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Ynones merge activation/conjugate addition of chalcogenoborates ArE-Bpin (E=Se, S)

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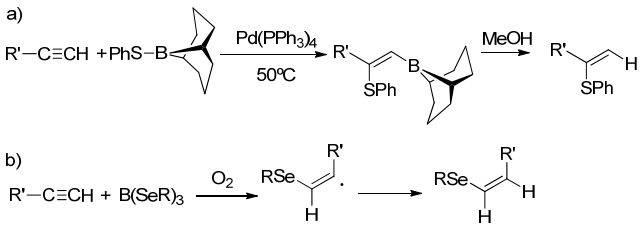
Abstract. The "pull push" effect of the Bpin moiety in ArE-Bpin reagents (E=Se, S) is demonstrated by the Lewis acid interaction with the carbonyl group of ynones and the concomitant delivery of ArSe or ArS to the electron deficient alkyne with impressive stereoselectivity. The two component reactivity is carried out in MeOH to generate (*Z*)-β-(arylseleno)-α,β-unsaturated ketones and (*Z*)-β-(arylsulfuro)-α,β-unsaturated ketones with a consensus between experimental and theoretical understanding of the mechanism.

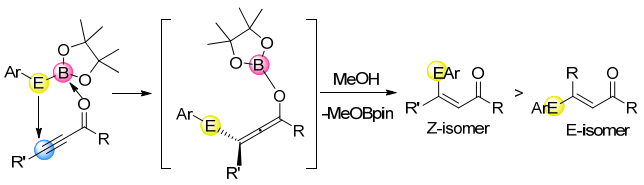
Keywords: chalcogenoborates; ynones; Lewis acid interaction; (*Z*)-β-(arylseleno)-α,β-unsaturated ketones; (*Z*)-β-(arylsulfuro)-α,β-unsaturated ketones

The synthesis of vinyl chalcogenides,[1-5] such as vinyl selenides and vinyl sulfides, has been deeply covered from multicomponent perspectives with particular emphasis on the influence of transition metal complexes to generate new C(sp^2)-Se and C(sp^2)-S bonds in a selective manner.[6] In that context, the thioboration of alkynes with 9-(alkylthio)-9-borabicyclo[3.3.1]nonanes has been reported to take place in the presence of $Pd(PPh_3)_4$ in a regio- and stereoselective way, which under subsequent protonolysis with methanol produces the corresponding Markovnikov product (Scheme 1a).[7-8] In a metal free context, the reaction of organoselenoboranes with acetylenes caused free radical 1,2-addition compounds (Scheme 1b).[9-10] The synthesis of vinyl selenides and vinyl sulfides utilizing chalcogenoborates has been limited to the previous examples despite the potential reactivity of these reagents.[11]



Scheme 1. Synthesis of vinyl selenides and vinyl sulfides throughout chalcogenoborates.

Here we report the feasible reactivity of ynones with PhSe-Bpin (**1**), PhS-Bpin (**2**) and BnS-Bpin (**3**), to promote the synthesis of vinyl selenides and vinyl sulfides in the absence of transition metal complexes or additives. The work hypothesis is based on the "pull-push" effect of Bpin moieties which easily form Lewis acid-base adducts and enhance the nucleophilic character of the interelement.[12] The concerted approach facilitates the stereoselective conjugate intramolecular addition of the ArSe- or ArS- units followed by protonolysis with the MeOH used as solvent. The study covers a wide range of α,β-acetylenic ketones and the mechanism is deeply analyzed from theoretical calculations to give some insight into the favored stereoselective formation of the (*Z*)-β-(arylseleno)-α,β-unsaturated ketones and (*Z*)-β-(arylsulfuro)-α,β-unsaturated ketones.



Scheme 2. Synthesis of vinyl selenides and vinyl sulfides throughout chalcogenoborates.

