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Ynones Merge Activation/Conjugate Addition of Chalcogenoborates ArE-Bpin (E = Se, S)

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Dedicated to Prof. Todd Marder on his 60th birthday.

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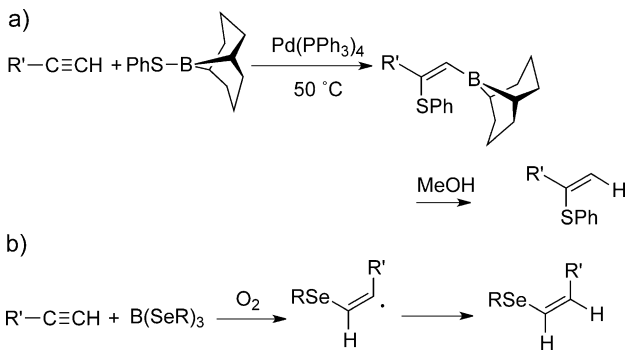
Abstract: The "pull–push" effect of the Bpin moiety in ArE-Bpin reagents (E = Se, S) is demonstrated by the Lewis acid interaction with the carbonyl group of ynones and the concomitant delivery of ArSe or ArS to the electron-deficient alkyne with impressive stereoselectivity. The two component reactivity is carried out in methanol 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.

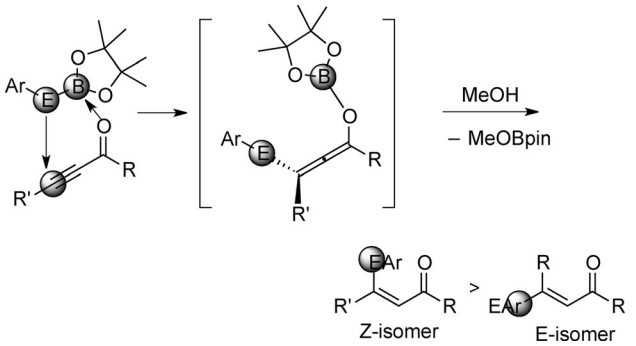
Keywords: (*Z*)-β-(arylseleno)-α,β-unsaturated ketones; (*Z*)-β-(arylsulfuro)-α,β-unsaturated ketones; chalcogenoborates; Lewis acid interaction; ynones

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 affords 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]

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 working 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 analyzed with theoretical calculations to give some insight into the favored stereoselective formation of the (*Z*)-β-(arylseleno)-



Scheme 1. Known syntheses of vinyl selenides and sulfides through chalcogenoborates.

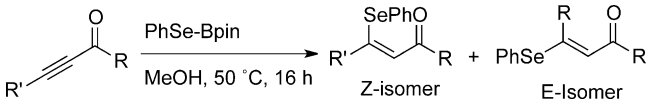


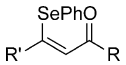
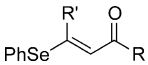
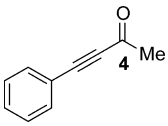
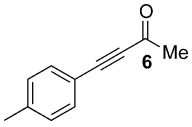
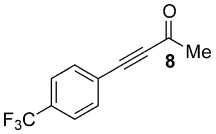
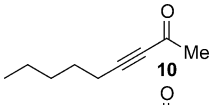
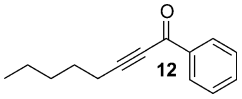
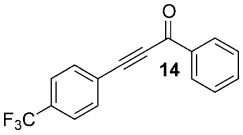
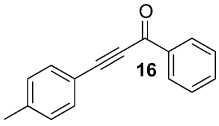
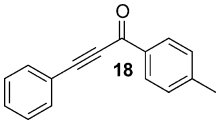
Scheme 2. New synthesis of vinyl selenides and sulfides through chalcogenoborates.

α,β-unsaturated ketones and (*Z*)-β-(arylsulfuro)-α,β-unsaturated ketones (Scheme 2).

