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Alkynylation of Thiols with Ethynylbenziodoxolone (EBX) Reagents: α- or β- π-Addition?

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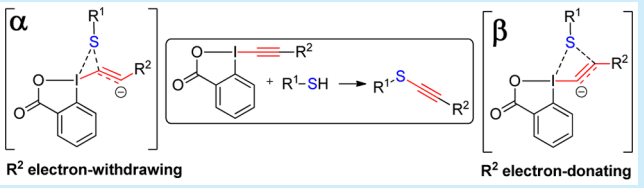
Supporting Information

ABSTRACT: The alkynylation of thiols with EthynylBenziodoXolone (EBX) reagents is a fast and chemoselective method for the synthesis of thioalkynes. Combined experimental and computational studies are reported, which led to the identification of a new mechanism for this reaction, proceeding via an initial sulfur−iodine interaction followed by β-addition, α-elimination, and a 1,2-shift. Depending on the substituent on the alkyne, this mechanism can be favored over the previously disclosed concerted α-addition pathway.

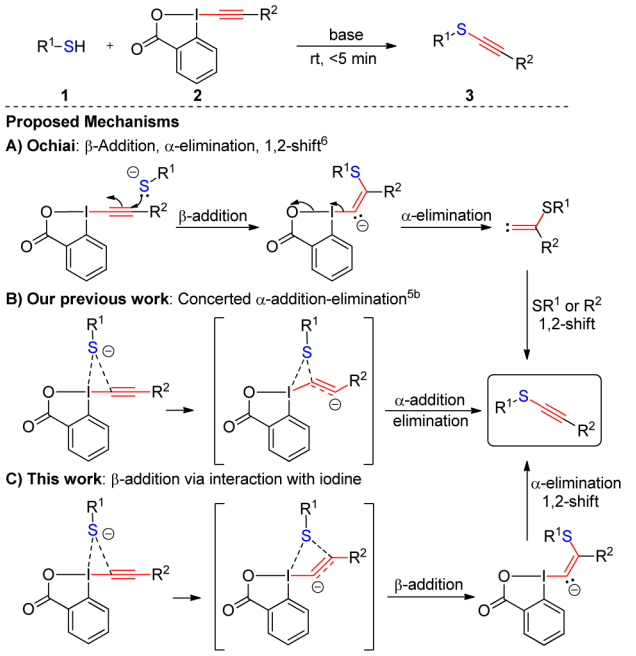


Alkynes are among the most versatile building blocks in synthesis due to their interesting structural properties and the numerous methods available for their transformation.[1] Additionally, they have found a multitude of applications in chemical biology and materials science. Heteroatom-substituted alkynes, such as ynamides and thioalkynes, are particularly interesting owing to their enhanced reactivity.[2] Whereas important breakthroughs have recently been realized in the efficient synthesis of ynamides, most methods for accessing thioalkynes require multiple steps and/or the use of highly reactive intermediates, such as lithium acetylides.[3] Recently, milder metal-catalyzed methods for the alkynylation of thiols have emerged.[4] Our group developed a metal-free alternative approach based on the use of EthynylBenziodoXolone (EBX) hypervalent iodine reagents.[5] Originally limited to the transfer of silyl alkynes, the method was later extended to the synthesis of aryl and alkyl acetylenes and was also applied to the functionalization of cysteines in proteins in the living cell.

Most reactions of nucleophiles with alkynyliodonium salts involve a conjugate addition, α-elimination, and 1,2-shift pathway (Ochiai's mechanism, Scheme 1A).[6] Based on Density Functional Theory (DFT) computations, we proposed in 2014 an unprecedented concerted α-addition mechanism proceeding via a low energy three-atom transition state for the alkynylation of thiols with EBX reagents (Scheme 1B).[5b] Herein, we present further computational results which reveal a third unexpected mechanism, resulting from the shift of a van der Waals complex characterized by a favorable sulfur−iodine interaction directly to a low lying transition state for β-addition (Scheme 1C). Computations predict that either α- or β-addition can be favored depending on the reagent substituents, as supported by a ^{13}C-labeling experiment.

In our previous studies, we demonstrated that thiols could be alkynylated in high yields with both silyl- and alkyl-substituted EBX reagents.[5b] DFT computations led to the discovery of a new concerted α-addition pathway, which was 12.2 kcal/mol lower in energy than β-addition for the alkynylation of benzylthiol **1a** with the commercially available TIPS-EBX reagent **2a** (Scheme 2). However, for Me-EBX **2b** we were able to isolate a side product **4** coming from a β-addition pathway. Computations indeed showed that the difference in energy between the two pathways was smaller for methyl than silyl substituents (4.7 instead of 12.2 kcal/mol). Nevertheless, the α-addition pathway was still significantly lower in energy and the isolation of **4** was therefore intriguing.

Scheme 1. Alkynylation of Thiols and Proposed Mechanisms



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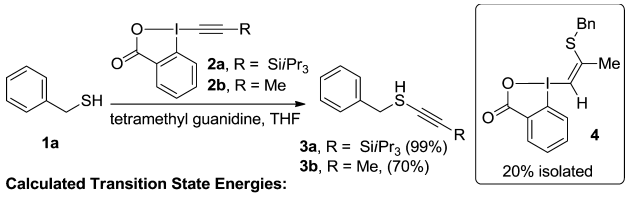
Scheme 2. Alkynylation of Benzyl Thiol 1a and Computed Transition State Energies



Consequently, we conducted additional computations for the alkynylation with EBX reagents (at the PBE0-dDsC/TZ2P//M06-2X/def2-SVP theoretical level; see computational details in the Supporting Information for additional information).[7] Thiophenol **1b** was used as a substrate, rather than the previously employed benzylthiol, to minimize conformational freedom (Figure 1). Lower energy pathways involving direct β-addition of thiophenolate **1b′** on the triple bond could not be identified. In fact, all these attacks involve a nonfavorable van der Waals interaction with the β-position of the alkyne ($\mathbf{b_0}^{old}$). However, when we reinvestigated pathways starting from the more favorable van der Waals interaction complex $\mathbf{a_0}$ between the sulfur and the iodine atom, which was previously identified as the entry point for the concerted α-addition ($\mathbf{a_{TS1}}$), a new low energy pathway proceeding via transition state $\mathbf{b_{TS1}}$ was found. This corresponds to a direct attack of the sulfur atom on the alkyne β-position and is lower in energy than the α-addition pathway (9.3 vs 10.1 kcal/mol). In this new transition state, the sulfur atom attacks at a trajectory 180° to the arene ring, rather than 90° as in the previously identified β-addition pathway.[8] After formation of vinyl intermediate $\mathbf{b_1}$, elimination of iodine occurs readily via transition state $\mathbf{b_{TS2}}$, followed by a barrierless 1,2-silicon shift to give the observed product **5a** and 2-iodobenzoate (**6**).

The new reaction pathway was also computed for Me-EBX **2b** (Figure 2). In this case, β-addition via transition state $\mathbf{b_{TS1}}$ was favored by 5.8 kcal/mol. Furthermore, the obtained vinyl intermediate $\mathbf{b_1}$ was more stable, with a barrier of 12.2 kcal/mol for carbon−iodine bond cleavage. Interestingly, intermediate $\mathbf{b_2}$, corresponding to a vinylidene carbene, could also be identified, as the sulfur shift was significantly slower than the silicon shift. Finally, a relatively facile (8.4 kcal/mol activation energy) 1,2-sulfur shift gives the observed product **5b**.