We initiated our studies with the addition of 1eq. of PhSe-Bpin (**1**) to the electron deficient alkyne 4-phenyl-3-butyn-2-one (**4**), in THF at room temperature, but no product formation was observed after the aqueous work up. We increased the temperature to 50ºC and the β-(phenylseleno)-α,β-unsaturated ketone **5** was obtained in 48% conversion with a ratio **5-*Z*/5-*E*** = 78/22, after addition of 2eq MeOH. Both stereoisomers could be isolated and unequivocally characterized accordingly to NMR spectroscopy. We also computed the ^{1}H NMR shifts by DFT (see SI for details) and interestingly we confirmed these results. At this point, we were able to correct a previous NMR data assigned to **5-*Z*** which was isolated from the mixture of isomers **5-*Z*/5-*E*** = 66/34 after the addition of PhSeZnCl to 4-phenyl-3-butyn-2-one (**4**).[13] Our optimized reaction conditions included the use of MeOH as solvent and 2eq. of PhSe-Bpin (**1**) to obtain complete conversion and total stereoselection towards **5-*Z*** (Table 1, entry 1). Subtituents on the phenyl group that provide more electron donating or electron withdrawing properties on substrates 4-(4-methylphenyl)-3-butyn-2-one (**6**) and 4-(4-trifluoromethylphenyl)-3-butyn-2-one (**8**), respectively, did not change the reaction outcome but slightly affected the stereoselectivity with a ratio for **7-*Z*/7-*E*** = 95/5 and **9-*Z*/9-*E*** = 86/14 (Table 1, entries 2 and 3). The alkylic ketone 3-nonyn-2-one (**10**) was efficiently α,β-seleniated despite the diminished electrophilic character on C_β, with a stereoselection **11-*Z*/11-*E*** = 95/5 (Table 1, entry 4). A similar result was attained in the β-seleniation of **12** with the corresponding ratio **13-*Z*/13-*E*** = 92/8 (Table 1, entry 5). Quantitative conversion and stereoselectivity was achieved for the 1,3-diphenylprop-2-yn-1-one substrates **14** and **18** (Table 1, entries 6 and 8) with a slight decrease on stereoselectivity on the transformation from **16** to **17-*Z*/17-*E*** = 90/10 (Table 1, entry 7). The full characterization of **19-*Z***, from its exclusive formation, included diffraction X-ray data (Figure 1)

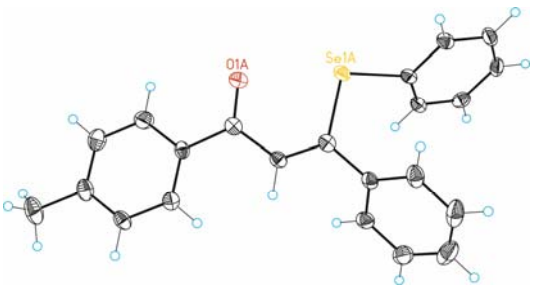
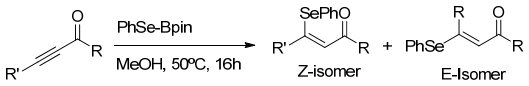
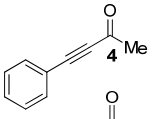
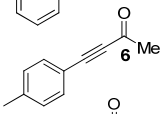
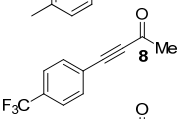
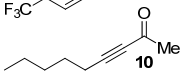
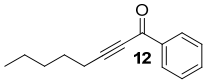
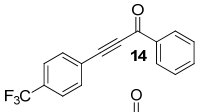
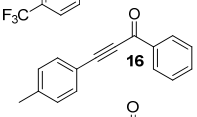
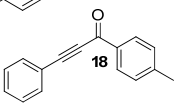


Figure 1. Ball and stick diagram of **19-*Z***.

