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Stereoselective Direct Chlorination of Alkenyl MIDA Boronates: Divergent Synthesis of *E* and *Z*- α-Chloro Alkenyl Boronates

Yao-Fu Zeng, Wei-Wei Ji, Wen-Xin Lv, Yunyun Chen, Dong-Hang Tan, Qingjiang Li, and Honggen Wang*

Abstract: The individual molecules of α-chloro alkenyl boronates include both an electrophilic C-Cl bond and a nucleophilic C-B bond, which makes them intriguing organic synthons. Reported herein is a stereodivergent synthesis of both *E* and *Z*-α-chloro alkenyl *N*-methyliminodiacetyl (MIDA) boronates by the direct chlorination of alkenyl MIDA boronates using *t*-BuOCl and PhSeCl reagents, respectively. Both reaction processes are stereospecific and the use of sp^3-B MIDA boronate is the key contributor to the reactivity. The synthetic value of the boronate products was demonstrated.

The rapid assembly of complex molecules has been a long-standing challenge in modern organic synthesis.[1] For this purpose, the discovery and application of easily accessible building blocks that combine multiple functional groups with orthogonal chemical reactivities represents an appealing approach. Organoboron compounds are of vital importance in modern organic chemistry due to their versatility for involvement in diverse transformations.[2] The introduction of easily transformable functional groups into organoborons would, in principle, greatly enhance the synthetic values of organoboron compounds for facilitating the modular and rapid synthesis of complex molecules, provided reactions could be performed in a chemoselective manner.[3] As an excellent example of this high synthetic value, α-halo alkenyl boronates are amphoteric compounds containing both nucleophilic (C-B bond) and electrophilic (C-halo bond) sites (Figure 1).[4] These organoboron compounds have, for instance, been utilized as synthons in poly-substituted alkene synthesis.[5] They have also served as precursors for the synthesis of α-amino boronic acids,[6,7] which are key pharmacophores in proteasome inhibitors.[8] Nevertheless, only a handful of methods have been developed thus far for the synthesis of α-halo alkenyl boronates.[9] Among these, *Z*-α-halo alkenyl boronates can typically be prepared via the hydroboration of corresponding 1-halogenated alkynes (Figure 1a).[9a-9d] The *E* isomer, on the other hand, can be synthesized through the hydrozirconation of alkynylboronates with Schwartz's reagent ($Cp_2Zr(H)Cl$) followed by quenching with electrophilic halogenation reagents (Figure 1b).[9e] Although the resulting α-halo alkenyl boronates are stereoselective and undoubtedly useful, the features of the synthesis methods, such as the required harsh reaction conditions, the use of organometallic reagents, and the relatively poor functional group tolerance, may limit their potential range of applications.

We have recently developed an oxidative difunctionalziation of alkenyl MIDA N-methyliminodiacetyl (MIDA) boronates for the synthesis of halogenated and trifluoromethylated α-boryl ketones.[10] The use of sp^3-B MIDA boronates,[11] which are typically bench-top and chromatographically stable solids,[12] circumvented the potential C-to-O 1,3-boryl migration, and was the key to successful synthesis. This result suggests the possibility of assembling α-halo alkenyl boronates by the direct halogenation of the corresponding alkenyl MIDA boronates. If this could be successfully conducted, the resulting α-halo alkenyl MIDA boronates, with the boron presenting in its protected form, might serve as ideal synthons for chemoselective iterative coupling reactions.[13] To realize such a process, however, the following potential challenges must be addressed. 1) The well-known deborylative halogenation reaction process may lead to an undesired alkenyl halide product.[14] With respect to this challenge, we note that the attenuated nucleophilicity of the C-B(MIDA) bond can be expected to make this process less likely for both electronic and steric reasons.[15] 2) The unselective alkene halogenation may result in the formation of different regioisomers and stereoisomers, and thus render the reaction unproductive. Herein, we report on our realization of a stereodivergent synthesis of both *E* and *Z*-α-chloro alkenyl MIDA boronates via the direct chlorination of *E*-alkenyl MIDA boronates with a Cl^+ and Cl^- source, respectively (Figure 1c). The reaction provides a high tolerance for the use of diversely substituted alkenyl MIDA boronate substrates by retaining a high product yield. Moreover, the synthetic utility of the products are explored and the reaction mechanisms of both processes are proposed.

