Z-Selective synthesis of vinyl boronates through Fe-catalyzed alkyl radical addition

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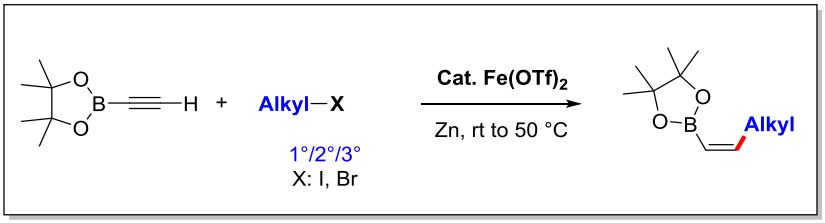
Supporting Information Placeholder



ABSTRACT: Z-selective synthesis of vinyl boronates is challenging. This work describes Fe-catalyzed addition of alkyl radicals, formed by the corresponding alkyl halides,to ethynyl ethynylboronic acid pinacol ester that gives rise to Z-vinyl boronates in high stereoselectivity. The method works best for tertiary and secondary alkyl iodides. The Z-vinyl boronate products are easily converted to other Z-alkenes by transformation of the boronate group. The method is applied for the formal total synthesis of a 5-HT_{2c} receptor agonist.

Z-Selective synthesis of 1,2-disubstituted alkenes is an important yet challenging task in organic synthesis.[1,2] Because the boronate group can be readily transformed into many common functional groups,[3] Z-olefins might be conveniently accessed from Z-vinyl boronates. While hydroborylation of terminal alkynes is an efficient method to synthesize vinyl boronates, it typically leads to the thermodynamically more stable E-isomers (Figure 1a).[4–11]There are until now only several reports of Z-selective hydroboration of terminal alkynes, with limited scope for alkyl alkynes.[12–15] Here we describe an alternative approach to the synthesis of Z-vinyl boronates. Our approach is based on Fe-catalyzed stereoselective addition of an alkyl radical, generated from an alkyl halide under reductive conditions, to ethynylboronic acid pinacol ester (**1**, Figure 1b). The approach is built upon our previous work[16–18] Which showed that an alkyl radical was generated through the reaction of an alkyl halide with an Fe(I) species, produced by reduction of an Fe(II) catalyst with Zn (Figure 1c and 1d). The alkyl radical could be trapped by a terminal aryl alkyne to form a vinyl radical stabilized by an aryl group. Recombination of the vinyl radical with Fe(I) gave an Fe(II) vinyl intermediate. This step was stereoselective and favored a cis-arrangement of the aryl and alkyl groups. Transmatallation of the Fe(II) vinyl intermediate to Zn(II), followed by protonation, yielded the cis-alkene. In this chemistry, the aryl substituent of the alkyne was essential. Replacement of the aryl group by another electron-withdrawing group such as keto, ester, nitrile, or amide led to no formation of alkene. Here we show that the boronic acid pinacol ester group (Bpin) can serve the same function of an aryl group in stabilizing the vinyl radical. An important advantage of the Bpin group over an aryl group is that the former could be readily converted to numerous other functional groups, making this method of Z-alkene synthesis truly general.