Table 1. β-PhSe addition to α,β-acetylenic ketones[a]

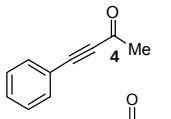
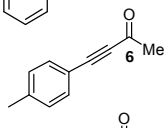
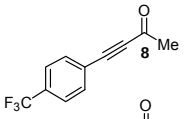
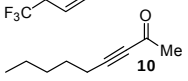
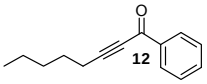
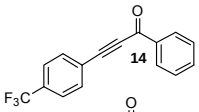
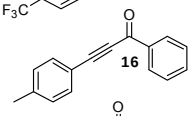
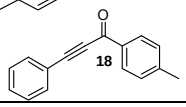


Entry	Substrate	Conv [b] (%)	SePhO	R' O PhSe R
1		99	99[87] (**5-*Z***)	nd
2		99	95[86] (**7-*Z***)	5(**7-*E***)
3		99	86[81] (**9-*Z***)	14(**9-*E***)
4		99	95[88] (**11-*Z***)	5(**11-*E***)
5		99	92[58] (**13-*Z***)	8(**13-*E***)
6		99	99[84] (**15-*Z***)	nd
7		99	90[84] (**17-*Z***)	10(**17-*E***)
8		99	99[85] (**19-*Z***)	nd

[a]Standard conditions: α,β–acetylenic ketones (0.1 mmol), PhSe-Bpin (2eq), MeOH (2 mL), 50ºC, 16h. [b]Conversion and regioselectivity determined by NMR spectroscopy. Values in parenthesis are isolated yields.

The straightforward reactivity between ynones and PhSe-Bpin (**1**) simplified previous attempts to obtain (Z)-α,β-(arylseleno)-α,β-unsaturated ketones via selenocarbonylation addition of arylselenoesters to alkynes catalyzed by copper (I).[14] Our next goal was to extend the assembly protocol to chalcogenoborates PhS-Bpin (**2**) and BnS-Bpin (**3**) to synthesize vinyl sulfides from accessible ynones. Table 2 includes the most remarkable data from this study which highlights that the addition of ArS groups to the α,β-acetylenic ketones takes place regioselectively in the C_β position with a stereoselectivity around ***Z*/*E*** = 3/1, independently of the nature of the Ar group in the thiodioxaborolane reagent. The alkylic nature of the substituents in C_β on substrates **10** and **12** favored the relative formation of the *E* isomer (Table 2, entries 4 and 5). The trend to form the (*Z*)-α,β-(arylsulfuro)-α,β-unsaturated ketone, as the major isomer, by mixing the thiodioxaborolanes and the ynones, contrast with the lower stereoselectivity observed in alternative methodologies such as the addition of thiols to the electrondeficient alkynes methyl propiolate and dimethyl acetylenedicarboxylate, in the presence of Ru catalysts.[15]

Table 2. β-ArS addition to α,β-acetylenic ketones[a]

Entry	Substrate	ArS-Bpin	Conv [b] (%)	SAr O / R' R	R' O / ArS R
1		**Ph**	99	73[69][d](**20-*Z***)	27(**20-*E***)
		Bn	99	71[65][d](**21-*Z***)	29(**21-*E***)
2		**Ph**	99[80][c]	70(**22-*Z***)	30(**22-*E***)
		Bn	94[83][c]	72(**23-*Z***)	28(**23-*E***)
3		**Ph**	99	76[65][d](**24-*Z***)	24(**24-*E***)
		Bn	99	74[62][d](**25-*Z***)	26(**25-*E***)
4		**Ph**	99	64[57][d](**26-*Z***)	36[30][e](**26-*E***)
		Bn	99	58[52][d](**27-*Z***)	42[38][e](**27-*E***)
5		**Ph**	99[68][c]	47(**28-*Z***)	53(**28-*E***)
		Bn	99[75][c]	59(**29-*Z***)	41(**29-*E***)
6		**Ph**	99[85][c]	78(**30-*Z***)	22(**30-*E***)
		Bn	99[83][c]	75(**31-*Z***)	25(**31-*E***)
7		**Ph**	99	76[59][d](**32-*Z***)	24(**32-*E***)
		Bn	99	72[64][d](**33-*Z***)	28(**33-*E***)
8		**Ph**	99	76[69][d](**34-*Z***)	24(**34-*E***)
		Bn	98	85[65][d](**35-*Z***)	15(**35-*E***)