An important difference between silyl and alkyl reagents in the β-addition pathway is the identity of the migrating group: silicon vs sulfur.[9] In the case of TIPS-EBX **2a**, introducing a ^{13}C label onto the alkyne would unambiguously differentiate the two pathways. Indeed, when thiophenol **1b** was reacted with ^{13}C-labeled reagent **2c**,[10] a 1:1.2 mixture of products labeled in the α- and β-positions to silicon was obtained (products **5a′** and **5a″**; Scheme 3). This result supports the coexistence of the two reactions pathways and agrees well with the small energy difference (0.8 kcal/mol) obtained by computation.

In order to better understand the factors determining the relative energies of the two possible reactions pathways, we computed the reaction of EBX reagents with systematically varied heterocyclic cores (**2**, **7**−**9**) and alkynyl substituents (Figure 3).[11]

From these computations, it appears that the structure of the hypervalent iodine heterocycle has only a marginal effect on the energy of the transition state (Figure 4). In contrast, the substituent on the alkyne had a strong influence on the transition state energy. With an electron-withdrawing substituent, such as an ester, α-addition is favored, as the resulting partial negative charge is stabilized. With silyl and phenyl substituents, both pathways are competitive. Finally, electron-donating groups make the α-pathway less favorable and at the same time lower the energy for the transition state of the β-pathway.[12] Interestingly, alkynes bearing either a highly electron-rich or an electron-withdrawing substituent are expected to react faster with nucleophiles (activation energy around 5 kcal/mol). Unfortunately, to date we have been unable to synthesize reagents bearing a methoxy or an ester group for experimental verification. It is also worth mentioning that alkynyliodonium salts, such as **9**, displayed very similar behavior to EBX reagents, although they cannot be used for the

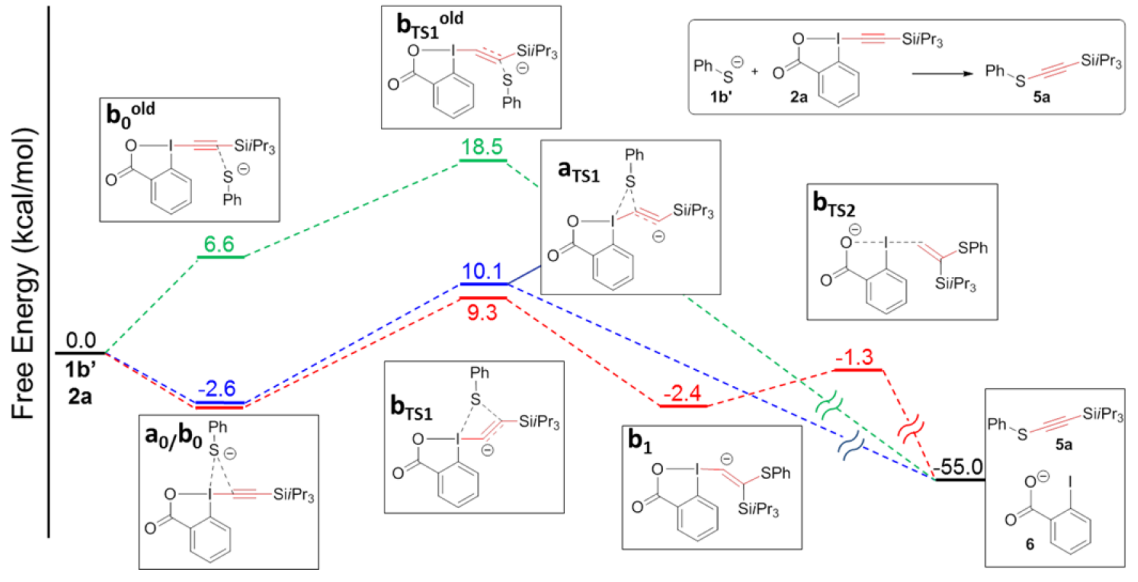


Figure 1. Reaction free energy profile [PBE0-dDsC/TZ2P//M06-2X/def2-SVP level in implicit THF solvent (COSMO-RS)] for the three possible mechanistic pathways **a** (blue), $\mathbf{b}^{old}$ (green), and **b** (red) for the reaction of TIPS-EBX **2a** with thiolate **1b′**.

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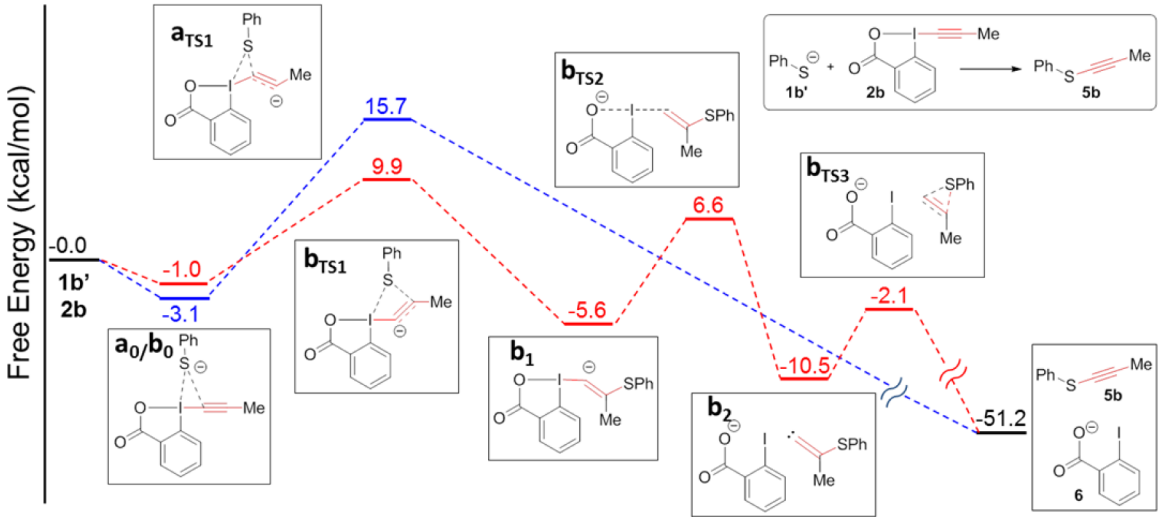
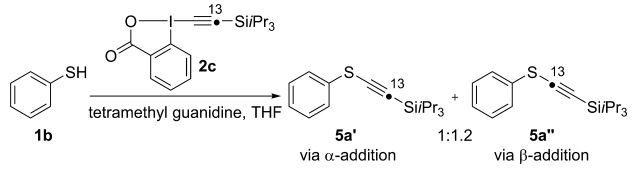
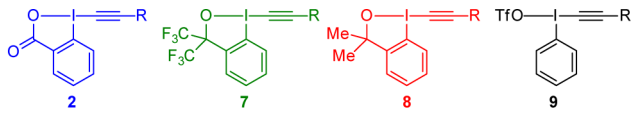


Figure 2. Reaction free energy profile [PBE0-dDsC/TZ2P//M06-2X/def2-SVP level in implicit THF solvent (COSMO-RS)] for the two possible mechanistic pathways **a** (blue) and **b** (red) for the reaction of Me-EBX **2b** with thiolate **1b**′.