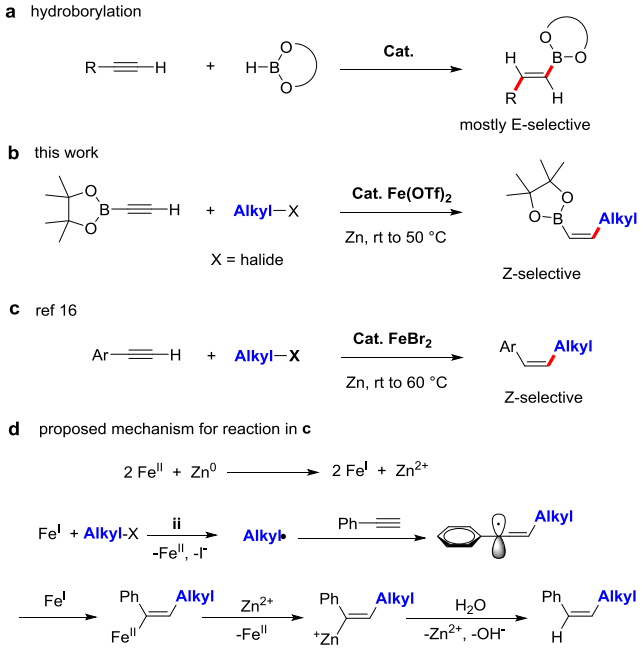
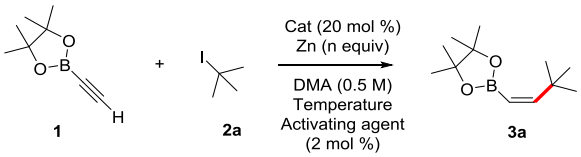


Figure 1. (a) Hydroborylation of alkyne to give vinyl boronates; (b) Synthesis of Z-vinyl boronates by Fe-catalyzed alkyl radical

addition to **1;** (c) Synthesis of Z-styrenes by Fe-catalyzed alkyl radical addition to aryl alkynes; (1d) The proposed mechanism for the reaction in c.

The reaction of **1** with tert-butyl iodide (**2a**) was chosen as the test reaction (Table 1). At first, the conditions previously developed for the reductive coupling of ethynylbenzene with **2a**, that is, 1 equiv **1**, 3 equiv of **2a**, 20 mol% of $FeBr_2$, 3 equiv of Zn metal, and 2 mol% of I_2 activator, DMA as solvent, 80°C, were employed (Table 1, entry 1). To our delight, a yield of 48% and a Z:E selectivity of 92:8 was obtained. Other metal salts such as $CuBr_2$, NiI_2, and CoI_2 were tested as catalysts. NiI_2 gave no yield, while $CuBr_2$ and CoI_2 gave lower yields but similar Z:E selectivity (Table 1, entries 2-4). FeI_2 had a similar efficiency to $FeBr_2$, but $Fe(OTf)_2$ (OTf = Triflate) gave a much higher yield of 82% when the reaction was conducted at 50°C (Table 1, entries 5-6). Unfortunately the Z:E selectivity dropped to 6:1. Replacement of the I_2 activator by TMS-I (TMS = tetramethyl silyl) led to a yield of 95% and a Z:E selectivity of 44:1 (Table 1, entry 7). When the loading of $Fe(OTf)_2$ was decreased to 10 mol%, the yield dropped to 42% (Table 1, entry 8). When the loading of Zn was decreased to 2 or 1 eq., the yields also dropped significantly (Table 1, entries 9-10).

Table 1. Optimization of conditions for the reaction of 1 with 2a.[a]



entry	cat.	n	a.a.	temp. (°C)	yield (%)	Z:E[b]
1	$FeBr_2$	3	I_2	80	48	12:1
2	$CuBr_2$	3	I_2	80	33	13:1
3	NiI_2	3	I_2	80	0	n.d.
4	CoI_2	3	I_2	80	22	16:1
5	FeI_2	3	I_2	80	53	12:1
6	$Fe(OTf)_2$	3	I_2	50	82	6:1
7	$Fe(OTf)_2$	3	TMS-I	50	**95**	44:1
8	$Fe(OTf)_2$[c]	3	TMS-I	50	42	53:1
9	$Fe(OTf)_2$	1	TMS-I	50	2	n.d.
10	$Fe(OTf)_2$	2	TMS-I	50	47	130:1

[a]General conditions: Alkynyl Boronate Ester (0.5 mmol), terbutyl iodide (1.5 mmol), under N_2, in DMA (1 mL),. a.a. = activating agent; temp. = temperature; n.d. = not determined. [b]According to quantification by GC analysis. [c]10 mol% loading of catalyst.