[a]Standard conditions: α,β–acetylenic ketones (0.1 mmol), ArS-Bpin (2eq), MeOH (2 mL), 50ºC, 16h. [b]Conversion and regioselectivity determined by NMR spectroscopy. [c]Values in parenthesis are isolated yields of the mixture of stereoisomers. [d]Values in parenthesis are isolated yields of the (*Z*) stereoisomer. [e]Values in parenthesis are isolated yields of the (*E*) stereoisomer

The favored formation of (*Z*)-vinyl selenides and vinyl sulfides is opposite to the trend observed for the (*E*)-vinyl amines through β-amination of ynones with Bpin-NMe_2 and Bpin-NEt_2 from the adduct [RO^- →Bpin-NMe_2]. This is probably due to the different activation mode of the chalcogenoborate reagents PhSe-Bpin, PhS-Bpin and BnS-Bpin, with respect to aminoboronates[16] or phosphinoboronates.[17] In parallel, we have recently unravelled theoretically the mechanism for the selenoboration and thioboration of α,β-unsaturated aldehydes and ketones, demonstrating the activation mode of chalcogenoborate reagents by the carbonyl group in α,β-unsaturated carbonyl compounds (Figure 2).[18,19] Here we describe a new hypothesis of mechanistic pathway to assembly the chalcogenoborates and ynones and to understand the feasible reactivity but in particular the favored stereoselectivity on (*Z*)-β-(arylseleno)-α,β-unsaturated ketones.

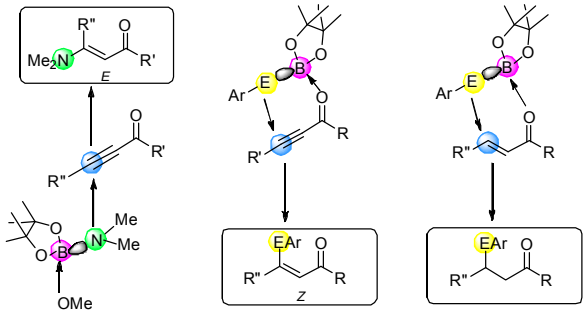
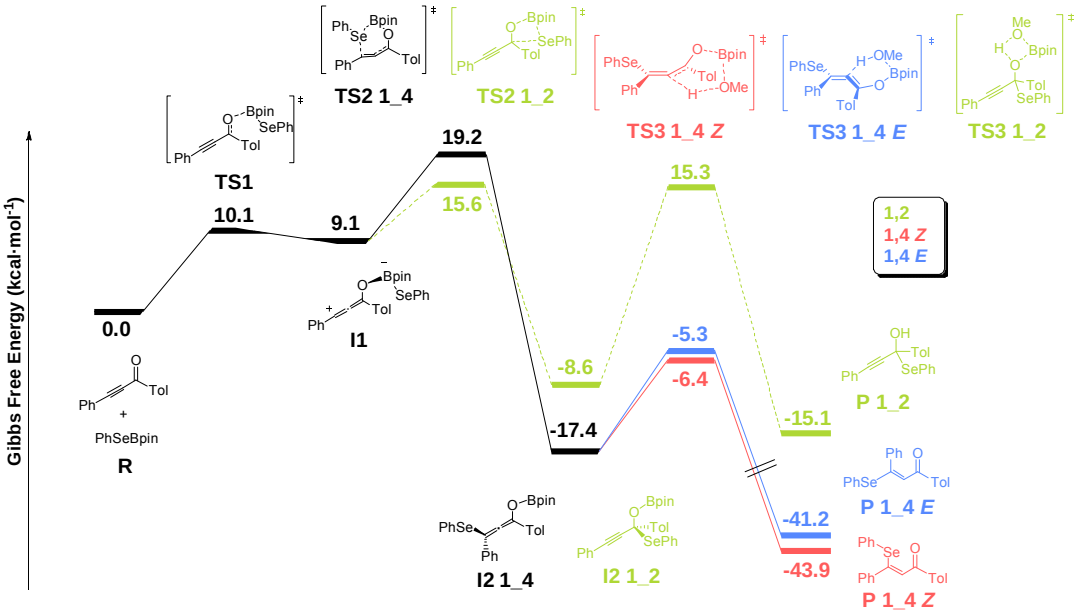


Figure 2. Activation modes of ynones and α,β-unsaturated carbonyl compounds by chalcogenoborate (E=Se, S) and aminoboronate reagents.