Scheme 3. Reaction of thiophenol 1b with ^{13}C-labelled reagent 2c





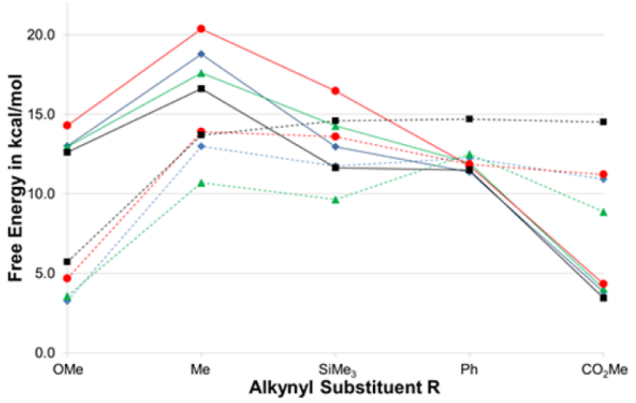


Figure 3. Transition state energies for α (full lines) and β (dotted lines) pathways for EBX reagents depending on the R group and heterocyclic core **2** (blue diamond), **7** (green triangle), **8** (red circle), and **9** (black square).

alkynylation of thiols due to the formation of disulfides as major products.[5a] The superiority of EBX reagents, therefore, can be assigned not to a faster alkynylation of thiols, but to a slower oxidation to disulfides.

In conclusion, further in-depth computational studies prompted discovery of a new mechanism for the alkynylation of thiols with EBX reagents proceeding via an initial sulfur–iodine interaction followed by a concerted β-addition. This mechanism is favored in the presence of electron-donating

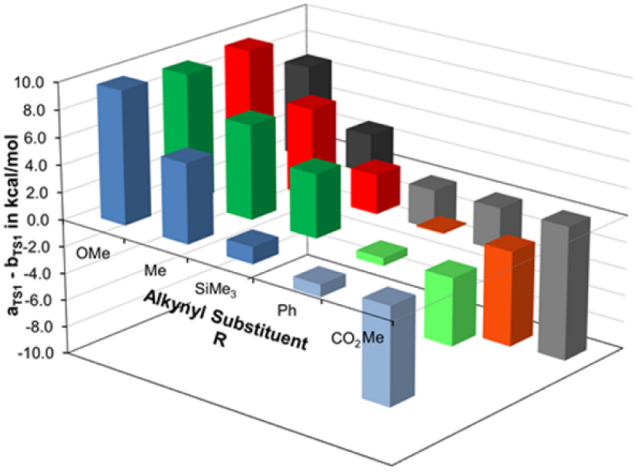


Figure 4. Energy difference $a_{TS1}-b_{TS1}$ depending on the R group and heterocyclic core **2** (blue), **7** (green), **8** (red), and **9** (black).

groups on the alkyne, whereas the previously reported α-addition pathway dominates in the presence of electron-withdrawing groups. With the commercially available reagent TIPS-EBX **2a**, both pathways are accessible, as supported by a labeling experiment. With this study, a more complete picture of the mechanism of the alkynylation of thiols has emerged, which will be highly useful for the design of new transformations using the versatile EBX reagents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03241.

Experimental procedures and analytical data for the labeling experiments and computational details (energies) (PDF)

Cartesian coordinate .xyz files (ZIP)

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Notes

The authors declare no competing financial interest.

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(8) See Figure S1 in Supporting Information for the computed structures.

(9) A methyl shift is much higher in energy and was not observed by computation.

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(11) Preliminary computations were also performed with phenolate and tolyl anions as nucleophiles. For the case of the oxygen nucleophile, pathways corresponding to α and β addition could also be identified and were close in energy. For the carbon nucleophile, the β addition pathway via preliminary interaction with the iodine atom could not be easily located and requires further study.

(12) The fact that the transition state energy of the α pathway is lower for methoxy than methyl could be tentatively explained by the inductive effect of the oxygen atom.

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Supporting Information for

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4. Cartesian Coordinates: Files (.xyz) submitted as separate Supporting Information

1. Computational Details

Geometries of all structures were optimized at the M06-2X[1,2]/def2-SVP level using the "Ultrafine" grid in Gaussian09.[3] Refined energy estimates, obtained by single-point computations on the M06-2X/def-SVP geometries, using a density-dependent dispersion correction (-dDsC[4-7]) appended to the PBE0[8,9] functional using the TZ2P slater-type orbital basis set as implemented in ADF.[10,11] Reported free energies include electronic energies at the PBE0-dDsC/TZ2P//M06-2X/def2-SVP level, free energy corrections at the M06-2X/def2-SVP level, and solvation corrections (at the PBE0-dDsC/TZ2P level, in implicit THF) from COSMO-RS.[12]

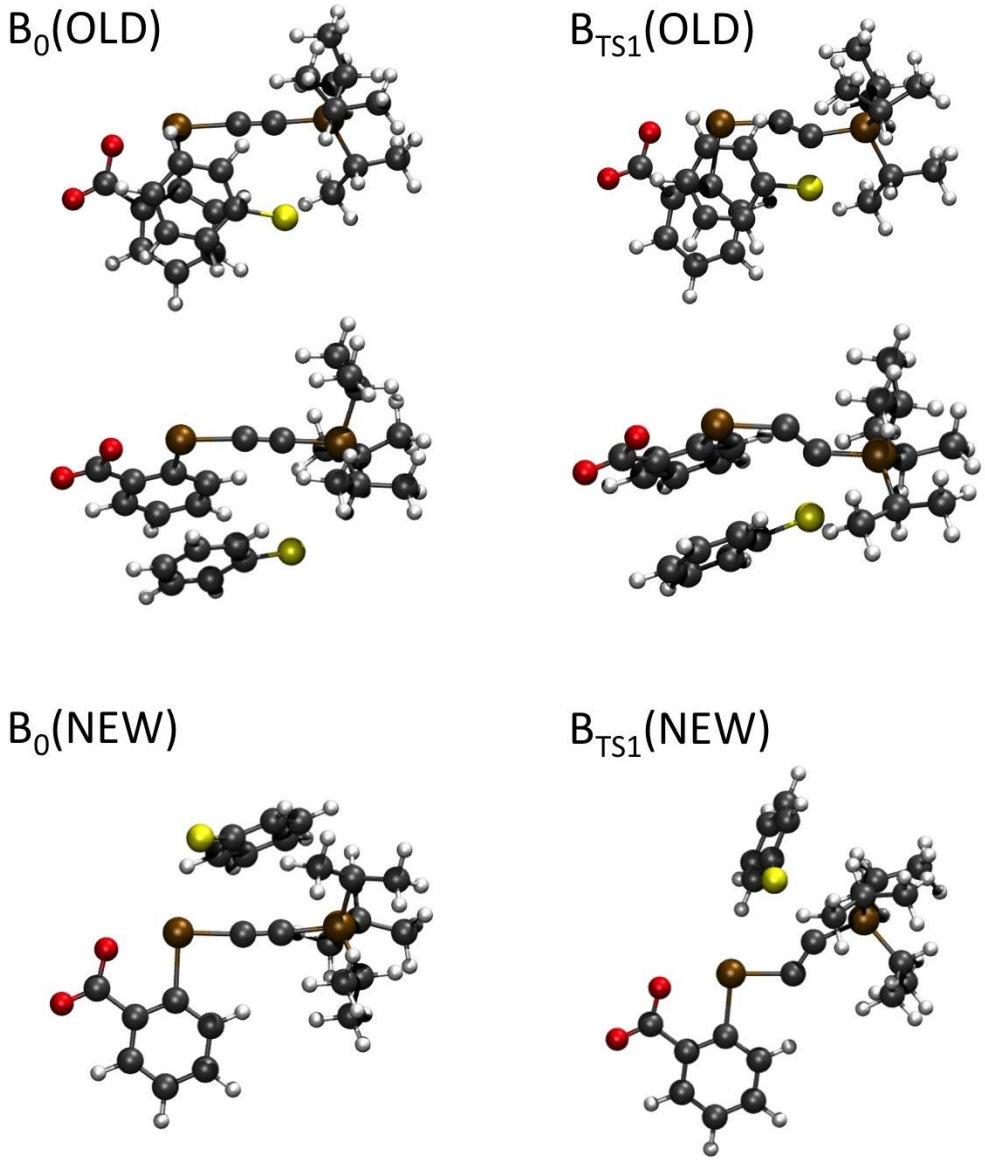


Figure S1. 3D structures of the van der Waals and TS1 complexes for the b-addition pathway involving TIPS-EBX.

