol % of TMG was used (eq 3). The isolation of 6 constituted



strong support for the conjugate-addition/ α -elimination/1,2-shift mechanism. Furthermore, the relatively good yield of isolated alkynylation product was in accordance with a shift of the sulfur atom, as the migration of the methyl group was expected to be too slow to be productive.

Nevertheless, no intermediate could be observed in the case of TIPS-EBX (1a). To gain a more comprehensive understanding of the mechanistic details leading to thioalkyne formation, density functional theory (DFT) computations were undertaken using benzyl thiol (2) as a substrate. As described above, in the most likely scenario, a deprotonated thiol directly attacks TIPS-EBX (1a). This occurs either by direct attack onto the hypervalent iodine atom (pathway a in Scheme 3) or through a conjugate addition (pathway b in Scheme 3). Computations (at the PBE0-dDsC/TZ2P//M06-2X/def2-SVP theoretical level, see Computational Details for additional information) designed to probe the potential energy surface revealed two low-energy van der Waals complexes that roughly correspond to the entry points into the two mechanistic pathways a and b. The first, **a**₀ in Figure 1, is a lower energy

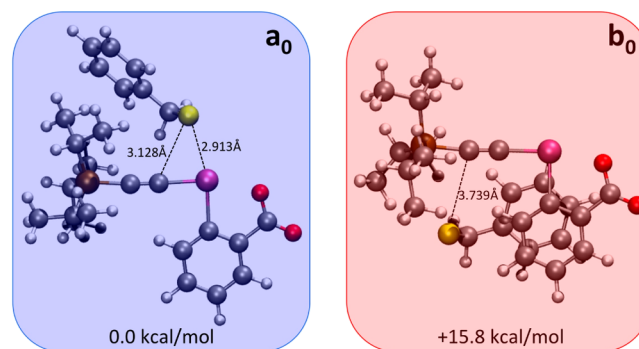


Figure 1. Computed geometries (M06-2X/def2-SVP level) of the van der Waals complexes **a**₀ and **b**₀ for TIPS-EBX (1c) and thiolate 2'. Free energies computed at the PBE0-dDsC/TZ2P//M06-2X/def2-SVP level and include solvation correction in THF determined using COSMO-RS.

conformation in which the sulfur atom and the iodine atom are in close proximity (2.913 Å). However, the sulfur atom is not exactly opposite to the aryl ring as generally expected for interaction of nucleophiles with hypervalent iodine reagents, but instead lies in a position roughly equidistant between the iodine (2.913 Å) and α -carbon (3.128 Å) atoms of the acetylene. A second complex (**b**₀ in Figure 1), lying \sim 15.8 kcal/mol higher in energy, was found to correspond to the aforementioned conjugate addition pathway b. Here, the sulfur atom of the deprotonated thiol can clearly participate in a direct attack on the β -carbon of the acetylene unit.

