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Jean Michalland, Samir Zard. A Convergent, Stereoselective Route to Trisubstituted Alkenyl Boronates. *Organic Letters*, 2021, 23 (20), pp.8018-8022. 10.1021/acs.orglett.1c03022. hal-03416821

HAL Id: hal-03416821

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Submitted on 5 Nov 2021

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Journal:	<i>Organic Letters</i>
Manuscript ID	Draft
Manuscript Type:	Communication
Date Submitted by the Author:	n/a
Complete List of Authors:	Michalland, Jean; Ecole Polytechnique, Chemistry Zard, Samir; Ecole Polytechnique, Chemistry

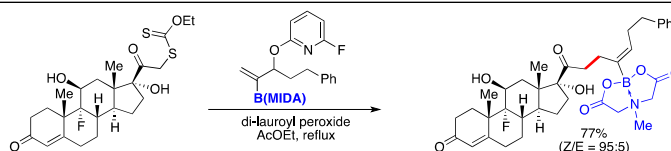
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A Convergent, Stereoselective Route to Trisubstituted Alkenyl Boronates

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Supporting Information Placeholder



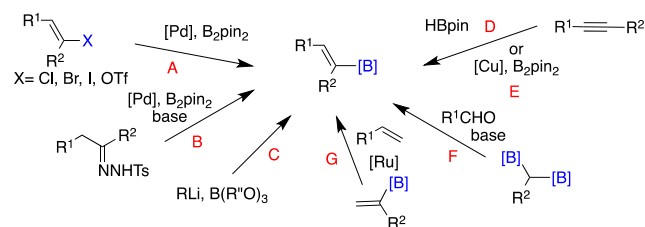
ABSTRACT: A modular, stereoselective route to trisubstituted (*Z*)-alkenyl (MIDA)boronates is described, consisting in the radical addition-fragmentation of dithiocarbonates to 2-(MIDA)boronyl-3-(2'-fluoro-pyridyl-6'-oxy)-alkenes. The bulky (MIDA)boronate ensures a highly stereoselective fragmentation that is enhanced by the poor stabilization of the radical adjacent to the tetravalent boron atom. The vinyl boronate precursors are prepared from propargyl alcohols by copper-catalyzed regioselective hydroborylation of their fluoropyridoxy derivatives, with the fluoropyridine acting as an internal directing group.

The importance of organoboron compounds to organic synthesis, medicinal chemistry, and material sciences is overwhelming.¹ Indeed, the Suzuki-Miyaura cross-coupling ranks in the top five reactions used by medicinal chemists in drug discovery and development.² The stability, low toxicity, and versatile reactivity of organoboronates are considerable advantages that make them almost ideal synthetic intermediates.

As partners in the Suzuki-Miyaura cross-coupling, alkenyl boronates occupy a particularly important position within the larger family of organoborons. The main routes to these substances are outlined in Scheme 1.³ The Miyaura palladium-catalyzed coupling of alkenyl halides or triflates with organodiboron reagents (**A**),⁴ including the recent variation consisting in generating the palladium complex from a tosylhydrazone (**B**),^{4b} as well as the boron-Heck (**A**, **X** = H);⁵ the direct borylation of alkenyllithiums (**C**)⁶ and the hydroboration (and carboboration) of alkynes (**D,E**),⁷ constitute the most common approaches. Other less employed methods include bora-Wittig condensation of *gem*-bis-boronates with aldehydes and ketones (**F**),⁸ rhodium catalyzed conjugate addition of *gem*-bis-boraalkenes and *gem*-borazirconocenes to enones,⁹ and the cross-metathesis between an alkenyl boronate and an alkene (**G**).¹⁰ As with all

chemical reactions, each of these routes has its drawbacks. In some instances, it is the limited availability of the substrates; in others, it is the incompatibility with the presence of polar groups, as is the case with reactions involving alkenyllithiums; or, as in the hydroborylation of unsymmetrical internal alkynes, the problem can be a low regioselectivity.