Table S1. Relative free energies (in kcal/mol) of intermediates and products and their associated transition states for the addition of the phenylthiolate anion to relevant hypervalent iodine reagents. Values computed at the PBE0-dDsC/TZ2P//M06-2X/def2-SVP theoretical level including free energy corrections from M06-2X/def2-SVP computations and solvation corrections (in THF) from COSMO-RS.

Species	Pathway	a_0/b_0	a_{TS1}/b_{TS1}	a_1/b_1	a_{TS2}/b_{TS2}	a_2/b_2	a_{TS3}/b_{TS3}	Products
2-TIPS	C(α)	-2.6	10.1	--	--	--	--	-55.0
	$C(\beta)_{OLD}$	6.6	18.5	--	--	--	--	-55.0
	$C(\beta)_{NEW}$	-2.6	9.3	-2.4	-1.3	--	--	-55.0
2-TMS	C(α)	-3.3	9.7	--	--	--	--	-54.5
	C(β)	-0.6	8.4	-5.3	-3.6	--	--	-54.5
2-OMe	C(α)	0.7	13.7	--	--	--	--	-49.5
	C(β)	0.8	4.0	-12.1	7.4	-11.3	-8.5	-49.5
2-Me	C(α)	-3.1	15.7	--	--	--	--	-51.2
	C(β)	-1.0	9.9	-5.6	6.6	-10.5	-2.1	-51.2
2-Ph	C(α)	-0.7	10.7	--	--	--	--	-52.1
	C(β)	-0.4	11.6	-7.7	7.3	-7.2	2.8	-52.1
2-CO_2Me	C(α)	-4.0	-0.2	--	--	--	--	-54.8
	C(β)	-2.8	6.9	-15.2	1.9	-12.6	1.0	-54.8
7-TMS	C(α)	1.0	14.7	--	--	--	--	-44.6
	C(β)	0.5	10.1	-0.1	4.6	--	--	-44.6
7-OMe	C(α)	1.3	14.3	3.3	11.0	--	--	-40.9
	C(β)	2.7	4.9	-6.3	15.2	-1.9	0.5	-40.9
7-Me	C(α)	0.8	18.1	--	--	--	--	-41.5
	C(β)	0.5	11.2	-0.6	15.6	-0.2	6.5	-41.5
7-Ph	C(α)	1.6	13.6	--	--	--	--	-42.0
	C(β)	2.2	14.1	-2.4	16.7	-0.5	8.1	-42.0
7-CO_2Me	C(α)	-1.2	2.9	--	--	--	--	-44.5
	C(β)	-0.1	7.7	-9.7	11.5	-3.9	10.7	-44.5
8-TMS	C(α)	4.3	20.8	--	--	--	--	-27.2
	C(β)	5.5	17.9	12.6	21.5	--	--	-27.2
8-OMe	C(α)	6.8	21.1	11.0	21.4	--	--	-24.3
	C(β)	7.1	11.5	1.7	30.0	13.8	18.2	-24.3
8-Me	C(α)	2.9	23.3	21.7	24.6	--	--	-25.9
	C(β)	5.3	16.8	9.6	29.9	14.8	23.4	-25.9
8-Ph	C(α)	6.3	18.0	--	--	--	--	-26.4
	C(β)	6.2	18.1	7.9	31.2	15.7	25.5	-26.4
8-CO_2Me	C(α)	3.9	8.2	0.8	-1.7	--	--	-26.6
	C(β)	8.7	15.1	-0.5	25.7	15.6	29.9	-26.6
9-TMS	C(α)	-6.8	4.7	--	--	--	--	-84.1
	C(β)	-7.0	7.6	--	--	--	--	-84.1
9-OMe	C(α)	-4.4	8.2	--	--	--	--	-80.2
	C(β)	-3.2	1.3	-21.9	-10.7	-31.7	-28.3	-80.2
9-Me	C(α)	-7.1	9.0	--	--	--	--	-81.8
	C(β)	-7.6	6.1	-15.3	-10.3	-30.5	-22.2	-81.8
9-Ph	C(α)	-5.8	3.8	--	--	--	--	-82.8
	C(β)	-7.7	7.0	-18.1	-11.6	--	--	-82.8
9-CO_2Me	C(α)	-7.9	-5.0	--	--	--	--	-86.7
	C(β)	-8.5	6.0	-25.9	-15.0	-34.7	-19.8	-86.7

Table S2. Electronic energies, free energy corrections, and solvation corrections for relevant species. Electronic energies and free energy corrections in hartree. Solvation corrections in kcal/mol. M06-2X electronic energies and free energy corrections correspond to computations at the M06-2X/def2-SVP level. PBE0-dDsC electronic energies correspond to single point computations at the PBE0-dDsC/TZ2P level on optimized M06-2X/def2-SVP geometries. Note that ADF computes energies relative to basic atom fragments rather than separated particles as is done in Gaussian. The result is very different magnitudes seen for the PBE0-dDsC energies (ADF) and M06-2X energies (Gaussian).

Species	Pathway	Structure	M06-2X Electronic Energy	M06-2X Free Energy Correction	PBE0-dDsC Electronic Energy	COSMO-RS Solvation Energy
NA	NA	Ph-S$^-$	-629.544937	0.060838	-3.435106	-51.31
		2-Iodine Product	-716.877680	0.056949	-4.247718	-53.44
		7-Iodine Product	-1316.262867	0.077149	-6.031482	-49.90
		8-Iodine Product	-721.383227	0.126940	-5.623761	-50.80
		9-Iodine Product -1	-529.000334	0.059224	-3.258741	-6.43
		9-Iodine Product - 2	-960.806887	-0.003604	-2.382215	-50.03
		Ph-S-TIPS Product	-1350.084374	0.330611	-11.400497	-12.48
		Ph-S-TMS Product	-1114.514940	0.167644	-7.048160	-10.52
		Ph-S-OMe Product	-820.468796	0.107952	-5.309109	-9.17
		Ph-S-Me Product	-745.360230	0.103256	-5.001091	-8.01
		Ph-S-Ph Product	-936.891100	0.151867	-7.311965	-10.52
		Ph-S-CO_2Me Product	-933.706168	0.115291	-6.079507	-10.01
2-TIPS	Reactant	EBX	-1437.329185	0.330554	-12.122062	-19.15
	C(α)	a_0	-2066.902723	0.413896	-15.611759	-52.93
		a_{TS1}	-2066.877601	0.412718	-15.594884	-50.07
	$C(\beta)_{OLD}$	b_0	-2066.895532	0.411758	-15.596401	-52.03
		b_{TS1}	-2066.876521	0.416850	-15.585678	-50.01
	$C(\beta)_{NEW}$	b_0	-2066.902723	0.413903	-15.611759	-52.93
		b_{TS1}	-2066.879912	0.412633	-15.595175	-50.64
		b_1	-2066.899423	0.412990	-15.606697	-55.31
		b_{TS2}	-2066.898636	0.411314	-15.596610	-59.50
2-TMS	Reactant	EBX	-1201.760405	0.167612	-7.770784	-17.07
	C(α)	a_0	-1831.330173	0.248392	-11.255228	-53.23
		a_{TS1}	-1831.306209	0.246603	-11.238346	-49.74
	C(β)	b_0	-1831.329695	0.249448	-11.253150	-52.52
		b_{TS1}	-1831.310107	0.247687	-11.240099	-50.54
		b_1	-1831.334405	0.248424	-11.256643	-54.31
		b_{TS2}	-1831.332550	0.246361	-11.243685	-59.53
2-OMe	Reactant	EBX	-907.716694	0.104359	-6.035341	-16.22
	C(α)	a_0	-1537.284660	0.186196	-9.516750	-50.95
		a_{TS1}	-1537.255971	0.184891	-9.497846	-48.99
	C(β)	b_0	-1537.283987	0.186455	-9.513248	-53.24
		b_{TS1}	-1537.273466	0.184578	-9.509013	-51.53
		b_1	-1537.298828	0.185600	-9.533424	-52.89
		b_{TS2}	-1537.269556	0.182536	-9.487708	-60.21
		b_2	-1537.299401	0.182136	-9.507864	-65.93
		b_{TS3}	-1537.293770	0.180815	-9.497516	-68.79
2-Me	Reactant	EBX	-832.607308	0.100430	-5.725312	-15.06
	C(α)	a_0	-1462.174804	0.179332	-9.205668	-52.38
		a_{TS1}	-1462.142336	0.180785	-9.182303	-49.16
	C(β)	b_0	-1462.175054	0.182000	-9.206019	-51.72
		b_{TS1}	-1462.152940	0.181132	-9.191113	-49.66
		b_1	-1462.179028	0.182722	-9.212943	-52.43
		b_{TS2}	-1462.162151	0.178391	-9.176565	-60.34
		b_2	-1462.188387	0.177751	-9.195514	-65.21
		b_{TS3}	-1462.171840	0.175471	-9.177065	-66.92