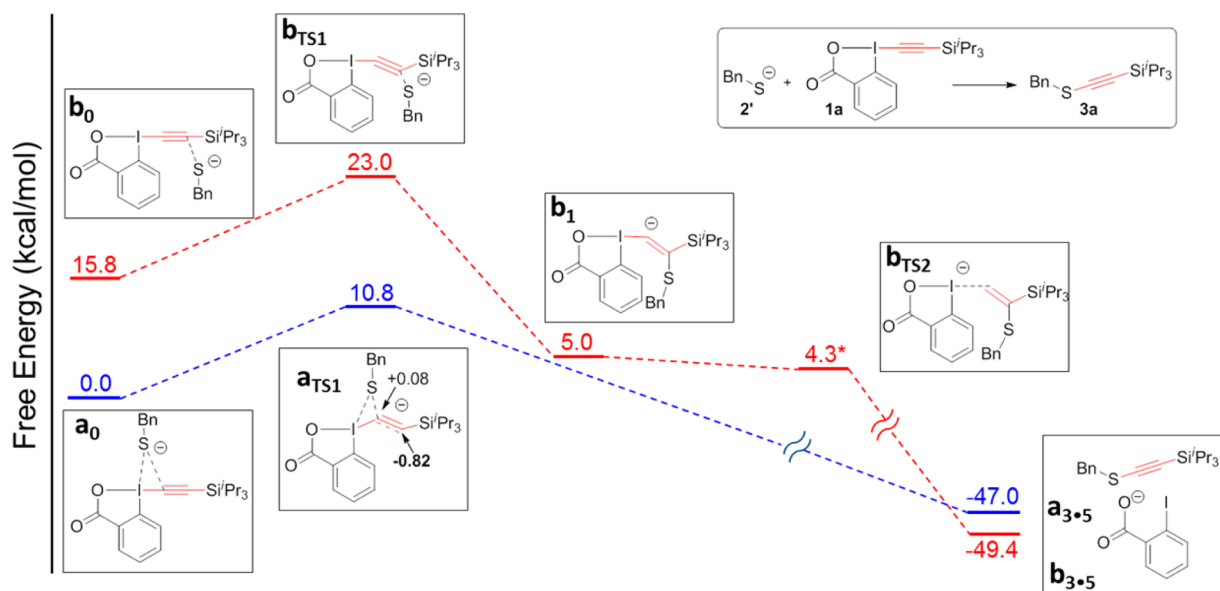


Figure 2. Reaction free energy profile [PBE0-dDsC/TZ2P//M06-2X/def2-SVP level in implicit THF solvent (COSMO-RS)] for the two possible mechanistic pathways a (blue) and b (red) for the reaction of TIPS-EBX (1a) with thiolate 2'. *Positive ΔE at the M06-2X/def2-SVP level.

Our initial assumption was that complex a_0 (depicted in blue) is the reactant species leading to formation of a S–I bond, as represented by intermediate a_1 . To our surprise, no minima containing a formal S–I bond could be located on the potential energy surface (Figure 2, blue pathway). Instead, the quasi-triangular atomic arrangement between the sulfur, iodine, and α -carbon atoms results in a direct addition of the sulfur onto the α -carbon atom of the acetylene unit with simultaneous breaking of the C–I bond.²⁰ This process is associated with a quite modest a_{TS1} barrier height of only 10.8 kcal/mol.²¹ Upon formation of the new S–C bond (Figure 3, a_{TS1} in blue), the thioalkyne-iodobenzoic acid complex $a_{3.5}$ is spontaneously formed in a highly exergonic process. Importantly, we find no computational evidence predicting formation of a stable intermediate, which is in agreement with our failure to isolate any side products with TIPS-EBX (1a) as reagent.

The conjugate addition pathway **b** (Figure 2, red pathway), begins from the higher energy (+15.8 kcal/mol, red) van der Waals complex b_0 . Here, the reaction proceeds as originally proposed by Ochiai.¹⁸ Formation of the new S–C bond occurs in a facile process, requiring only ~ 7.2 kcal/mol of energy (b_{TS1}). In contrast to the previously discussed pathway, the β -carbon conjugate addition route **b** does lead to the formation of the expected intermediate species b_1 . However, the TS barrier associated with cleavage of the I–C bond (b_{TS2} , Figure 3) is negligible ($\Delta G = -0.7$ kcal/mol at the PBE0-dDsC/TZ2P//M06-2X/def2-SVP level, $\Delta E = +0.3$ kcal/mol at the M06-2X/def2-TZVP//M06-2X/def2-SVP level), meaning the species is likely short-lived, making experimental characterization, observation or even protonation highly unlikely. As in pathway **a**, formation of the final product complex is highly exergonic, proceeding via a 1,2-shift of the silicon atom. No minima corresponding to a free carbene b_2 could be located on the potential energy surface.

From the reaction free energy profile in Figure 2, it is clear that both the **a** (blue) and **b** pathway (red) mechanisms are easily accessible at room temperature. While the β -conjugate addition pathway **b** involves a slightly lower TS barrier b_{TS1} corresponding to S–C bond formation, the lower relative

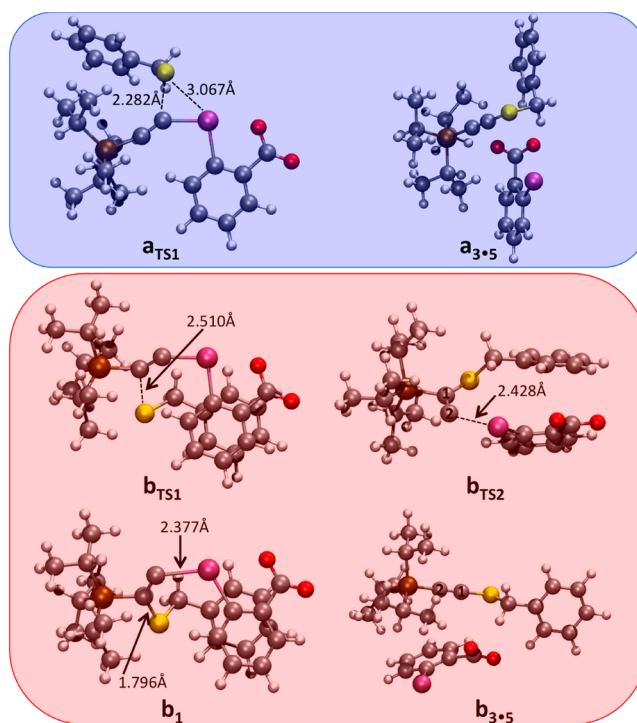


Figure 3. Computed geometries (M06-2X/def2-SVP level) of the relevant structures.

energy of the α -addition van der Waals complex a_0 (blue, Figure 1) results in pathway **a** being the overall energetically preferred reaction mechanism by 12.2 kcal/mol. This is highly interesting, considering that a mechanism involving addition to the α -carbon atom concerted with elimination of the iodine has never seriously been considered for alkynyl hypervalent iodine reagents.