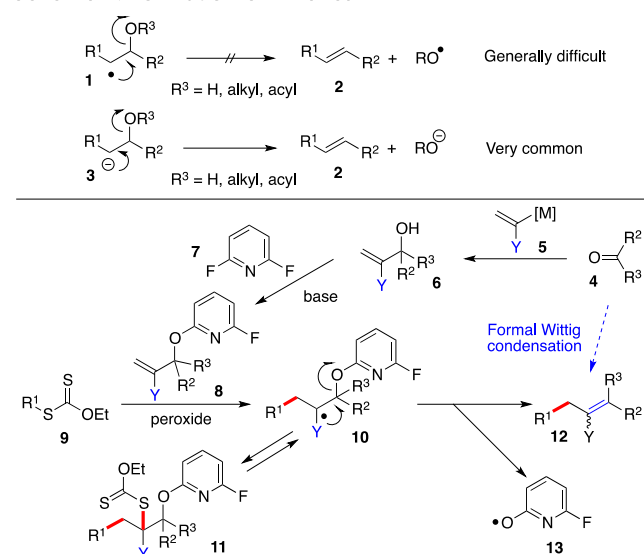
Scheme 1. Main Routes to Alkenyl Boronates



Radical processes have seldom been applied to the synthesis of alkenyl boronates.¹¹ As part of our work on the unusual radical chemistry of dithiocarbonates (xanthates),¹² we decided to exploit an earlier observation to develop a convergent, stereoselective approach to these important derivatives. One feature of radical intermediates is that β -scission by homolysis of carbon-oxygen bonds (**1** \rightarrow **2**, Scheme 2) is generally a difficult process (i. e. very slow on radical reactions timescale) that is not normally observed.¹³ This is in stark contrast to the heterolytic β -elimination (**3** \rightarrow

2) that is often encountered in ionic and organometallic chemistry. The lack of β -scission in the case of radical intermediates is a considerable synthetic asset when working with carbohydrates and terpenes, among others, where carbon-oxygen bonds are found in abundance.¹⁴ However, the ability of forcing the homolytic β -scission of a carbon-oxygen bond opens up numerous synthetic opportunities not hitherto available. We discovered that the fluoropyridoxy group, in conjunction with the relative long lifetime of radicals generated from xanthates, can indeed undergo the homolytic β -scission ($10 \rightarrow 12$, Scheme 2).¹⁵ This alliance translates into a powerful synthesis of alkenes, as outlined in the lower part of Scheme 2 ($9 \rightarrow 12$).¹⁶

Scheme 2. Formation of Alkenes

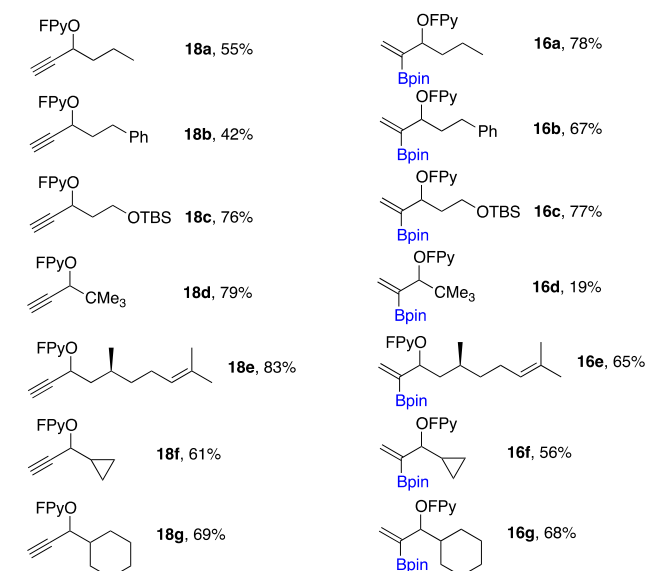
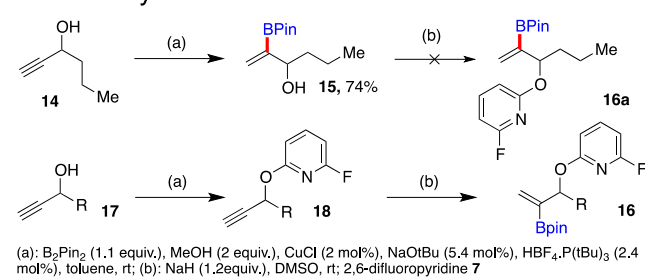