2-Ph	Reactant	EBX	-1024.137328	0.149801	-8.036089	-17.20
	C(α)	a_0	-1653.706869	-1653.706869	-11.518071	-53.14
		a_{TS1}	-1653.684263	-1653.684263	-11.504977	-49.07
	C(β)	b_0	-1653.707110	0.231709	-11.517508	-53.07
		b_{TS1}	-1653.685359	0.232260	-11.502352	-50.94
		b_1	-1653.713307	0.231999	-11.528384	-53.70
		b_{TS2}	-1653.692199	0.228479	-11.487019	-62.45
		b_2	-1653.729519	0.232734	-11.523195	-56.96
		b_{TS3}	-1653.711955	0.233003	-11.500454	-61.43
2-CO_2Me	Reactant	EBX	-1020.949647	0.112681	-6.798965	-16.63
	C(α)	a_0	-1650.519920	0.194155	-10.284782	-53.11
		a_{TS1}	-1650.508368	0.192747	-10.280711	-50.95
	C(β)	b_0	-1650.520759	0.194576	-10.285471	-51.70
		b_{TS1}	-1650.501609	0.193362	-10.270068	-50.92
		b_1	-1650.538221	0.194549	-10.301659	-53.94
		b_{TS2}	-1650.510820	0.189151	-10.257641	-61.04
		b_2	-1650.534475	0.190854	-10.273936	-66.43
		b_{TS3}	-1650.509969	0.189386	-10.254321	-64.23
7-TMS	Reactant	EBX	-1801.160680	0.187097	-9.566381	-15.58
	C(α)	a_0	-2430.727939	0.269388	-13.045681	-51.67
		a_{TS1}	-2430.702571	0.268890	-13.029390	-47.79
	C(β)	b_0	-2430.727336	0.268461	-13.045424	-51.73
		b_{TS1}	-2430.707396	0.267756	-13.033442	-49.17
		b_1	-2430.724445	0.267877	-13.047598	-50.52
		b_{TS2}	-2430.719027	0.265665	-13.027948	-56.80
7-OMe	Reactant	EBX	-1507.116868	0.125202	-7.830870	-14.33
	C(α)	a_0	-2136.682630	0.206209	-11.309173	-49.85
		a_{TS1}	-2136.652749	0.203545	-11.289573	-47.53
		a_1	-2136.677210	0.208026	-11.309294	-48.98
		a_{TS2}	-2136.670753	0.208664	-11.296570	-49.60
	C(β)	b_0	-2136.680896	0.206364	-11.304842	-51.27
		b_{TS1}	-2136.670185	0.204554	-11.301734	-49.91
		b_1	-2136.688803	0.206824	-11.320697	-50.64
		b_{TS2}	-2136.655776	0.202923	-11.273183	-56.56
		b_2	-2136.684667	0.202594	-11.291093	-62.14
		b_{TS3}	-2136.679026	0.201458	-11.281983	-64.81
7-Me	Reactant	EBX	-1432.007497	0.120378	-7.521487	-13.27
	C(α)	a_0	-2061.572911	0.201349	-10.996784	-51.18
		a_{TS1}	-2061.539051	0.201519	-10.974631	-47.91
	C(β)	b_0	-2061.572520	0.201784	-10.998520	-50.68
		b_{TS1}	-2061.550069	0.200660	-10.984044	-48.35
		b_1	-2061.570225	0.202589	-11.003003	-49.44
		b_{TS2}	-2061.548101	0.198856	-10.962031	-56.64
		b_2	-2061.573687	0.198598	-10.979885	-61.08
		b_{TS3}	-2061.557100	0.193999	-10.962010	-62.71
7-Ph	Reactant	EBX	-1623.537818	0.168865	-9.831747	-15.61
	C(α)	a_0	-2253.105134	0.251387	-13.309608	-52.07
		a_{TS1}	-2253.081356	0.251555	-13.297755	-47.67
	C(β)	b_0	-2253.105345	0.252487	-13.309924	-52.04
		b_{TS1}	-2253.082762	0.252355	-13.294800	-49.46
		b_1	-2253.105160	0.252112	-13.318919	-50.69
		b_{TS2}	-2253.077887	0.247966	-13.271712	-58.63
		b_2	-2253.105040	0.247782	-13.291997	-63.03
		b_{TS3}	-2253.087669	0.245838	-13.274308	-64.23
7-CO_2Me	Reactant	EBX	-1620.350880	0.131880	-8.595430	-14.77
	C(α)	a_0	-2249.919395	0.214099	-12.076932	-51.56
		a_{TS1}	-2249.908338	0.214442	-12.073211	-50.08
	C(β)	b_0	-2249.919659	0.216131	-12.077970	-51.11
		b_{TS1}	-2249.900570	0.213193	-12.063841	-50.33
		b_1	-2249.930446	0.215520	-12.092280	-51.36
		b_{TS2}	-2249.896900	0.210435	-12.043678	-57.48
		b_2	-2249.919615	0.207613	-12.057849	-62.17
		b_{TS3}	-2249.892610	0.207328	-12.033851	-62.47
8-TMS	Reactant	EBX	-1206.308912	0.236677	-9.190463	-13.77
	C(α)	a_0	-1835.868256	0.316966	-12.653073	-55.71
		a_{TS1}	-1835.840053	0.318255	-12.637228	-49.99
	C(β)	b_0	-1835.870419	0.318966	-12.656008	-53.97