To ensure that other mechanisms that include either direct attack by a protonated thiol or explicit involvement of the base (TMG) are not more energetically favorable, we computed a number of additional pathways (see SI for details). However,

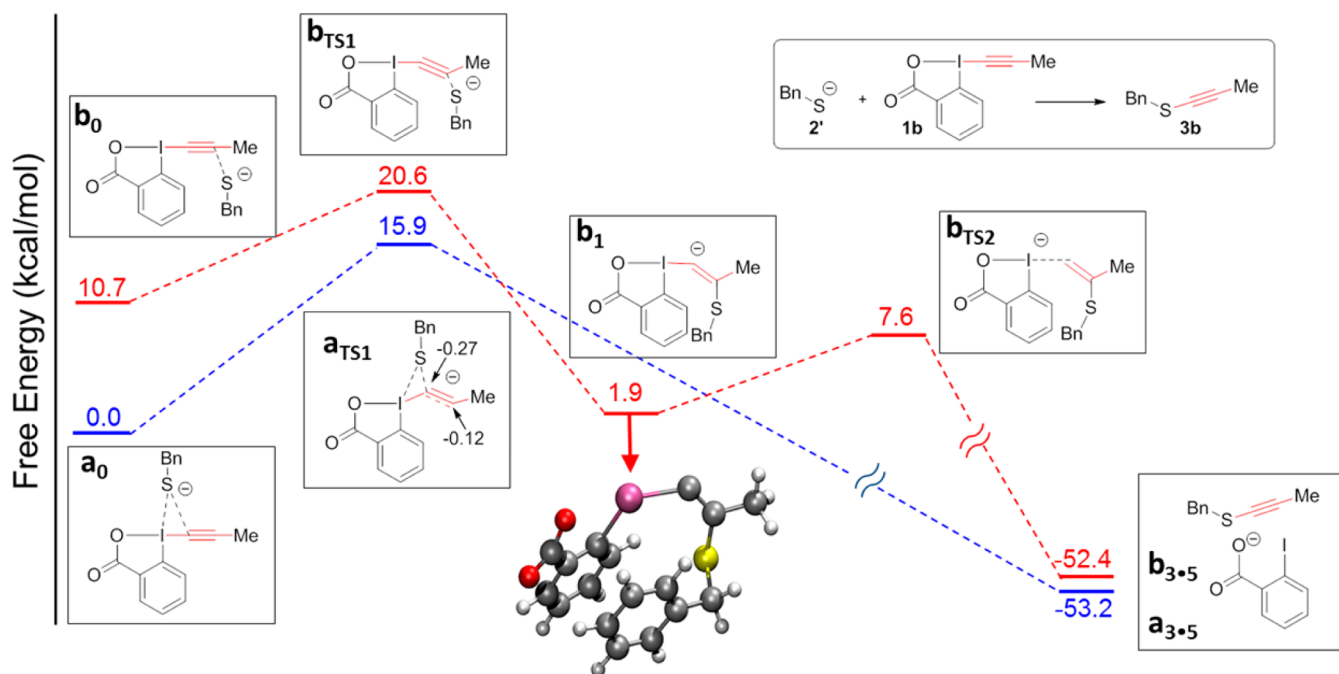


Figure 4. Reaction free energy profile [PBE0-dDsC/TZ2P//M06-2X/def2-SVP level in implicit THF solvent (COSMO-RS)] for the two possible mechanistic pathways a (blue) and b (red) for the reaction of Me-EBX (**1b**) with thiolate **2'**.

none were found to be energetically competitive with the direct attack of thiolate mechanism described above. As an example, direct attack by the protonated thiol species involves a TS barrier of 32.6 kcal/mol for S–C bond formation. This compares quite unfavorably to the 10.8 kcal/mol barrier seen when the deprotonated thiol is involved in a direct attack type mechanism.²²