The optimized conditions in Table 1 (entry 7) were applied for the coupling of **1** with various tertiary and secondary alkyl iodides, yielding the corresponding Z-alkenes (Figure 2). Tert-butyl (**3a**), 1-adamantyl (**3b**), and tert-pentyl (**3c**) groups were added in high yields. Secondary alkyl groups such as 2-octyl (**3d**), cyclohexyl (**3e**), cyclooctyl (**3f**), 2-butyl (**3g**), 1-tert-butyl-4-cyclohexyl (**3h**) were added in good yields and selectivity as well. The Z-isomer of **3h** was obtained in 14:1 trans/cis diastereoselectivity. Addition of 2-propylbenzene (**3i**) and an ester-functionalized alkyl group (**3j**), on the other hand, had modest yields of about 40%. More sensitive functional groups were not tolerated. Alkyl bromides were then tested as substrates, but lower yields were obtained compared with alkyl iodides (e.g., for **3a**, **3c**, **3d**, **3f**, **3k**). In some cases ((**3f, 3k**) a difference in stereoselectivity was observed using wither alkyl iodides or bromides as the substrates. This difference is likely due to experimental uncertainty as a low yield and small amount of products were obtained using alkyl bromides. Cyclohexyl chloride was also tested, but no coupling was found.

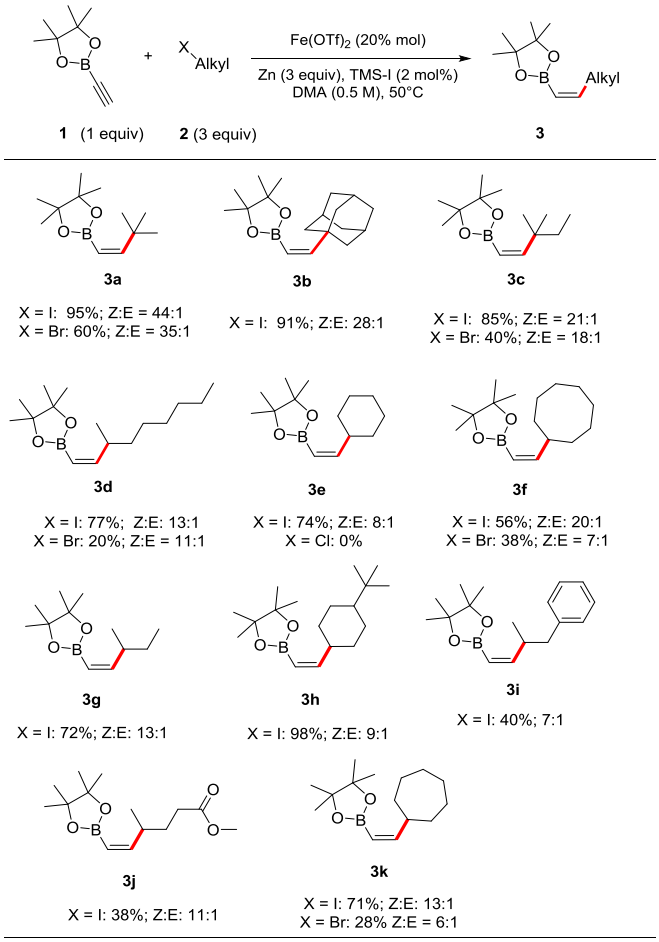


Figure 2. Scope of the coupling of 1 with tertiary and secondary alkyl halides. The *Z:E* ratio was determined by ^{1}H NMR after purification.

When the same conditions were applied for the coupling of **1** with primary alkyl iodides, very low yields were obtained.