		b_{TS1}	-1835.846314	0.319139	-12.642265	-50.26
		b_1	-1835.855077	0.319751	-12.650782	-50.57
		b_{TS2}	-1835.840730	0.314280	-12.620363	-57.38
8-OMe	Reactant	EBX	-912.263764	0.174996	-7.453949	-12.43
	C(α)	a_0	-1541.824641	0.258000	-10.918548	-52.32
		a_{TS1}	-1541.791942	0.255714	-10.897602	-49.74
		a_1	-1541.812160	0.257906	-10.915262	-50.18
		a_{TS2}	-1541.796908	0.257954	-10.898245	-50.49
	C(β)	b_0	-1541.823638	0.258075	-10.917501	-52.75
		b_{TS1}	-1541.808462	0.255235	-10.909715	-51.45
		b_1	-1541.823301	0.256700	-10.926933	-51.32
		b_{TS2}	-1541.777108	0.251937	-10.868377	-56.81
		b_2	-1541.804458	0.250626	-10.883648	-62.60
		b_{TS3}	-1541.798750	0.251126	-10.872572	-65.43
8-Me	Reactant	EBX	-837.155015	0.171534	-7.144624	-11.25
	C(α)	a_0	-1466.712992	0.250808	-10.603950	-55.99
		a_{TS1}	-1466.677910	0.251053	-10.581405	-49.92
		a_1	-1466.687335	0.253142	-10.587603	-48.94
		a_{TS2}	-1466.680740	0.253493	-10.582199	-49.63
	C(β)	b_0	-1466.714526	0.253004	-10.606853	-53.21
		b_{TS1}	-1466.688955	0.251867	-10.592204	-50.13
		b_1	-1466.701350	0.253297	-10.605057	-50.22
		b_{TS2}	-1466.669085	0.247512	-10.556811	-56.55
		b_2	-1466.693585	0.247574	-10.573455	-61.22
		b_{TS3}	-1466.679047	0.246236	-10.555567	-63.07
8-Ph	Reactant	EBX	-1028.686102	0.220611	-9.455065	-13.92
	C(α)	a_0	-1658.247945	0.303112	-12.918645	-54.67
		a_{TS1}	-1658.220533	0.301747	-12.907456	-49.10
	C(β)	b_0	-1658.247719	0.302875	-12.918496	-54.66
		b_{TS1}	-1658.222232	0.301381	-12.903806	-51.08
		b_1	-1658.237288	0.303715	-12.922339	-51.16
		b_{TS2}	-1658.199226	0.297848	-12.867362	-58.65
		b_2	-1658.225038	0.297602	-12.884356	-63.33
		b_{TS3}	-1658.209639	0.298163	-12.867137	-64.64
8-CO_2Me	Reactant	EBX	-1025.501185	0.183595	-8.221609	-13.51
	C(α)	a_0	-1655.063455	0.265622	-11.688774	-54.13
		a_{TS1}	-1655.051145	0.266823	-11.687129	-51.59
		a_1	-1655.064395	0.264483	-11.695236	-52.46
		a_{TS2}	-1655.059686	0.262485	-11.695193	-53.70
	C(β)	b_0	-1655.057436	0.264299	-11.675497	-56.85
		b_{TS1}	-1655.043308	0.265277	-11.670481	-54.18
		b_1	-1655.064105	0.265473	-11.698145	-52.48
		b_{TS2}	-1655.021296	0.259275	-11.641970	-57.71
		b_2	-1655.040005	0.260176	-11.651220	-62.52
		b_{TS3}	-1655.011968	0.257205	-11.624843	-62.92
9-TMS	Reactant	EBX	-1974.667004	0.180857	-9.127132	-22.78
	C(α)	a_0	-2604.245246	0.263713	-12.622785	-56.66
		a_{TS1}	-2604.227580	0.263234	-12.608945	-53.65
	C(β)	b_0	-2604.247783	0.265053	-12.626784	-55.23
		b_{TS1}	-2604.226331	0.264830	-12.606300	-53.37
9-OMe	Reactant	EBX	-1680.624288	0.120083	-7.392753	-21.68
	C(α)	a_0	-2310.199046	0.201385	-10.883242	-55.51
		a_{TS1}	-2310.177083	0.202145	-10.868409	-52.69
	C(β)	b_0	-2310.198618	0.202986	-10.881771	-56.20
		b_{TS1}	-2310.191377	0.203573	-10.877488	-54.79
		b_1	-2310.228018	0.204479	-10.919135	-52.41
		b_{TS2}	-2310.210594	0.201311	-10.893211	-55.49
		b_2	-2310.245077	0.201029	-10.924077	-56.96
		b_{TS3}	-2310.239289	0.201815	-10.915196	-59.63
9-Me	Reactant	EBX	-1605.514609	0.115891	-7.082508	-20.61
	C(α)	a_0	-2235.091257	0.197094	-10.575220	-55.62
		a_{TS1}	-2235.066181	0.196471	-10.552777	-53.25
	C(β)	b_0	-2235.091228	0.196329	-10.575182	-55.71
		b_{TS1}	-2235.069364	0.197283	-10.557463	-53.74
		b_1	-2235.108304	0.201054	-10.598484	-51.68
		b_{TS2}	-2235.100386	0.196769	-10.580858	-55.12
		b_2	-2235.133999	0.198691	-10.612526	-56.64

		b_{TS3}	-2235.117594	0.196423	-10.594103	-58.49
9-Ph	Reactant	EBX	-1797.043931	0.164395	-9.392374	-22.70
	C(α)	a_0	-2426.621698	0.248000	-12.886878	-56.79
		a_{TS1}	-2426.605081	0.247218	-12.875884	-53.63
	C(β)	b_0	-2426.621715	0.246262	-12.887902	-56.99
		b_{TS1}	-2426.599889	0.247352	-12.867608	-55.72
		b_1	-2426.642140	0.249023	-12.913550	-53.04
		b_{TS2}	-2426.638967	0.246617	-12.895393	-56.45
9-CO_2Me	Reactant	EBX	-1793.853886	0.126952	-8.153459	-21.86
	C(α)	a_0	-2423.433829	0.210609	-11.652612	-55.22
		a_{TS1}	-2423.425652	0.209114	-11.648502	-54.01
	C(β)	b_0	-2423.433845	0.210951	-11.653205	-55.65
		b_{TS1}	-2423.413592	0.209968	-11.629475	-55.41
		b_1	-2423.467423	0.212904	-11.686266	-53.47
		b_{TS2}	-2423.450690	0.209981	-11.661138	-56.55
		b_2	-2423.480801	0.210358	-11.692016	-57.15
		b_{TS3}	-2423.454220	0.209258	-11.666921	-57.30

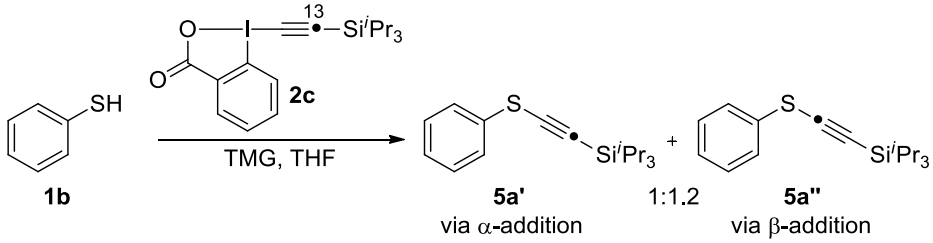
Cartesian coordinates of all computed structures are provided as .xyz files as separate Supporting Information.

2. General Methods

Technical grade solvents were used for quantitative flash chromatography. HPLC grade solvents purchased from Sigma-Aldrich or freshly distilled solvents were used for flash chromatography for compounds undergoing full characterization. Reaction solvents were dried by passage over activated alumina under nitrogen atmosphere (H_2O content < 30 ppm, Karl-Fischer titration). We note; however, that the thiol-alkynylation reaction gives identical results when using HPLC grade THF purchased from Sigma-Aldrich or dried THF from the solvent system. Commercially available reagents were purchased from Acros, Aldrich, Fluka, VWR, Aplichem or Merck and used without any further purification. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar pressure. TLC was performed on Merck silica gel 60 F254 TLC plates and visualized with UV light and permanganate stain. Melting points were measured on a calibrated Büchi B-540 melting point apparatus using open glass capillaries. ^{1}H NMR spectra were measured on a Brucker DPX-400 400 MHz spectrometer, all signals are reported in ppm with the corresponding internal solvent peak or TMS as standard. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration; interpretation). ^{13}C NMR spectra were carried out with ^{1}H-decoupling on a Brucker DPX-400 100 MHz. All signals are reported in ppm with the corresponding internal solvent signal or TMS as standard. Infrared spectra were obtained on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm^{-1} (w = weak, m = medium, s = strong, sh = shoulder). High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API.