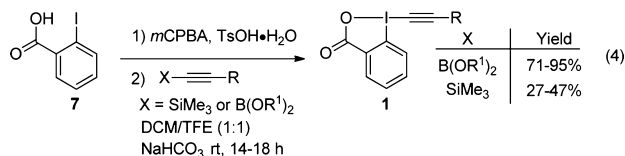
The computational results obtained for the reaction of TIPS-EBX (**1a**) are highly interesting. Nevertheless, they seemed to be in contradiction with the isolation of side product **6** when Me-EBX (**1b**) was used (eq 3), as **6** would be generated from very short-lived intermediate **b₁** via the least favored pathway **b**. To see if this result could be rationalized by computation, we also examined the reaction free energy profile for Me-EBX (**1b**) (Figure 4). Like for TIPS-EBX (**1a**) (Figure 2), a mechanism featuring attack on the α -carbon is favored based on enhanced stability of the prereaction van der Waals complex **a₀** and **b₀**. In contrast, however, the TS barrier associated with formation of the S–C bond (**a_{TS1}** and **b_{TS1}**, Figure 4) lie relatively close to each other (within 5 kcal/mol at the PBE0-dDsC/TZ2P level and within 2 kcal/mol at the M06-2X/def2-TZVP level).²³ Since this first transition state represents the highest point along the reaction pathway for both mechanisms, it can be envisaged that a small percentage of reactions proceed via the red pathway **a**, as opposed to the more energetically favorable blue pathway **b**. Furthermore, a significant **b_{TS2}** barrier height (+5.7 kcal/mol) is obtained, in contrast to the reaction with silylated reagent **1c**. This enhanced barrier, probably due to the less favorable shift of the sulfur group in this case, likely equates to a longer-lived intermediate that can be protonated and observed as **6** (eq 3).

When comparing the lowest energy pathway **a** for the reaction of TIPS-EBX (**1a**) and Me-EBX (**1b**), a strong accelerating effect of the silicium atom (about 5 kcal/mol) is apparent. Although understanding fully this effect will require more in-depth studies, some insights can already be gained by

looking closely at the unsymmetrical structure of transition state **a_{TS1}**. Indeed, the sulfur atom is already in close proximity to the α carbon atom of the alkyne, and the geometry around the β carbon is strongly distorted from sp to sp^2 . This would lead to the formation of a partial charge on the β carbon. Indeed, calculations indicated an iterative Hirshfeld charge of -0.82 at this position in the case of TIPS-EBX (**1a**) (Figure 2). In contrast, no strong charge transfer was observed in the case of Me-EBX (**1b**) (charges of -0.27 and -0.12 at the α and β positions, respectively, Figure 4). Silicium is well-known to stabilize negative charges on adjacent carbons (α -silicium effect).²⁴ Consequently, a lower activation barrier could be expected in this case through transition state stabilization.

■ SCOPE EXTENSION

The previous method developed in our group was very efficient using TIPS-EBX (**1a**) as a reagent. However, to introduce a fluorophore or other functional groups on the alkyne, two further steps were required (silyl deprotection and cycloaddition), making the approach less convergent.^{14a} Furthermore, sensitive substrates could potentially not resist in the desilylation step using basic TBAF. Consequently, it would be highly desirable to install the desired functionality on the alkyne on the cyclic hypervalent iodine reagent before carrying out the thioalkynylation reaction. On the basis of the side reactions observed by Ochiai and co-workers with alkyl-substituted alkynylodonium salts and carbon nucleophiles,¹⁸ a generalization of the scope appeared highly challenging to us when we started this project. However, the surprisingly good results obtained with Me-EBX (**1b**) during our mechanistic investigations and the very low activation energies obtained by computation indicated that sulfur nucleophiles should behave differently and have a much broader scope in the alkynylation reaction. To test this hypothesis, benziodoxolone hypervalent iodine reagents were first synthesized via Olofsson's one-step method starting from alkynyl boronic esters (eq 4).¹⁹ This



protocol turned out to be very efficient and easily scalable giving the EBX reagents in 71–95% yield in up to 9 g scale in the case of Me-EBX (**1b**). Nevertheless, in case of more functionalized alkynes, it was not possible to access the very sensitive alkynyl boronic esters. In this case, the use of more stable silylated alkynes gave the desired products in 27–47% yield. Importantly, EBX reagents bearing functional groups such as alkenes, alkynes, halogens, azides or alcohols were synthesized for the first time. Although the yield was moderate, the procedure was easily scalable to the multigram scale and the enhanced stability of benziodoxolone compared to alkynylidonium salts allowed easy purification by column chromatography to obtain pure reagents **1**. A significant amount of silyl acetylenes could also be recovered.²⁵

Due to the significance of aromatic thiols as important structural motifs in the synthesis of pharmaceutical, natural, and medicinal compounds and the excellent results obtained in our previous work, we decided to start our investigation with this class of substrates. *o*-Bromo thiophenol **8** was chosen as a substrate for studying the different EBX reagents, as the bromo group constitutes an ideal handle for further functionalization. In the case of aliphatic EBX reagents, we found that TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene) was superior to TMG as a base and THF was still the optimal solvent. When EBX reagent **1b** was added to the mixture consisting of *o*-bromo thiophenol (**8**), TBD, and THF at room temperature and stirred for 5 min in an open flask, the corresponding thioalkynylated product **9a** was obtained in 93% yield (Table 1, entry 1). Noteworthy, the reaction was not affected by the water which was added to increase the solubility of the formed thiolate salts in certain cases. The alkylation with longer alkyl chains (entries 2 and 3) or a *tert*-butyl group (entry 4) proceeded in quantitative yields. At this point, the use of functionalized alkyl-EBX reagents was investigated for the first time (entries 5–9).