By means of DFT studies (See the supporting information for the computational details) we were able to envisage the profile for the reaction of the model alkyne 1-(4-methylphenyl)-3-phenyl-2-propyn-1-one (**18**) with PhSe-Bpin (**1**) (Scheme 3). Three reaction pathways are possible concerning the two electrophilic functionalities of the substrate, the triple bond and the carbonyl group. The first step of the reaction is the activation of the boron atom of reagent **1** with the oxygen atom of the carbonyl group that occurs through a first transition step (**TS1**) and leads to the intermediate **I1**. Then, two pathways are possible: The attack of the nucleophilic -SePh moiety to the carbonyl group (**TS2 1_2**) or to the triple bond (**TS2 1_4**). After the **TS2 1_2** an intermediate **I2 1_2** is formed. This intermediate can finally undergo protonolysis with methanol to form the 1,2-addition product and the byproduct pinBOMe. When we conducted a NMR experiment of **4** with PhSe-Bpin in toluene-d_8, we were able to observe the formation of the **I2 1_2** which after addition of MeOH, proceed to recover the starting material (see SI).

Considering the other pathway, after the **TS2 1_4** occurs, an allene intermediate is formed (**I2 1_4**). This intermediate can also undergo protonolysis with methanol but in this case by two faces, leading to two different transition states **TS3 1_4 *Z*** and **TS3 1_4 *E*** that give rise to the isomers *Z* and *E* of the final product respectively. This **TS2 1_4** can also occur by the other face of the substrate, giving rise to the other enantiomer of the **I2 1_4** that gives the energetically exact pathway.

Our experimental results show that the obtained product for this reaction is the 1,4-addition product with *Z* configuration excluding the formation of the *E* isomer or the 1,2-addition product. These results are in good agreement with our mechanistic proposal as the pathway for the 1,2-addition is less favoured due to the lower stability of the intermediate **I2 1_2** and the high energy barrier for the **TS3 1_2** ($\Delta G^{\neq}$=23.9 kcal·mol^{-1}). Moreover, the formation of the *Z* versus the *E* isomer is favourable both kinetically ($\Delta\Delta G^{\neq}$=1.1 kcal·mol^{-1}) and thermodynamically ($\Delta\Delta G$=2.7 kcal·mol^{-1}).



Scheme 3. Relative Gibbs Free Energies for the reaction pathway of the 1,2- and 1,4-addition of the PhSe−Bpin (**1**) reagent to the model substrate 1-(4-methylphenyl)-3-phenyl-2-propyn-1-one (**18**). All energies are in kcal·mol^{-1}.

As a final conclusion we can now offer a more flexible and reliable route to stereodefined (*Z*)-alkenyl selenides and (*Z*)-alkenyl sulfides through the powerful "pull-push" properties of Bpin units in the chalcogenoborate reagents PhSe-Bpin, PhS-Bpin and BnS-Bpin when react with ynones, in a metal free context without any additive except MeOH as solvent. The mechanistic proposal allows to justify and to understand the selectivity of the reaction outcome.

Experimental Section

General Method: β-selenation and β-sulfonation of α,β-alkynyl ketones. The reagent PhSeBpin (**1**) or PhSBpin (**2**) (2 eq.) was weighted and transferred into an oven-dried schlenk tube inside the glovebox. The corresponding ynone substrate (0.10 mmol) was introduced in the Schlenk tube under argon and dry THF (2 mL) was added. The mixture was stirred for 16 hours at 50ºC. The solvent was removed under vacuum and the resulting residue was analysed by ^{1}H NMR. Conversion and selectivity were determined by ^{1}H NMR. The product was purified by flash chromatography using a silica gel column, and the mixture of petroleum ether and ethyl acetate adequate for each case.

Acknowledgements

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Ynones merge activation/conjugate addition of chalcogenoborates ArE-Bpin (E=Se, S)

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