Upon further optimization, complex **4** was found to be a better catalyst than $Fe(OTf)_2$ (Figure 3). A new set of conditions were also identified: 1 equiv **1**, 3 equiv of **2a**, 5 mol% of **4**, 3 equiv of Zn metal, and 2 mol% of I_2 activator, DMA as solvent, room temperature (rt). The scope of this coupling was however limited. While for addition of n-octyl (**3l**) and dec-1-ene (**3m**) groups, the yields were good, the addition of other alkyl groups (**3n**-**3r**) had yields in the range of 20-35%. The higher reactivity of primary alkyl radicals compared to secondary and tertiary radicals might be the origin of the decreased efficiency of the reactions with primary alkyl iodides.

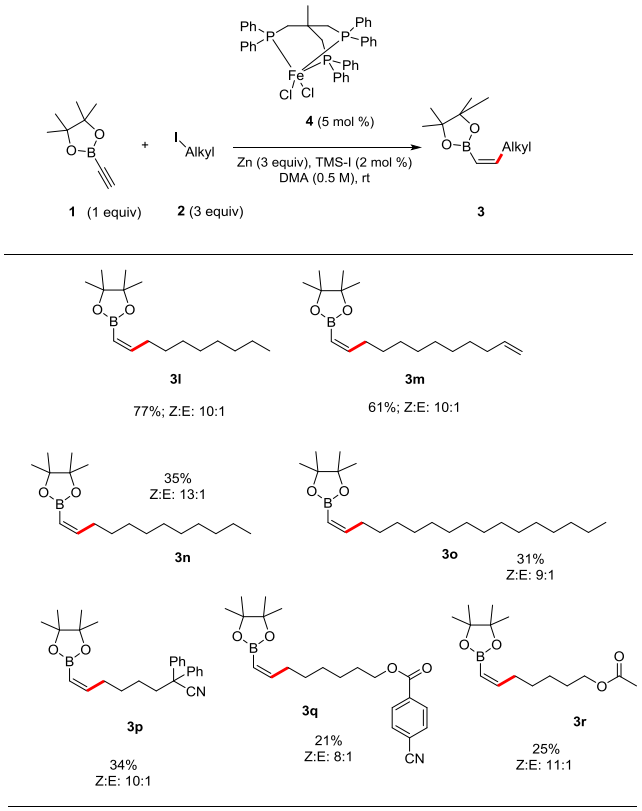
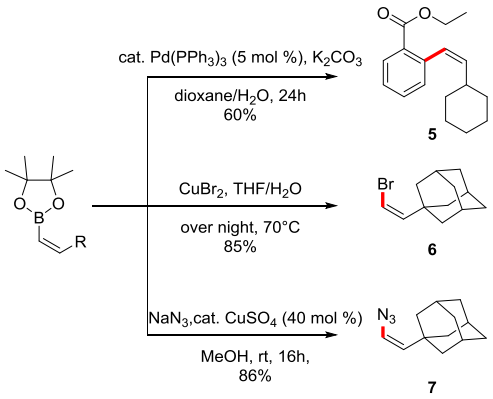


Figure 3. Scope studies for primary aliphatic halides. The *Z:E* ratio was determined by ^1H NMR after purification.