We initiated our studies with the addition of 1 equiv. 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 50 °C 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 2 equiv. MeOH. Both stereoisomers could be isolated and unequivocally characterized by NMR spectroscopy. We also computed the ^{1}H NMR shifts by DFT (see the Supporting Information for details) and interestingly we confirmed these results. At this point, we were

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



Entry	Substrate	Conversion[b] [%]		
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 (2 equiv.), MeOH (2 mL), 50 °C, 16 h.
[b] Conversion and regioselectivity determined by NMR spectroscopy. Values in parenthesis are isolated yields.

able to correct 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 2 equiv. of PhSe-Bpin (**1**) to obtain complete conversion and total stereoselection towards **5-*Z*** (Table 1, entry 1). Substituents 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 aliphatic 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,

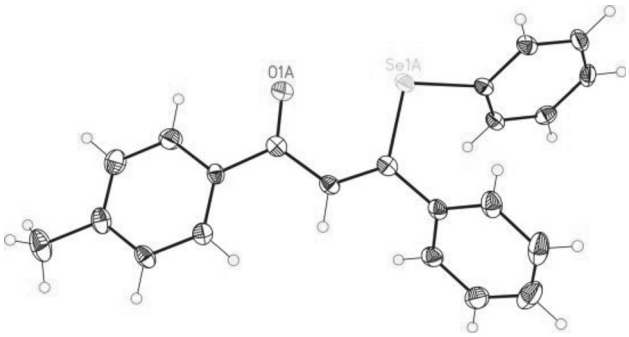
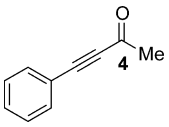
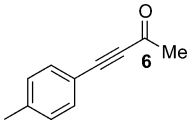
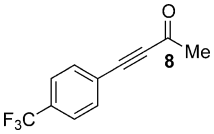
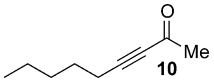
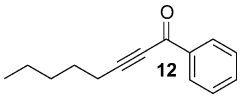
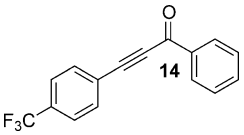
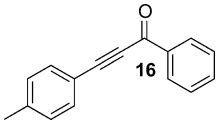
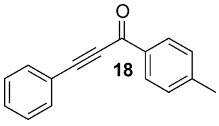


Figure 1. Ball and stick diagram of **19-*Z***.

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

Entry	Substrate	**Ar**S-Bpin	Conversion [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), 50 °C, 16 h.
[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

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 were achieved for the 1,3-diphenylprop-2-yn-1-one substrates **14** and **18** (Table 1, entries 6 and 8) with a slight decrease in 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).

The straightforward reactivity between ynones and PhSe-Bpin (**1**) simplified previous attempts to obtain (*Z*)-α,β-(arylseleno)-α,β-unsaturated ketones *via* addition of selenoesters 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 ***Z*/*E*** of *ca.* 3/1, independent of the nature of the Ar group in the thiodioxaborolane reagent. The aliphatic substituents in 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 ynones, contrasts with the lower stereoselectivity observed in alternative methodologies such as addition of thiols to the electron-deficient alkynes methyl propiolate and dimethyl acetylenedicarboxylate, in the presence of Ru catalysts.[15]

The favored formation of (*Z*)-vinyl selenides and vinyl sulfides is opposite to the trend observed for the (*E*)-vinylamines through β-amination of ynones with Bpin-NMe_2 and Bpin-NEt_2 from the adduct [$RO^- \rightarrow$ Bpin-NMe_2] (Figure 2, *left*). 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, *right*).[18,19] Here we describe a mechanistic pathway for assembly of the chalcogenoborates and ynones that also rationalizes the favored stereoselectivity on (*Z*)-β-(arylseleno)-α,β-unsaturated ketones.