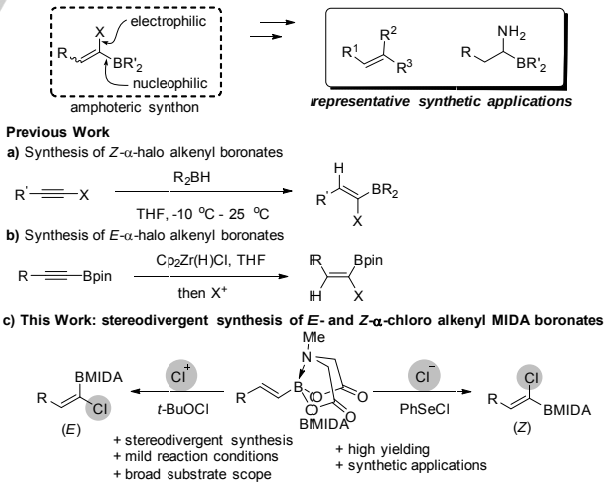

Figure 1. Synthesis of α-chloro alkenyl boronates

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We initially examined the reaction of alkenyl MIDA boronate **1a** with PhSeCl[16] at room temperature (r.t.) employing different concentrations of PhSeCl in conjunction with various solvents (DCM, CH_3CN, and THF) and additives (pyridine and isonicotinic acid). Delightedly, we observed a predominant formation of the *Z*-α-chlorinated product **2a** when employing

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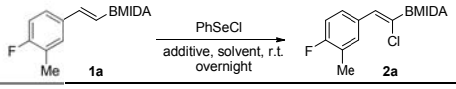
pyridine as an additive in DCM, albeit in only 7% yield (Table 1, entry 1). Omission of the base provided a higher yield of 24% (entry 3), although the use of isonicotinic acid as an additive provided a comparable yield (entry 2). It was found the addition of a 4 Å molecular sieve (MS) was beneficial for the reaction, and provided an improved yield of 31% (entry 4). Further screening of different solvents revealed that THF was optimal (entries 5 and 6), affording an optimal yield of 81%. Decreasing or increasing the PhSeCl loading provided lower yields (70% and 78%; entries 7 and 8).

Table 1 Optimization of the reaction conditions[a]



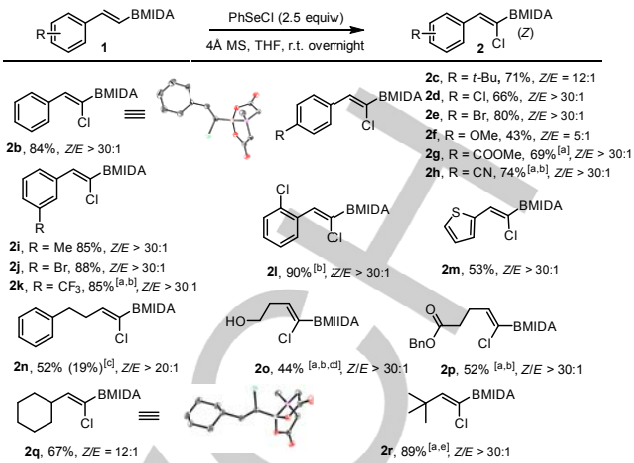
entry	PhSeCl (equiv)	additive (2.5 equiv)	solvent	4Å MS (mg)	yield (%)[b]
1	2.5	Py	DCM	–	7
2	2.5	isonicotinic acid	DCM	–	23
3	2.5	–	DCM	–	24
4	2.5	–	DCM	15	31
5	2.5	–	CH_3CN	15	30
6	2.5	–	THF	15	81(77[c])
7	2.0	–	THF	15	70
8	3.0	–	THF	15	78

[a] Reaction Conditions: **1a** (0.1 mmol, 1.0 equiv), PhSeCl (2.5 equiv), THF, 4Å MS, r.t.. [b] ^{19}F NMR yield based on **1a** using 4-fluoro-benzoic acid as the internal standard. [c] Isolated yield.

With the optimized reaction conditions established (Table 1, entry 6), we examined the generality of this *Z*-α-chloro alkenyl MIDA boronate synthesis process. Thus, diversely substituted aromatic vinyl MIDA boronates were employed as the substrates (Table 2). We were gratified to find that a number of commonly encountered functionalities, such as chloro (**2d**, **2l**), bromo (**2e**, **2j**), methoxy (**2f**), ester (**2g**), cyano (**2h**) and trifluoromethyl (**2k**), were well tolerated, affording moderate to good yields of the products. The geometry of **2b** was confirmed to be *Z*-α-chloro alkenyl MIDA boronate by single-crystal X-ray diffraction.[17] Of note, the chloro substituent residing at the *ortho*-position of the phenyl ring (**2l**) did not interfere with the efficiency of the reaction. Moreover, the heterocyclic thiophen-2-yl vinyl MIDA boronate (**2m**) was also moderately amenable to chlorination. The reaction is not limited to aryl-substituted MIDA boronates, and alkyl substitutes (**2n-2r**) were tolerated as well. It should be noted that, for substrates bearing electron-withdrawing or sterically demanding groups, increasing the loading of PhSeCl (3.5 equiv), raising the temperature (50 °C), or both were beneficial for ensuring a higher degree of conversion.