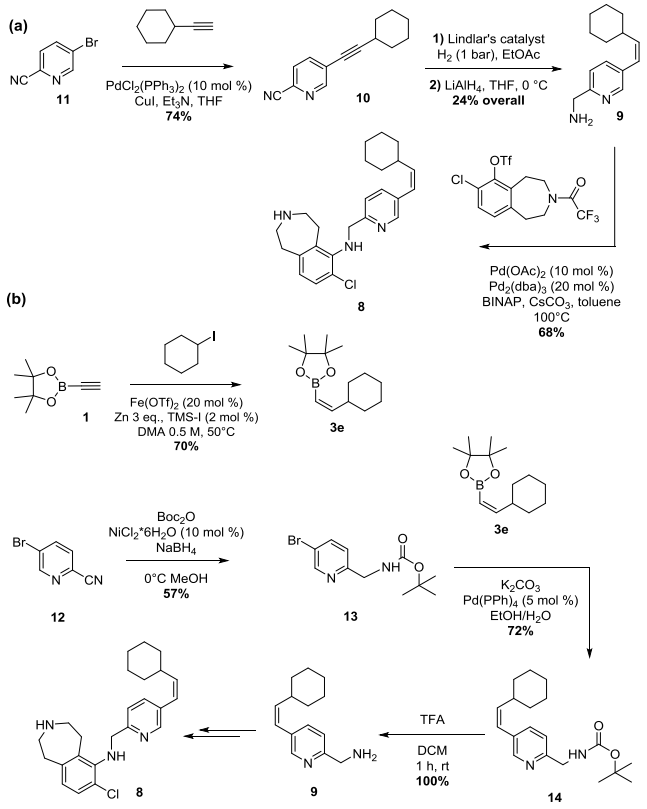
The Z-vinyl boronate products obtained above could be converted to Z-alkenes bearing various functional groups by transformation of the Bpin group. For example, Pd-catalyzed Suzuki coupling of **3e** with ethyl 2-bromobenzoate gave **5** in a 60% yield, bromination of **3b** with $CuBr_2$ gave **6** in an 85% yield, and Cu-catalyzed azidation of **3b** with NaN_3 gave **7** in an 86% yield (Scheme 1).

Scheme 1. Further transformations of Z-vinyl boronates



The Fe-catalyzed Z-alkene synthesis was then applied for the formal total synthesis of (Z)-7-chloro-6-{[5-(2-cyclohexyl-vinyl)-pyridin-2-ylmethyl]-amino}-2,3,4,5-tetrahydro-1H-benzo[d]azepine (**8**, Scheme 2). This compound was reported as a 5-HT_{2c} receptor agonist, which might lead to treatment of various neurological disorders.[19] The key intermediate to **8** was a Z-alkene **9**, which could be produced by Pd-catalyzed heterogeneous hydrogenation of 1,2-disubstituted alkyne **10**, but in a low yield (Scheme 2a). The latter was obtained by Pd-catalyzed Sonogashira coupling of ethynylcyclohexane with the corresponding pyridinyl bromide **11**. In our synthesis, the nitrile group in the commercially available reagent **12** was reduced by $NaBH_4$ in the presence of $NiCl_2{\cdot}6H_2O$ (10 mol%) followed by protection with BOC_2O to give **13** in a yield of 57% (Scheme 2b). Pd-catalyzed Suzuki coupling of **13** with **3e**, assembled by the Fe-catalyzed coupling of **1** with cyclohexyl iodide, gave the alkylated Z-olefin **14** in a yield of 72% (Scheme 2b). Removal of the Boc group by TFA (TFA = Trifluoroacetic acid) gave the key intermediate **9** in a quantitative yield (Scheme 2b). In previous route a terminal alkyl alkyne was needed while in the present route an alkyl iodide is used. For many of the secondary alkyl groups shown in Figure 2, alkyl iodides are easily accessible while the corresponding alkyl alkynes are not. Thus, our synthetic route can be advantageous for obtaining certain alkylated derivatives of **8**. Additionally, the stereoselective step in our synthesis has a higher yield than that in the previous route.

Scheme 2. Total synthesis of (Z)-7-chloro-6-{[5-(2-cyclohexyl-vinyl)-pyridin-2-ylmethyl]-amino}-2,3,4,5-tetrahydro-1H-benzo[d]azepine. (a) Previous route (ref 17); (b) This work



In summary, Fe-catalyzed reductive coupling of ethynylboronic acid pinacol ester with alkyl halides has been developed for the stereoselective synthesis of Z-vinyl boronates. A simple salt, Fe(OTf)2, could be used for the coupling of secondary and tertiary alkyl halides, particularly alkyl iodides, with good yields and high Z-selectivity. The coupling of primary alkyl halides has limited scope, even when using a defined Fe complex (**4**) as catalyst. The Z-vinyl boronates could be converted to other Z-alkenes by transformation of the Bpin group. The method was applied for a formal total synthesis of a 5-HT_{2c} receptor agonist (**8**).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interests.

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