3. Labeling experiment with Spectra

Labeled triisopropyl((phenylthio)ethynyl)silane (5a' and 5a'')



Following a reported procedure[13] benzenethiol (**1b**) (3.6 µl, 0.036 mmol) and 1,1,3,3-tetramethylguanidine (5.4 µl, 0.043 mmol, 1.2 equiv.) were dissolved in THF (0.5 mL, 0.08 M) under vigorous stirring. Upon dissolution of the starting material the labeled 1-[(triiso--propyllsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one (**2c**) (17 mg, 0.039 mmol, 1.1 equiv, 20% ^{13}C labelling at the indicated position.)[14] was added as a solid in one portion. The resulting reaction mixture was stirred in an open flask for 5 minutes at room temperature and then quenched by adding water (1 mL). The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting crude was purified by Flash chromatography in pure pentane to afford labeled triisopropyl((phenylthio)ethynyl)silane (8.4 mg, 0.029 mmol, 81% yield).

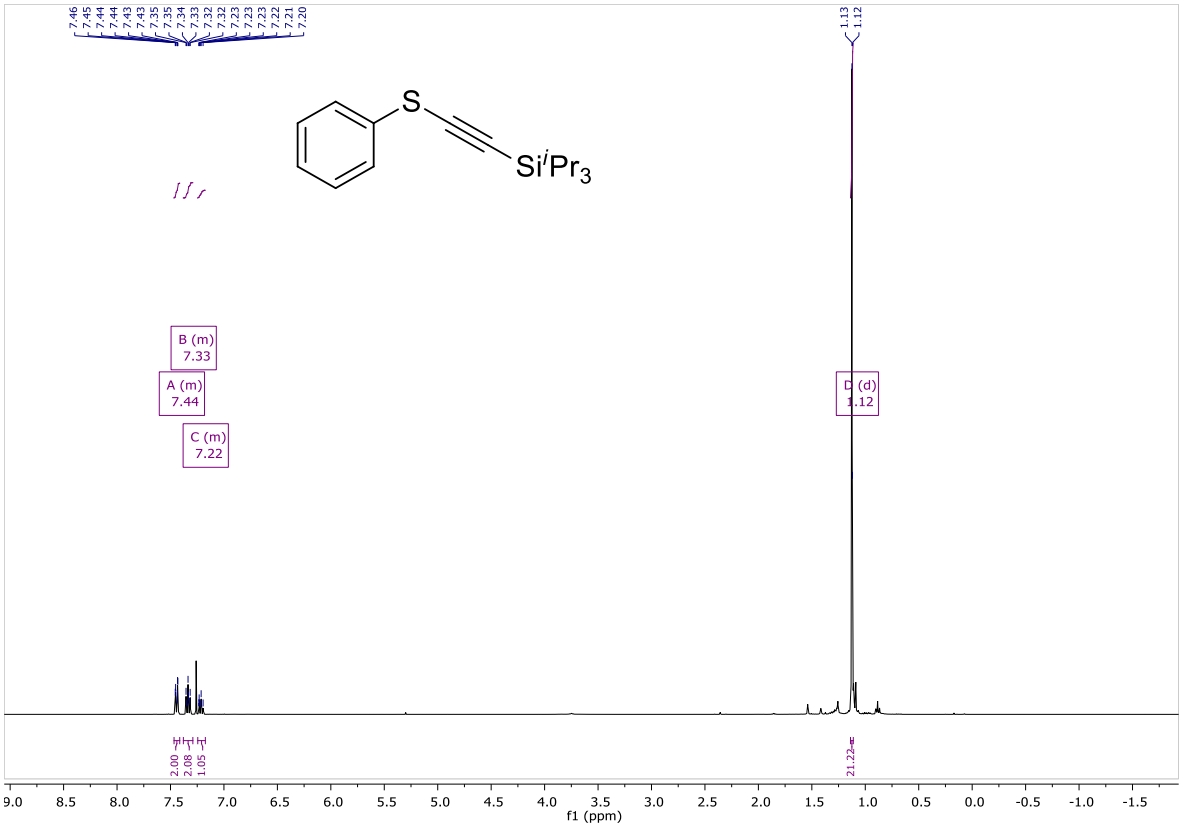
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 – 7.41 (m, 2H), 7.38 – 7.29 (m, 2H), 7.24 – 7.17 (m, 1H), 1.12 (d, *J* = 2.2 Hz, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 132.9, 129.3, 126.5, 126.1, **103.4**, **91.2**, 18.8, 11.5.

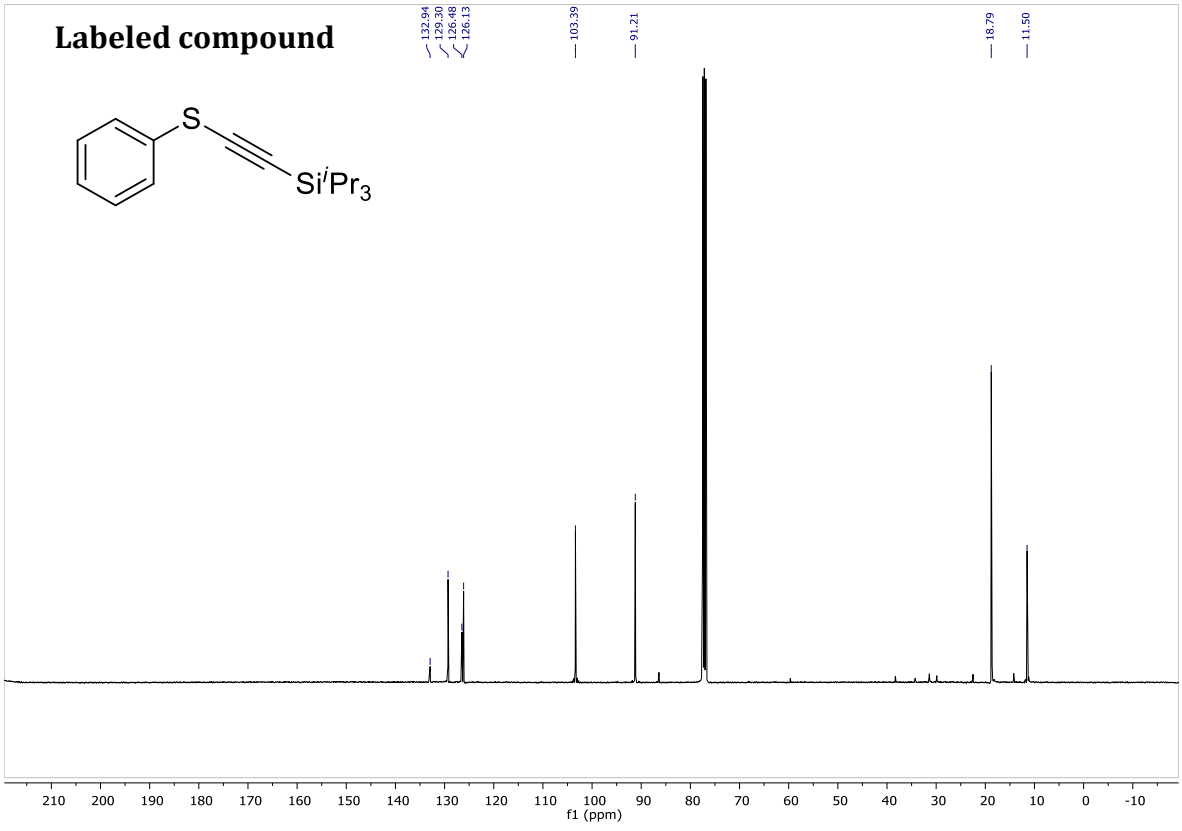
IR ν 2943 (s), 2866 (s), 2094 (s), 1585 (w), 1479 (m), 1464 (w), 884 (s).