By converting an allylic alcohol **6** into its fluoropyridoxy derivative **8** and taking advantage of the ability of xanthates **9** to mediate *intermolecular* additions even to electronically unbiased alkenes, an addition-fragmentation sequence can be accomplished to furnish alkene **12**. The β -scission of intermediate radical **10** is in most cases slower than transfer of the xanthate group to give xanthate **11**, but this is of no consequence since this transfer is reversible.¹² Radical **10** is continuously regenerated and ultimately collapses into the desired alkene **12**. Many functional groups are tolerated, both on xanthate **9** and on activated allylic alcohol **8**, allowing the synthesis of alkenes with numerous combinations of substituents and functionalities. One interesting observation is that, while the starting allylic alcohols **6** can be obtained by various methods, one of the main routes is by reaction of a vinylmetal **5** with a ketone or aldehyde **4**. The overall sequence would thus correspond to a formal equivalent of a Wittig condensation ($4 \rightarrow 12$, Scheme 2).

To extend this strategy to the synthesis of alkenyl boronates, it is necessary to devise a route to the requisite

precursors **8**, $Y = [B]$. We initially contemplated the obtention of the borylated allylic alcohols **6**, $Y = \text{pinacolato boronate (Bpin)}$, by addition of the corresponding vinyl lithium reagent **5**, $Y = [\text{Bpin}]$ and $[M] = \text{Li}$, to an aldehyde; however, the 1-bromovinylBpin precursor is tedious and expensive to make.¹⁷ We therefore explored the route proceeding by hydroboration of propargyl alcohols, inspired by earlier work by the groups of Hoveyda¹⁸ and Carretero¹⁹ on the regioselective reductive borylation of alkynes directed by substituents on the propargylic position. Using conditions developed by Carretero,^{19a} we succeeded in converting propargyl alcohol **14a** into vinyl pinacolato boronate **15** in good yield (Scheme 3). Unfortunately, its transformation into the desired precursor **16a** by reaction of the corresponding alcoholate with 2,6-difluoropyridine **7** proceeded poorly. The reaction was very slow, with only around 11% of product being formed after 3 days (by NMR).

Scheme 3. Synthesis of Precursors 16

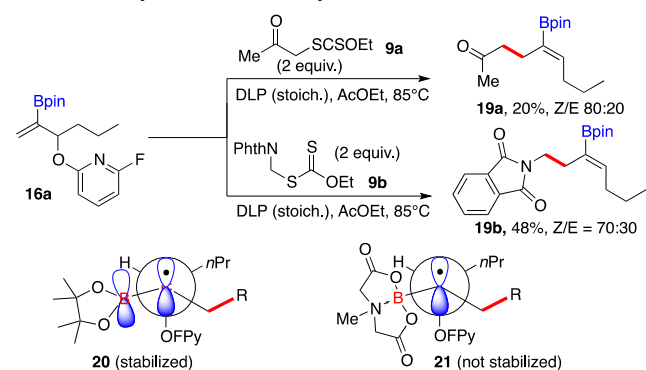


Following this setback, we reversed the order of the steps. The Carretero group previously used a propargylic 2-pyridylsufonyl group to direct the borylation of the alkyne,^{19a} so it seemed reasonable to expect a similar directing behavior from the fluoropyridoxy motif. Our radical "leaving group" would thus also act as a directing group for the regioselective borylation of the adjacent alkyne. To test this modified route,