The above success promoted us to investigate the reactivity of Cl^+ source in this reaction. Interestingly, we found that the use of *t*-BuOCl in lieu of PhSeCl also delivered a α-chlorinated product, but with inverse stereoselectivity (Table 3).[17] Thus, both stereoisomers of the α-chlorinated alkenyl MIDA boronate can be synthesized in a divergent manner by simply employing a different reagent. A reaction optimization investigation showed that a maximum isolated yield of 75% for *E*-α-chloro alkenyl MIDA boronate **3a** could be obtained when reacting the

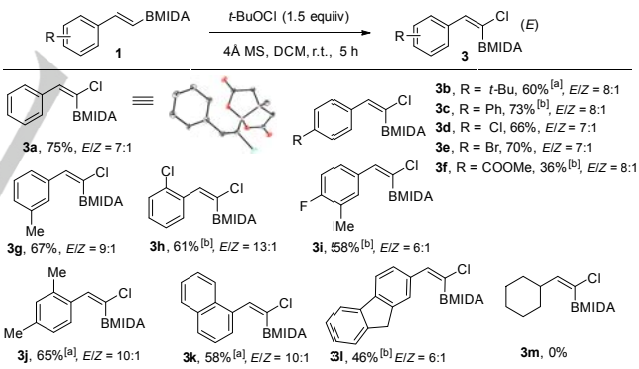
Table 2. Synthesis of (*Z*)-(α-chlorophenylalkenyl) MIDA boronates



[a] At 50°C. [b] PhSeCl (3.0 equiv). [c] Recovered starting material. [d] The TBS group on hydroxyl was deprotected. [e] PhSeCl (3.5 equiv).

corresponding alkenyl MIDA boronate with *t*-BuOCl (1.5 equiv) in DCM in the presence of a 4 Å MS at r.t.. The scope of this transformation was found to be again impressive. The resulting yields indicate that a variety of important functional groups, such as fluoro (**3i**), chloro (**3d**, **3h**), bromo (**3e**), ester (**3f**), and methyl groups (**3g**, **3i**, **3j**), could be tolerated. Intriguingly, for cases where the solubilities of the substrates were low (**3c**, **3f**, **3h**, **3i**, **3l**), the use of isonicontic acid (0.2 equiv) as an additive increased the reaction rate, thereby providing higher yields. Unfortunately, the use of alkyl-substituted substrate (**3m**) led only to the decomposition of the starting material.

Table 3. Synthesis of (*E*)-(α-chlorophenylalkenyl) MIDA boronates



[a] *t*-BuOCl (2.0 equiv). [b] *t*-BuOCl (2.0 equiv) and isonicontic acid (0.2 equiv).

The synthetic utility of the products was then explored. Upon treatment with *m*-CPBA, **2a** was converted to epoxide **4** with the C-B(MIDA) bond being intact in 48% yield (Scheme 1a).[3g] It is of interest that the C-B bond is generally susceptible to peroxide.[18] As such, the retention of the C-B bond in the product demonstrated a major advantage of our approach. The Lewis acid-mediated ring-opening of **4** yielded a chlorine-migration product acylborane **5**, rather than the expected boryl-shift product.[3g] The copper-mediated Chan-Lam type oxidative cyanation gave α-chlorine alkenyl cyanide **6** in good efficiency (Scheme 1b).[19a] In addition, the alkenyl C-B(MIDA) bond could be transformed to the C-I bond upon the treatment with I_2 (Scheme 1c).[19b] And the BMIDA group in **3a** could be converted to its congener Bpin **8** via ligand exchange (Scheme 1d).[20] The presence of both C-B(MIDA) and C-Cl bonds in the product