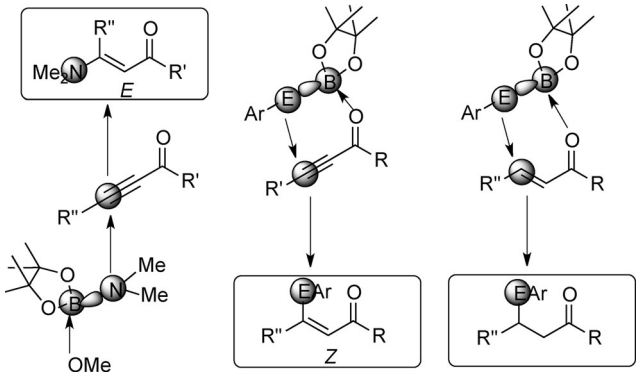
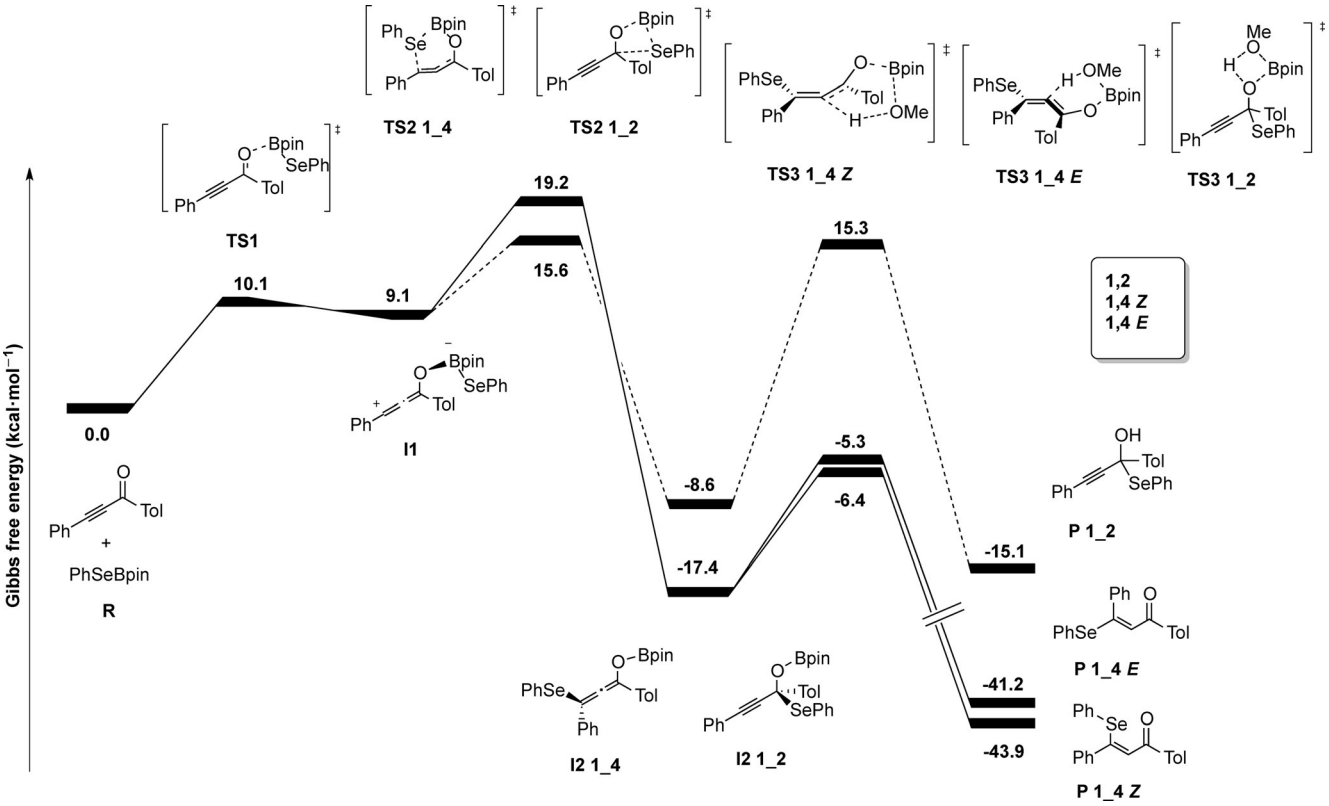


Figure 2. Activation modes of ynones and α,β-unsaturated carbonyl compounds by chalcogenoborate (E = Se, S) and aminoboronate reagents.

By means of DFT studies (see the Supporting Information for 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 on the carbonyl group (**TS2 1 2**) or on 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 by-product pinBOMe. When we conducted an 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 was converted back to the ynone starting material (see the Supporting Information). 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}).

As a final conclusion we can now offer a more flexible and reliable route to stereodefined (*Z*)-alkenyl



Scheme 3. Relative Gibbs free energies for the reaction pathways 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}.

selenides and (*Z*)-alkenyl sulfides through the powerful "pull–push" properties of Bpin units in the reactions of the chalcogenoborate reagents PhSe-Bpin, PhS-Bpin and BnS-Bpin with ynones, in a metal-free context without any additive except MeOH as solvent. Moreover, our mechanistic proposal, supported by DFT calculations, allows for an understanding of the selectivity.