a series of propargylic alcohols **17a-g** were converted into the corresponding fluoropyridoxy derivatives **18a-g** by reaction of the alcoholates with 2,6-difluoropyridine. Exposure to B_2Pin_2 under the cuprous chloride catalysis conditions specified by Carretero et al.^{19a} furnished indeed the long-sought derivatives **19a-g** in generally good yield, except for the *t*-butyl derivative **19d** which reacted poorly, presumably because of steric hindrance. In this case, the reaction did not go to completion, with 40% of starting material being isolated (yield based on recovered starting material is therefore ~30%). Furthermore, unlike the other alkynes where the regioselectivity was greater than 9:1 in favor of internal boronate, the regioselectivity of the hydroborylation of **18d** was only 3:2 (see SI for details).

With the requisite activated allylic alcohols in hand, we could now examine the formation of alkenyl boronates by the addition-fragmentation process. Compound **16a** was thus treated with two xanthates **9a** and **9b**, precursors to radicals of different stabilities and polar characteristics (Scheme 4). The reactions were conducted in refluxing ethyl acetate with portion-wise addition of stoichiometric amounts of di-lauroyl peroxide (DLP, also sold under lauroyl peroxide, Laurox® or Luperox®). It is necessary to use the peroxide in stoichiometric quantities because the fluoropyridoxyl radical **13**, generated in the fragmentation step (Scheme 2), does not propagate the chain.

Scheme 4. Synthesis of Alkenyl Pinacolato Boronates



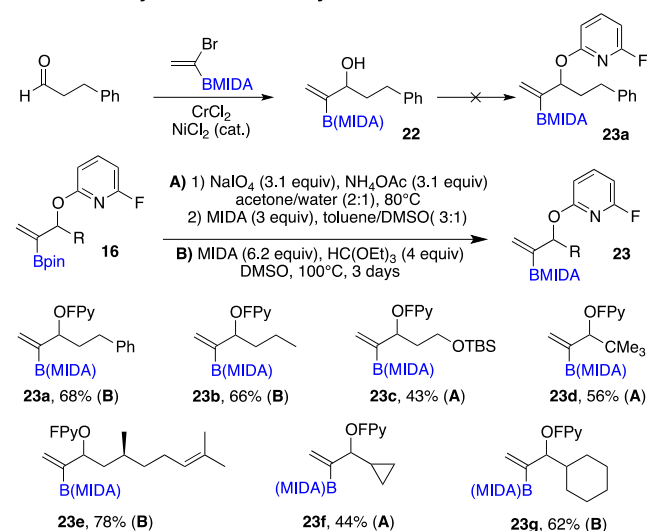
The desired reaction to give the corresponding alkenyl boronates **19a** and **19b** did indeed take place; unfortunately, the yield was modest and the stereoselectivity, while good, was below the level deemed synthetically useful. From previous experience with radical additions to vinyl boronates,²⁰ we surmised that the problematic step was the fragmentation, which was too slow because of the stabilization of the intermediate adduct radical **20** by spin delocalization into the empty orbital of the trivalent boron atom.²¹

As for the stereoselectivity, the pinacolato boronate group is clearly not sufficiently bulky to exert total control over the fragmentation.²² The most favorable conformation

corresponds to structure **20**, where the orbital containing the unpaired electron (the SOMO) is in the same plane as the C-O bond linking the fluoropyridoxy group, with the boronate located anti to the propyl. Fragmentation then furnishes the *Z* geometric isomer as the major product. To solve both problems of slow fragmentation and insufficient stereoselectivity, we decided to replace the pinacolato boronate with the bulkier MIDA boronate. The corresponding adduct radical **21** is less stabilized because the boron atom is now tetravalent with no vacant orbital available for delocalization,^{20c} and the significantly increased steric bulk should improve the stereoselectivity by favoring more strongly conformation **21** pictured in Scheme 4 and leading to the *cis* isomer.