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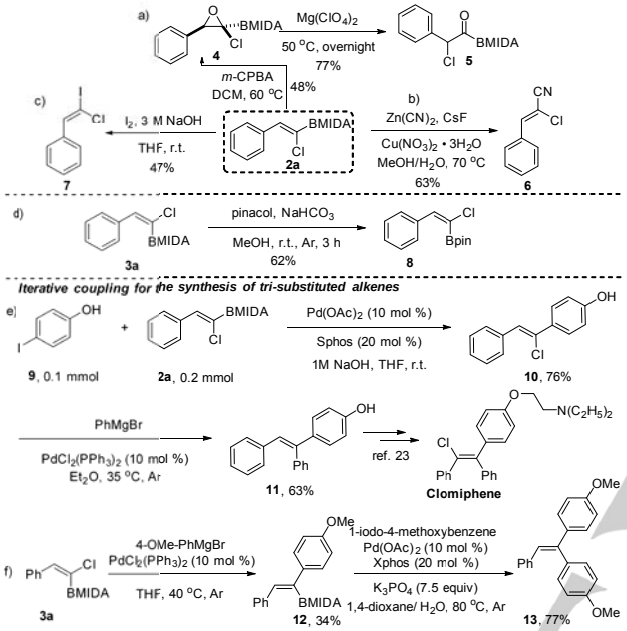
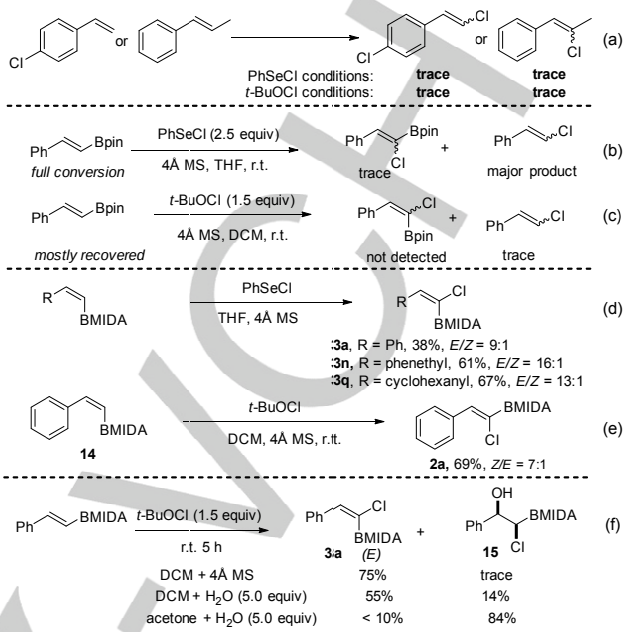
render it an ideal synthon for chemoselective iterative coupling reactions.[21] This is illustrated in Scheme 1e, where, under slow-release reaction conditions, the Suzuki-Miyaura coupling of **2a** with iodide **9** provided the alkenyl chloride **10** with a 76% yield.[22] A subsequent Kumada coupling provided the tri-substituted alkene **11** (63% yield), which is a key intermediate for the synthesis of the antiestrogen agent Clomiphene.[23] On the other hand, the Kumada coupling of **3a** with (4-methoxyphenyl)magnesium bromide led to the formation of the diarylated boryl-retentive alkene **12**, although in low yield (Scheme 1f). Not unexpectedly, **12** could be transformed into the tri-substituted alkene **13** though Suzuki-Miyaura coupling.



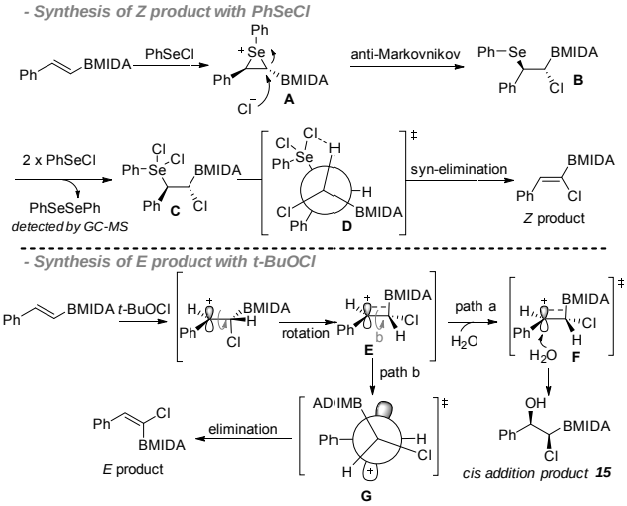
Scheme 1. Product derivatization.