We were pleased to see that the alkylation with reagents bearing an alkene, an alkyne, a chloride, an azide or a free alcohol proceeded in 87–98% yield. The fact that functional groups are tolerated both on the thiol and alkyne reagent makes the method more attractive for the synthesis of thioalkynes. Finally, the alkylation was not limited to the transfer of aliphatic alkynes: mesityl-substituted product **9j** was also obtained in quantitative yield (entry 10).

Inspired by the efficiency of the thioalkynylation reaction (Table 1), we further studied the use of EBX reagents for the multiple alkylation of benzene-1,3,5-trithiol (**10**) (eq 5). In

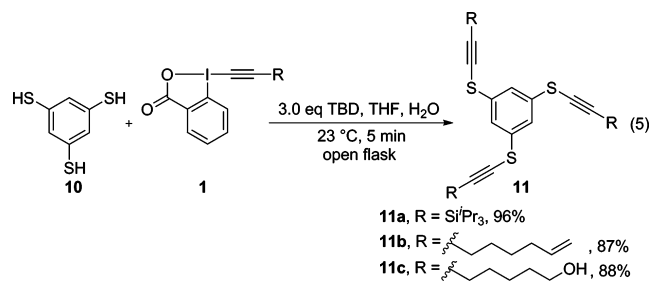


Table 1. Scope of EBX Reagents with *o*-Bromo Thiophenol^a

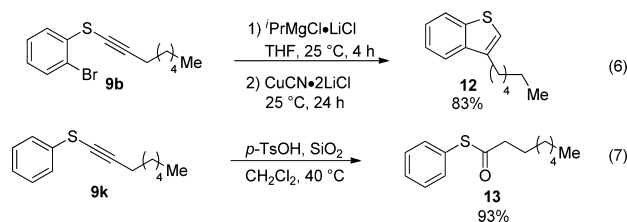
Entry	R-EBX	Product	Yield ^b
1	1b	9a	93%
2	1d	9b	98%
3	1e	9c	98%
4	1f	9d	quant.
5	1g	9e	93%
6	1h	9f	95%
7	1i	9g	87%
8	1j	9h	90%
9	1k	9i	98%
10	1l	9j	quant.

^a*o*-Bromo thiophenol (**8**, 0.30–0.80 mmol), alkyne transfer reagent (**1**, 0.33–0.88 mmol), base (0.30–0.80 mmol), THF (3.75–10.0 mL), 23 °C, 5 min, open flask. ^bIsolated yield after purification by column chromatography.

this context, TIPS-EBX (**1a**) and EBX reagents **1g** and **1k** were examined. We were able to isolate the corresponding triple-alkynylated products **11a–c** in 96%, 87% and 88% yield, respectively. Due to the efficiency of the reaction and the versatility of the introduced functional groups, the method is highly useful for the synthesis of dendrimers with potential applications in materials science or drug delivery.

To further demonstrate the utility of the synthesized thioalkyne products, we investigated their transformation into other useful building blocks. We first examined the transformation of thioalkyne **9b** into the corresponding benzothio-

phene **12** using a protocol developed by Knochel and co-workers (eq 6).²⁶ The addition of ^tPrMgCl·LiCl in THF to **9b**



followed by CuCN·2LiCl afforded the 3-alkyl benzothiophene **12** in 83% yield after 24 h. Thiolakyne **9k**, easily obtained from the alkylation of thiophenol with reagent **1d**, was subjected to acid hydrolysis to furnish the corresponding thioester **13** in 93% yield (eq 7).²⁷