Experimental Section

General Method for β-Selenation and β-Thiolation of α,β-Alkynyl Ketones (see also the Supporint Information, pp. S1 and S4).

The reagent PhSeBpin (**1**) or PhSBpin (**2**) (2 equiv.) was weighed and transferred into an oven-dried Schlenk tube inside the glove-box. 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 h at 50 °C. The solvent was removed under vacuum and the resulting residue was analyzed 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 a mixture of petroleum ether and ethyl acetate (see also the Supporting Information, p. S4, lines 7 and 15).

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References

[1] a) G. Perin, E. J. Lenardao, R. G. Jacob, R. B. Panatieri, *Chem. Rev.* **2009**, *109*, 1277.
[2] T. Kondo, T. Mitsudo, *Chem. Rev.* **2000**, *100*, 3205.
[3] *Organoselenium Chemistry – Modern Developments in Organic Synthesis*, *Topics in Current Chemistry*, (Ed.: T. Wirth), Springer Verlag: Heidelberg, **2000**.
[4] *Organoselenium Chemistry: A Practical Approach*, (Ed.: T. G. Back), Oxford University Press, New York, **1999**.
[5] *Selenium Reagents and Intermediates in Organic Synthesis*, (Ed.: C. Paulmier), Pergamon Press, Oxford, **1986**.
[6] I. P. Beletskaya, V. P. Ananikov, *Eur. J. Org. Chem.* **2007**, 3431.

[7] T. Ishiyama, K. Nishijima, N. Miyaura, A. Suzuki, *J. Am. Chem. Soc.* **1993**, *115*, 7219.
[8] Q. Cui, D. G. Musaev, K. Morokuma, *Organometallics* **1998**, *17*, 1383.
[9] T. Kataoka, H. Yoshimatsu, H. Shimizu, M. Hori, *Tetrahedron Lett.* **1990**, *31*, 5927.
[10] T. Kataoka, M. Yoshimatsu, Y. Noda, T. Sato, H. Shimizu, M. Hori, *J. Chem. Soc. Perkin Trans. 1* **1993**, 121.
[11] A. Owaga, *J. Organomet. Chem.* **2000**, *611*, 463.
[12] a) J. Cid, H. Gulyas, J. J. Carbó, E. Fernández, *Chem. Soc. Rev.* **2012**, *41*, 3558; b) R. D. Dewhurst, E. C. Neeve, H. Braunschweig, T. B. Marder, *Chem. Commun.* **2015**, DOI: 10.1039/c5cc02316e; c) S. Pietsch, E. C. Neeve, D. C. Apperley, R. Bertermann, F. Mo, D. Qiu, M. S. Cheung, L. Dang, J. Wang, U. Radus, *Chem. Eur. J.* **2015**, *21*, 7082.
[13] B. Mattistelli, T. Lorenzo, M. Tiecco, C. Santi, *Eur. J. Org. Chem.* **2011**, 1848.
[14] Ch.-Q. Zhao, X. Huang, J.-B. Meng, *Tetrahedron Lett.* **1998**, *39*, 1933.
[15] U. Koelle, C. Rietmann, J. Tjoe, T. Wagner, U. Englert, *Organometallics* **1995**, *14*, 703.
[16] C. Sole, E. Fernández, *Angew. Chem. Int. Ed.*; **2013**, *52*, 11351.
[17] E. N. Daley, C. M. Vogels, S. J. Geier, A. Decken, S. Doherty, S. A. Westcott, *Angew. Chem. Int. Ed.* **2015**, *54*, 2121.
[18] M. G. Civit, X. Sanz, C. M. Vogels, J. D. Webb, S. J. Geier, A. Decken, C. Bo, S. A. Westcott, E. Fernández, *J. Org. Chem.* **2015**, *80*, 2148.
[19] X. Sanz, C. M. Vogels, A. Decken, C. Bo, S. A. Westcott, E. Fernández, *Chem. Commun.* **2014**, *50*, 8420.