We initially attempted to access the desired MIDA boronate substrates by starting with 1-bromovinyl MIDA boronate which, unlike 1-bromovinylBpin, is easy to make and even commercially available.²³ After some effort, we found that it is possible to couple it with hydrocinnamaldehyde under typical Nozaki-Hiyama-Kishi conditions; however, our attempts to introduce the fluoropyridyl group on the resulting alcohol **22** failed to give the desired derivative **23a** (Scheme 5). We therefore resorted to another route, namely converting vinyl pinacolato boronates **19a-g** into the corresponding vinyl MIDA boronates **23a-g**. We employed two methods, as shown in Scheme 5.²⁴ In method **A**, the boronic acid is formed by cleaving the pinacol motif with periodate and then converted into the MIDA boronate by treatment with *N*-methyl iminodiacetic acid (MIDA).^{24a} In the second, method **B**, the pinacolato boronate is heated with MIDA and triethyl orthoformate in DMSO at 100 °C for three days. Even though slow, this method is nevertheless equally convenient for substrates that do not contain fragile functionality.^{24b}

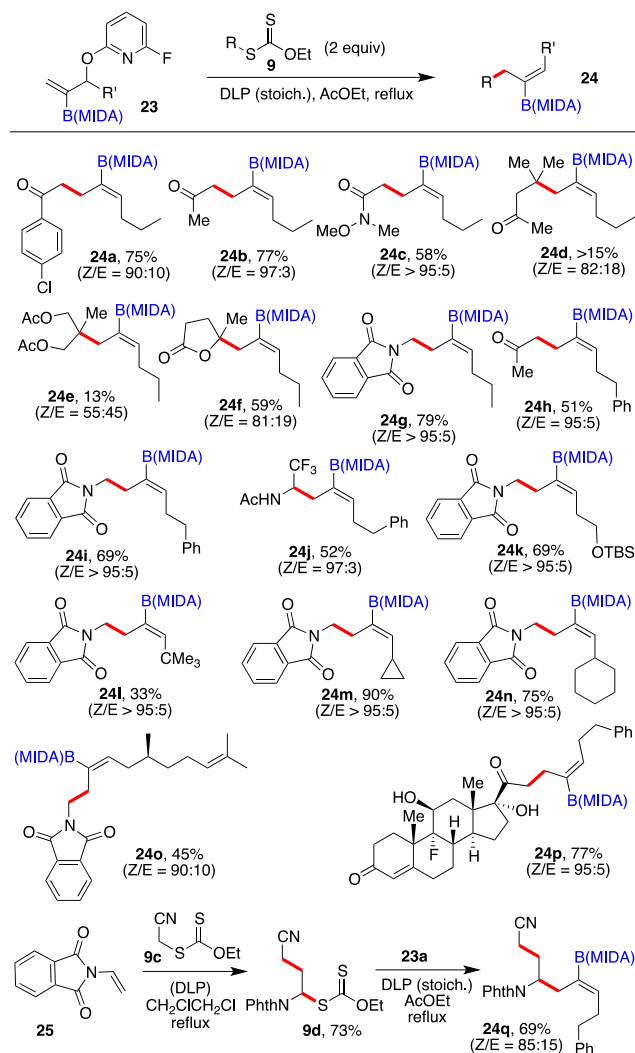
Scheme 5. Synthesis of Alkenyl Pinacolato Boronates



Our expectations were borne out in practice. Thus, addition of various xanthates to the fluoropyridoxy derivatized vinyl MIDA boronates **23a-g** furnished products **24a-p** (Scheme 6). The yields are generally good and the stereoselectivity is in most cases $\geq 95:5$ in favor of the desired *Z* isomer, as determined by NMR spectroscopy. The two notable exceptions, **23d** and **23e**, involve tertiary xanthates. The yield was disappointingly low and, for the latter, the stereoselectivity was also poor, presumably because the tertiary group introduced is also quite bulky. Further work is needed to better understand the source of difficulty in such cases.