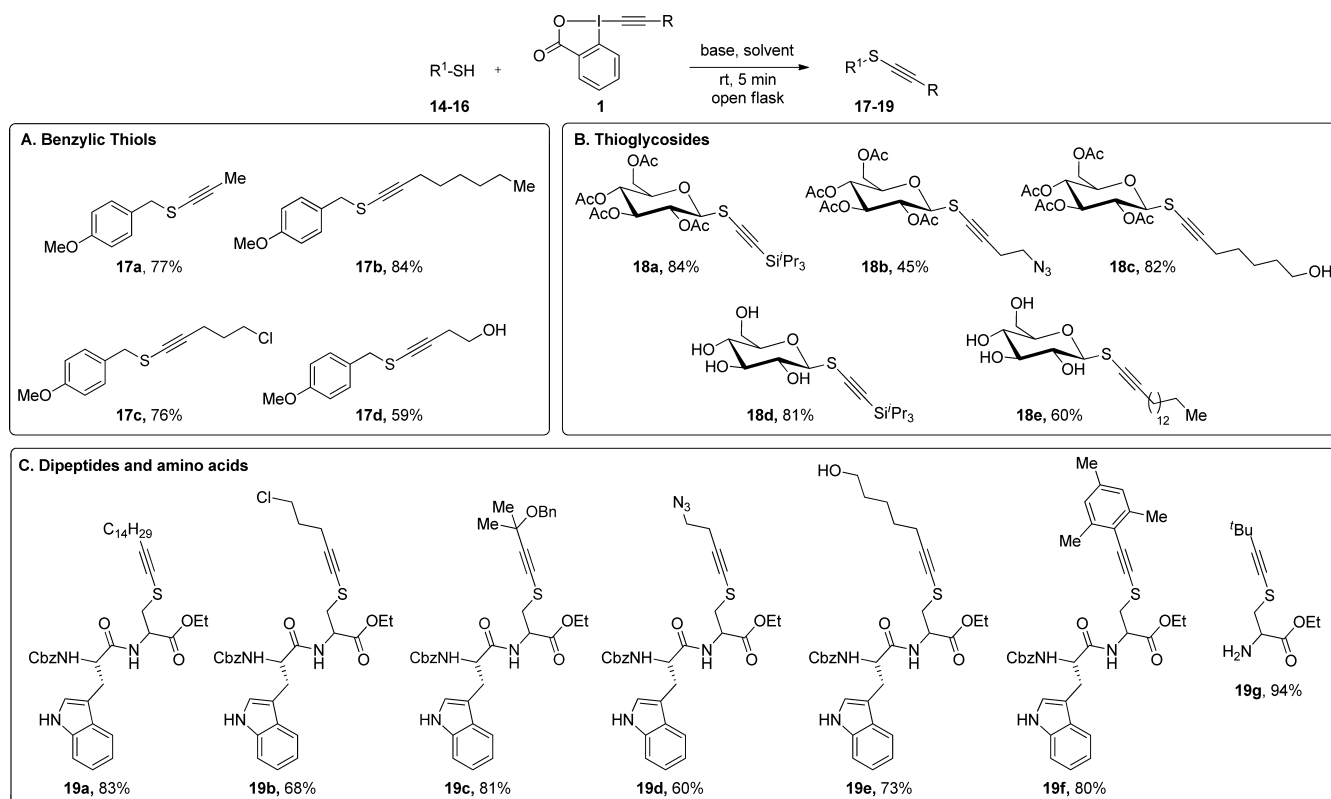
After having successfully extended the scope of the alkylation to alkyl- and aryl-substituted EBX reagents in the case of thiophenols, we turned to aliphatic thiols (Scheme 4). (4-Methoxyphenyl)methanethiol (**14**) was alkynylated successfully, furnishing alkylation products **17a–d** in 59–84% yield (Scheme 4A).²⁸ Again, long and short alkyl chains, as well as a chloride and an alcohol, were well tolerated on the reagent, although the yields were lower than in the case of thiophenols. As a second important class of aliphatic thiols, we decided to turn to thioglycosides (Scheme 4B). These compounds are key building blocks in carbohydrate synthesis and exhibit important biological activities.²⁹ Recently, Messaoudi and co-workers reported the alkylation of protected and unprotected thioglycosides using transition metal catalysts.^{13b,c} Our metal free thioalkynylation method provides a valuable alternative

that avoids the use of expensive or toxic metal catalysts, ligands, base and higher temperature. Furthermore, only the synthesis of aromatic alkynes had been reported to date. Using our method, protected thioglycoside **15a** was alkynylated with TIPS-EBX (**1b**) and reagents **1j** and **1k** in a few minutes at room temperature to afford the corresponding products **18a–c** in 45–84% yield. Protection of the hydroxy groups of the carbohydrate was not required: products **18d** and **18e** bearing four free hydroxy groups were also obtained in 81% and 60% yields, respectively.

After demonstrating that the reaction protocol worked well with simple aliphatic thiols and thioglycosides, we studied the alkylation of a cysteine containing dipeptide **16a** (TrpCys). In fact, cysteine is one of the natural amino acids and plays a key role in the activity and structure of proteins. It is also an ideal entry for bioconjugation reactions.^{9,30} As shown in Scheme 4C, the reaction worked efficiently for a variety of EBX reagents. Substituents containing an alkyl chain without (product **19a**) or with additional functional groups (products **19b–e**) were tolerated including a chloro, an ether,³¹ an azido and a hydroxy group. Finally, a mesityl-substituted alkyne group could also be introduced in 80% yield (product **19f**). The selective alkylation of dipeptide **16a** with different functionalized alkynes is an important preliminary result in view of the modification of more complex molecules, such as peptides and proteins. In addition, the alkylation of N-unprotected cysteine ester **16b** with ^tBu-EBX (**1f**) gave exclusively thiol alkylation in 94% yield.