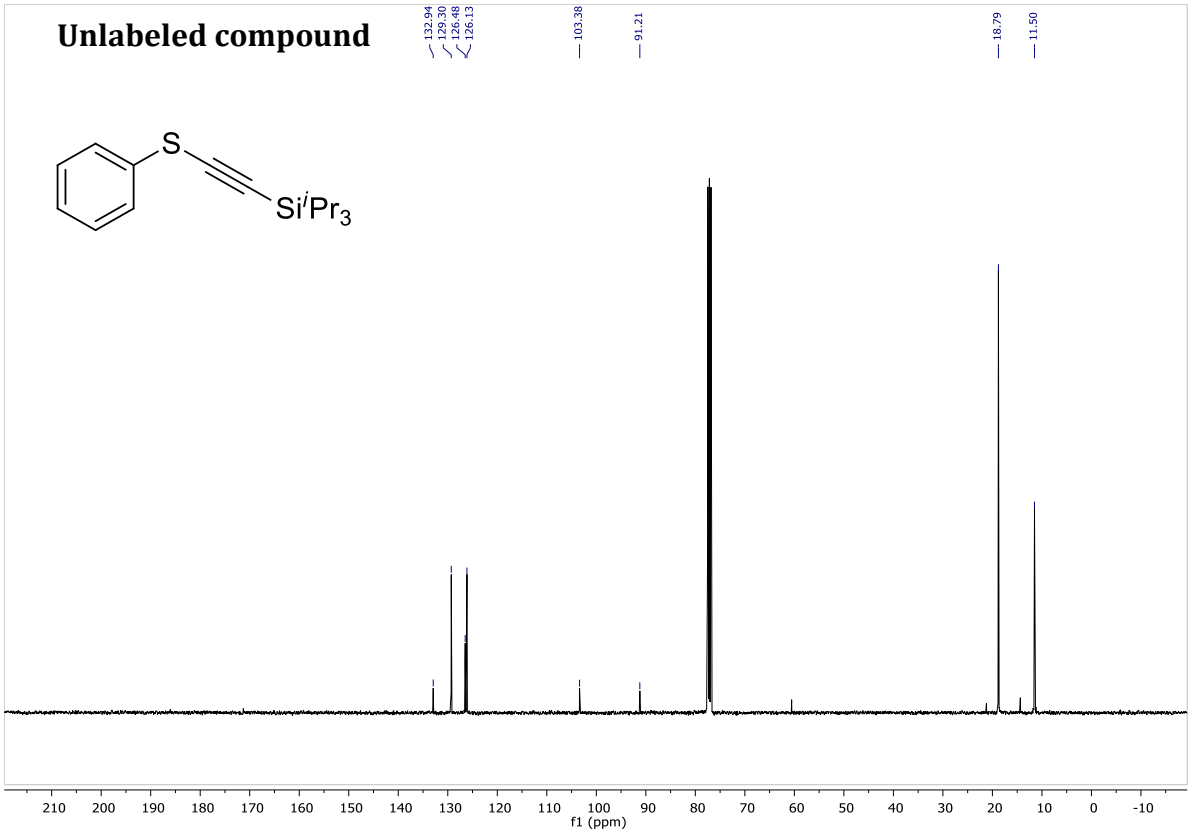
HRMS (ESI) calcd for $C_{17}H_{27}SSi^+$ $[M+H]^+$ 291.1597; found 291.1592.

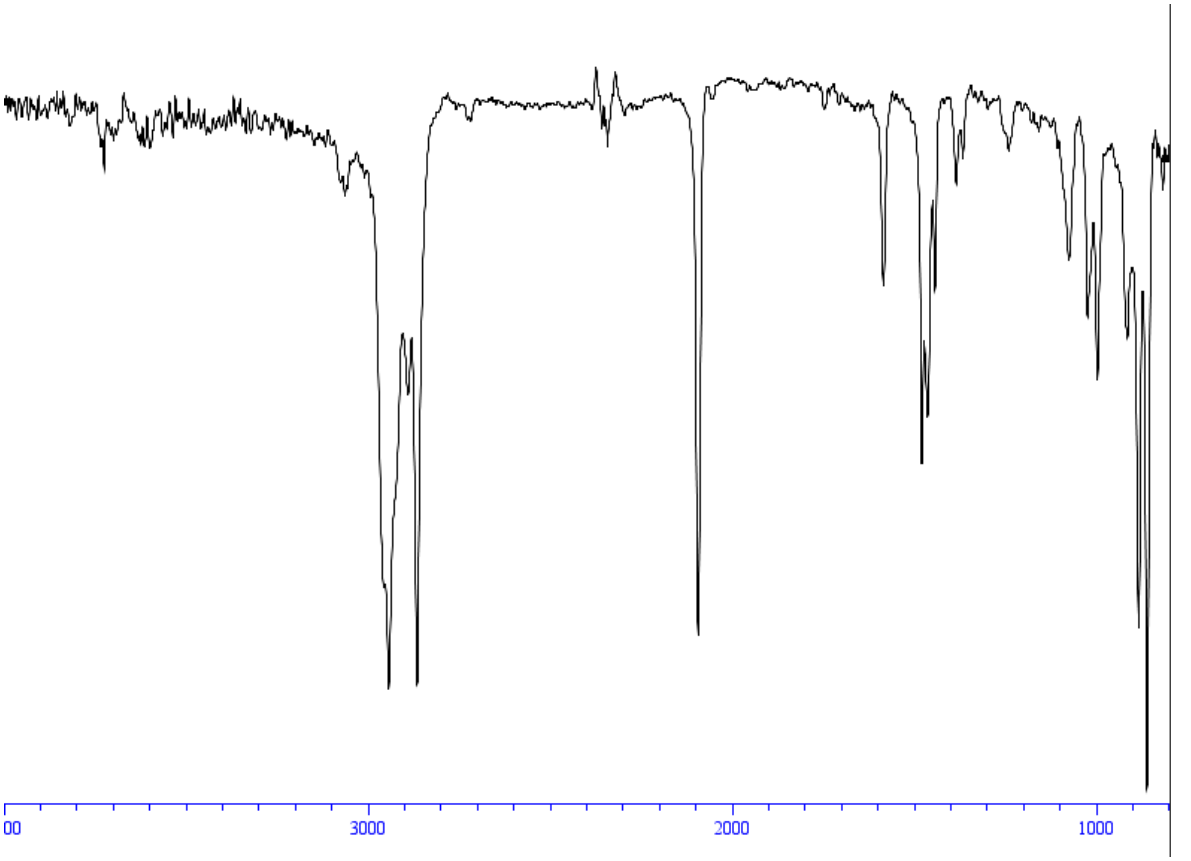
Comparison of the ^{13}C NMR with an unlabeled sample showed 12% ^{13}C incorporation at the 91.2 position (β to Si) and 9.8% at the 103.4 position (α to Si). The signal at 129.3 ppm was used as internal standard.



Labeled compound







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