The observed reactivity along with the intriguing stereoselectivity of the proposed synthesis process promoted us to investigate the reaction mechanism. Firstly, the use of 1-chloro-4-vinylbenzene or methyl substituted styrene rather than alkenyl MIDA boronate for both reaction processes led to only trace amounts of the chlorination product (Scheme 2a). The use of the sp^2-B Bpin substrate in the PhSeCl process led predominately to the deborylative chlorination product (Scheme 2b), while its employment in the *t*-BuOCl process resulted in mostly the recovery of the starting material (Scheme 2c). These results indicate the unique role of the BMIDA substituent for enhancing reactivity.[24] In addition, we noted that both reactions are stereospecific. The use of the *Z*-type styryl MIDA boronate substrate **14** in conjunction with the PhSeCl and *t*-BuOCl processes yields the opposite stereoisomers of the products as those obtained when employing the *E*-type substrate (Scheme 2d and 2e). By taking advantage of this stereospecificity, the targeted complementary stereoisomers for **2n** and **2q** can be accessed using the PhSeCl protocol starting with the corresponding *Z*-substrates (Scheme 2d). Moreover, the introduction of radical scavengers such as TEMPO or butylated hydroxytoluene (BHT) did not interfere with the reactivities, and thus the reactions exclude potential radical pathways.[25] A *cis*-oxychlorination product **15** was detected in the *t*-BuOCl reaction (Scheme 2f). By adding H_2O and changing the solvent to acetone, the formation of **15** predominated. However, control experiment showed **15** could not be converted to the final product under various reaction conditions, thus ruling out its intermediacy in the reaction.[25]



Scheme 2. Mechanistic studies.

Based on the above experiments and the precedents established by the literature, we propose the reaction mechanism described according to Scheme 3. For the synthesis of the *Z*-type product, the reaction of PhSeCl with alkenyl MIDA boronate firstly forms a seleniranium ion. The anti-Markovnikov nucleophilic attack of **A** by Cl^- produces an anti-addition adduct **B**. Subsequently, **B** reacts with excess PhSeCl to produce the selenium (IV) dichloride **C**.[16f] In this process, PhSeCl is reduced to PhSeSePh, which was detected by GC-MS. Thereafter, the β-*syn*-elimination of the benzylic proton leads to the stereospecific formation of the *Z*-type product.[26] For the *t*-BuOCl protocol,[27] the Cl^+ adds to the alkene in a Markovnikov fashion. In this process, the development of vacant p-orbital is accompanied by the rotation of C-B(MIDA) bond which leads to the parallel



Scheme 3. Proposed mechanism.

alignment of C-B(MIDA) σ-bond with the vacant p-orbital. Thereafter, the β-H elimination from **E** via TS **G** gives the final *E* type product. The significant steric repulsion between the phenyl ring and the BMIDA group may account for the reduced *E/Z* ratios observed. On the other hand, in the presence of water, a backside attack of H_2O on **E** would deliver a *cis* addition product, which was detected as a side product.

In conclusion, we have developed a stereodivergent synthesis of both *E* and *Z*-α-chloro alkenyl boronates by the direct chlorination of *E*-alkenyl MIDA boronates using *t*-BuOCl and PhSeCl reagents, all of which are readily available starting materials. The use of the sp^3-B MIDA boronate is an important contributor to the observed reactivity. The scope of the reaction was broad with good functional group tolerance and good yields observed. The synthetic value of the *E* and *Z*-α-chloro alkenyl boronate products was demonstrated and the reaction mechanisms of both processes were proposed.

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Keywords: alkenyl boron • chlorination • divergent synthesis • iterative coupling • stereoselective

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[24] We proposed the halogen bonding of the MIDA moiety with the chlorination reagent might be responsible for the observed reactivity.

[25] See supporting information for details.

[26] This process is similar to the well-established selenoxide elimination: R. F. Lauer, M. W. Young, K. B. Sharpless, *Tetrahedron Lett.* **1973**, *22*, 1979.

[27] Supporting information provides a detailed exploration and discussion on the mechanism of the *t*-BuOCl protocol.

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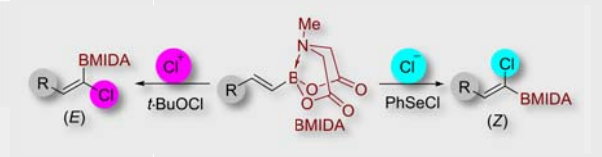

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Stereoselective Direct Chlorination of Alkenyl MIDA Boronates: Divergent Synthesis of *E* and *Z*- α-Chloro Alkenyl Boronates

Borrow Me a Handle: The amphoteric α-chloro alkenyl boronates are intriguing organic synthons. Reported herein is a stereodivergent synthesis of both *E* and *Z*-α-chloro alkenyl *N*-methyliminodiacetyl (MIDA) boronates by the direct chlorination of *E*-alkenyl MIDA boronates using *t*-BuOCl and PhSeCl reagents, respectively. Both reaction processes are stereospecific and the sp^3-B MIDA boronate plays the key role to the reactivity. Broad substrate scope was observed and the synthetic value of the boronate products was demonstrated.