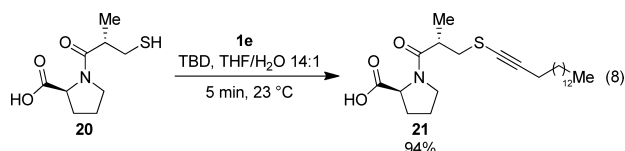
As a last example of more complex aliphatic thiol, angiotensin-converting enzyme (ACE) inhibitor Captopril (**20**), which is used as a drug to treat hypertension,³² was

Scheme 4. Scope of the Alkylation for Benzylic Thiol **14** (A), Thioglycosides **15** (B), and Amino Acid Derivative **16** (C)^a



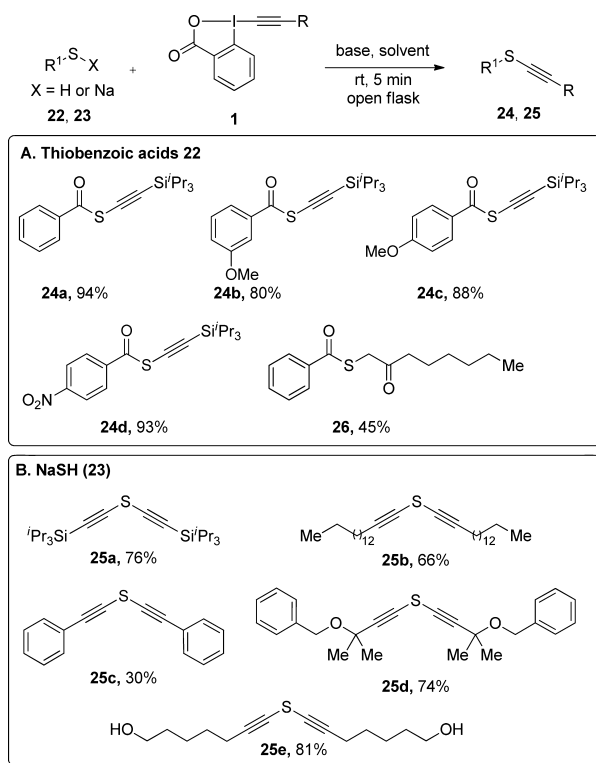
^aSee Supporting Information for experimental details (solvents, base).

successfully alkynylated with **1e** to give the corresponding thioalkyne **21** in 94% yield (eq 8). This result demonstrated that free carboxylic acid groups were tolerated in the alkylation reaction.



To further demonstrate the generality of the alkylation reaction, we studied two classes of sulfur nucleophiles which were not included in our previous studies: thiocarboxylic acids and sodium hydrogen sulfide, the simplest of all sulfur nucleophiles (Scheme 5). Thiocarboxylates are less nucleophilic

Scheme 5. Alkylation of Thioacids **22 (A) and Sodium Hydrogen Sulfide (**23**) (B)**

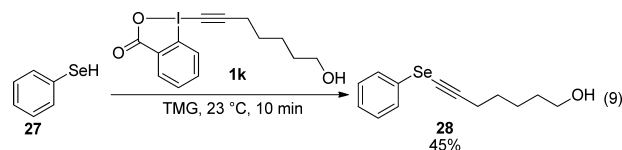


than thiolates. Nevertheless, TIPS-EBX (**1a**) was again an excellent reagent for the alkylation of thiobenzoic acid (**22a**) giving the desired product **24a** in 94% yield. Electron-donating and -withdrawing groups were well tolerated on the benzene ring (products **24b–d**). On the other hand, thioesters derived from aliphatic alkynes were unstable under the reaction conditions, and ketone product **26**, probably resulting from the hydration of the triple bond, was instead isolated in 45% yield. Only very low yields were obtained in the case of aliphatic thioacids (results not shown). Unlike other thiols, the alkylation of thioacids did not require the use of base, probably due to the higher acidity of these substrates.

Due to the significant properties of diethynyl sulfides in material and interstellar chemistry,³³ we then attempted their synthesis through the alkylation of sodium hydrogen sulfide. The resulting one-step protocol would be unprecedentedly fast

to access this class of compounds. The double alkylation worked for all three classes of alkynes: silyl (product **25a**), alkyl (product **25b**) and aryl (product **25c**). The lower yield of the latter is probably due to the low solubility of the reagent Ph-EBX (**1o**). The reaction also worked for the introduction of a propargylic ether (product **25d**) or an alcohol (product **25e**).³⁴

We then examined if the alkylation method could be extended to selenium nucleophiles. In fact, alkynyl selenium compound **28** was obtained in 45% yield from phenylselenol (**27**) without further optimization of the reaction conditions. This preliminary result is promising for the development of a more general method for the alkylation of selenols.