At any rate, trisubstituted alkenyl boronates with defined geometry and bearing a variety of functional groups can be readily prepared. In particular, the compatibility with polar functionalities, such as ketones, lactones, imides, amides, including Weinreb amides, free hydroxy groups, and fluorinated motifs, are a hallmark of radical processes and a unique synthetic asset. Indeed, many of the compounds displayed in Scheme 6 would be accessible only tediously by any of the established routes summarized in Scheme 1. The formation of corticosteroid boronate **24p**, without the need for any prior protection, illustrates nicely the broad functional group tolerance.

Scheme 6. Synthesis of Alkenyl MIDA Boronates



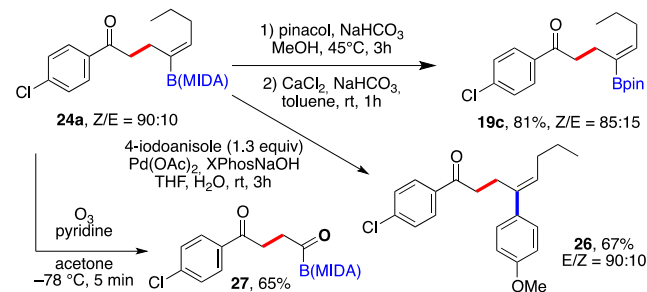
Increase in complexity can be achieved by taking advantage of another property of the xanthate-based technology, namely that the addition of a xanthate to an alkene leads to another xanthate, which in turn can be converted into an alkenyl boronate by the chemistry described herein. This variation is exemplified by the sequence at the bottom of Scheme 6, whereby cyanomethyl xanthate **9c** is added to *N*-vinyl phthalimide **25** to provide a new xanthate **9d**,²⁵ which is then made to react with alkene **23a** to give alkenyl boronate **24q**. The first step is a true radical chain, requiring sub-stoichiometric amounts of the peroxide initiator. In this manner, three different molecules have been combined and two new C-C bonds created in an *intermolecular* fashion. Different functional groups can be present on each partner allowing for numerous combinations in principle.

To summarize, we have developed a modular, versatile, and highly stereoselective route to alkenyl MIDA boronates. It is tolerant of many of the functional groups encountered in modern synthesis and is easily scalable. Thus, alkenyl

boronate **24a** could be prepared on 1.4 g scale without loss of efficacy. Indeed, the yield was slightly higher (81% vs 75%) and the stereoselectivity remained the same (90:10). The stereoselectivity could in principle be further increased by the use of substituents on the boron that are bulkier than MIDA, as for example the pinene derived iminodiacetic (PIDA), which has the further advantage of allowing subsequent diastereoselective transformations of the resulting alkenyl boronate.²⁶

MIDA boronates offer many advantages as compared to the popular pinacolato boronates.²⁷ They are more robust, more stable towards chromatographic purification, can be precipitated by dilution with a non-polar solvent such as ether, and are much less subject to protodeborylation. They can nevertheless be converted into the free boronic acid or other boronates, if so desired.²⁸ This is illustrated by the straightforward conversion of boronate **24a** into pinacolato boronate **19c** depicted in Scheme 7. This indirect route to alkenyl pinacolato boronates **19** circumvents the shortcomings of the initial approach discussed in Scheme 3. Another useful transformation is of course the Suzuki-Miyaura cross-coupling, in this case with *p*-iodoanisole to give **26** with essentially no erosion of the stereochemical integrity.^{27c} Finally, ozonolysis of the alkene, as described by Bode, Ito and co-workers,^{24b} furnishes acyl boronate **27**. Acyl boronates are relatively rare substances that are emerging as quite useful synthetic intermediates.²⁹

Scheme 7. Examples of Post-Modifications of an Alkenyl MIDA Boronate



ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full spectroscopic data, and copies of ¹H and ¹³C NMR for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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ACKNOWLEDGMENTS

We thank Ecole Polytechnique for a scholarship to J. M., and Mrs Sophie Bourcier and Mr Vincent Jactel (both at Ecole Polytechnique) for HRMS measurements.

DEDICATION

This article is affectionately dedicated to Professor Troels Skrydsrup (Aarhus University) on the occasion of his 60th birthday.

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