CONCLUSION

In summary, in this manuscript we described the first computational studies of the alkylation of thiols using ethynyl benziodoxolone (EBX) reagents. An unprecedented concerted mechanism involving the sulfur, iodine and α -carbon atoms of the alkyne was discovered by computation, leading directly to the alkylation products with a low activation barrier. In case of silyl-substituted EBX reagents, the activation energy was exceptionally low (10.8 kcal/mol), which made this pathway the most favorable according to the computations and may explain the high rate observed for the reaction. For the case of alkyl-substituted reagents, a second mechanism involving conjugate addition, followed by simultaneous α elimination of iodobenzoic acid and sulfur 1,2-shift was also found to be competitive. This latter result rationalizes the isolation of small amounts of vinyl benziodoxolone intermediate **6** resulting from conjugate addition of benzylthiol (**2**) on Me-EBX (**1b**) followed by protonation.

The unique properties of thiolates in reaction with EBX reagents led us to anticipate that the transformation may have a broader scope than reactions involving carbon nucleophiles. This was indeed the case, and we could use, for the first time, functionalized alkyl- and aryl-substituted EBX reagents for the alkylation of both aromatic and aliphatic thiols. Functional groups such as alkenes, alkynes, ethers, chlorides, azides and alcohols were tolerated on the alkynes. In addition to simple thiophenols and benzylic thiols, the alkylation of cysteine in a dipeptide, thioglycosides, thiobenzoic acid derivatives and sodium hydrogen sulfide was also successful. The practical and user-friendly character of the method (5 min reaction time, open-flask, water tolerance, room temperature) and a deeper understanding of the reaction mechanism have set the stage for a broader application in the functionalization of materials and biomolecules in the future.

COMPUTATIONAL DETAILS

All geometries were optimized using Truhlar's M06-2X³⁵ density functional with the def2-SVP basis set in Gaussian09.³⁶ M06-2X computations employed the "Ultrafine" grid to remove known problems with the size of the integration grid for this functional family.³⁷ To obtain refined energy estimations that explicitly account for nonbonded interactions, a density dependent dispersion correction³⁸ was used appended to the PBE0³⁹ functional (PBE0-dDsC). PBE0-dDsC single point computations made use of the Slater

type orbital 3- ζ basis set, TZ2P, as implemented in ADF.⁴⁰ To confirm the accuracy of the PBE0-dDsC computations, a second set of single point energies was obtained at the M06-2X/def2-TZVP level. All reported free energies include the effects of solvation (in THF) using the implicit continuum model for realistic solvents⁴¹ (COSMO-RS), also as implemented in ADF, as well as free energy correction derived from M06-2X/def2-SVP computations. Iterative Hirshfeld charges⁴² were computed using Q-Chem⁴³ at the M06-2X/def2-SVP level.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures and analytical data for all new compounds. Additional computational, data including Cartesian coordinates of relevant compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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- (21) Computed free energies at the M06-2X/def2-TZVP//M06-2X/def2-SVP level in implicit THF solvent (COSMO-RS) yielded the same trends, albeit with a slightly lower energy difference between the two pathways (Energy a_{TS1} , 11.8 kcal/mol; b_{TS1} , 20.1 kcal/mol; difference, 8.3 kcal/mol. See Supporting Information for details.
- (22) Computation of the transition state a_{TS1} for other nucleophiles was also done in order to better understand the observed chemoselectivity. With methanol and dimethyl phosphite, no transition state could be located. Higher energies were observed for methylamine and acetate as nucleophiles (+30.8 and +18.1 kcal/mol, respectively). In contrast, a low energy transition state (+12.2 kcal/mol) was observed in the case of deprotonated dimethyl phosphite. Indeed, the facile alkylation of this class of nucleophiles was recently reported by our group (ref 14h). See Supporting Information for details.
- (23) Computed free energies at the M06-2X/def2-TZVP//M06-2X/def2-SVP level in implicit THF solvent (COSMO-RS): a_{TS1} , 18.9 kcal/mol; b_{TS1} , 20.8 kcal/mol; difference, 1.9 kcal/mol. In addition, the difference in free energies obtained using B3LYP-dDsC and B3LYP-D3 methods was situated in between the other results (4.3 and 3.3 kcal/mol, respectively). Nevertheless, the importance of the three-atom concerted pathway should not be overestimated at this stage. See Supporting Information for details.
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