

Cite this: *Chem. Sci.*, 2022, 13, 6413

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 15th February 2022

Accepted 22nd April 2022

DOI: 10.1039/d2sc00954d

rsc.li/chemical-science

Regiocontrolled allylic functionalization of internal alkene *via* selenium- π -acid catalysis guided by boron substitution†

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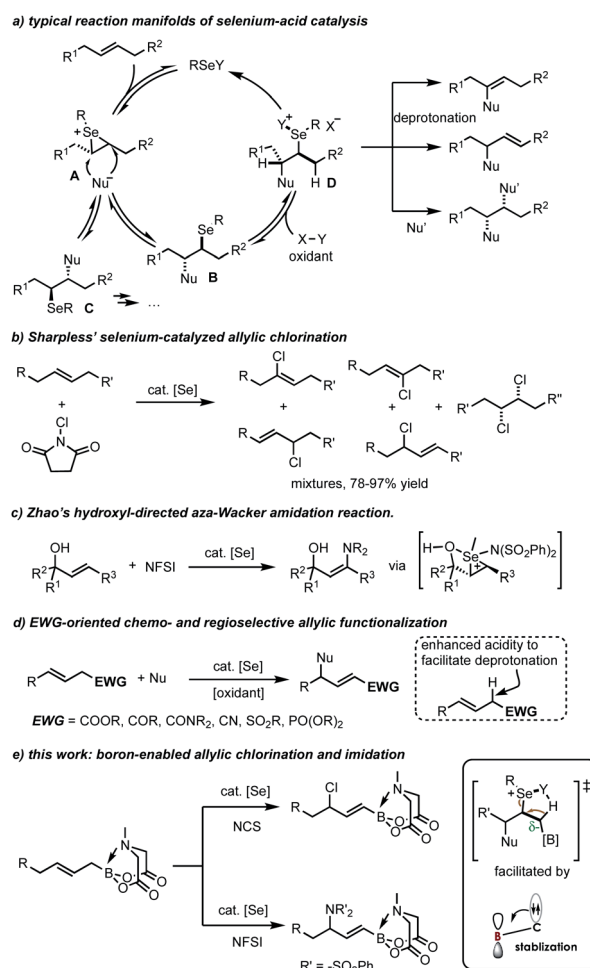
The selenium- π -acid-catalysis has received increasing attention as a powerful tool for olefin functionalization, but the regioselectivity is often problematic. Reported herein is a selenium-catalyzed regiocontrolled olefin transpositional chlorination and imidation reaction. The reaction outcome benefits from an allylic B(MIDA) substitution. And the stabilization of α -anion from a hemilabile B(MIDA) moiety was believed to be the key factor for selectivity. Broad substrate scope, good functional group tolerance and generally good yields were observed. The formed products were demonstrated to be valuable precursors for the synthesis of a wide variety of structurally complex organoborons.

Introduction

The past few years have witnessed considerable progress in electrophilic chalcogen-catalysis.¹ In this research realm, the selenium- π -acid catalysis,² wherein a selenium catalyst chemoselectively activates an alkene or alkyne, is particularly interesting by offering unique reactivities which could be complementary to those of transition metal catalysts³ (*e.g.*, gold,⁴ platinum⁵ and palladium⁶ complexes). The high carbophilicity of selenium catalyst offers additional advantages such as good functional group tolerance, simplicity of synthetic operation and mild conditions. However, the utility of selenium- π -acid catalysis may be plagued by the intrinsically challenging regioselectivity when nonpolarized internal alkenes are used as reaction partners (Scheme 1a).^{2c} In a typical reaction manifold, an initial coordination of selenium ion onto olefinic π -bond leads to the formation of a highly electrophilic selenanium intermediate **A**. This intermediate could be stereoselectively, but not regioselectively, trapped by a nucleophile to form two sets of selenide adducts (**B** and **C**). Depending on the reaction parameters (for examples, substituents on the double bond and the oxidant), both adducts could be potentially converted to either allylic, vinylic or 1,2-difunctionalization product.¹ This was reflected by the seminal work of Sharpless,⁷ wherein the use of unsymmetrical internal alkenes produced the unselective chlorination mixtures (Scheme 1b).

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† Electronic supplementary information (ESI) available. For ESI and crystallographic data in CIF or other electronic format see <https://doi.org/10.1039/d2sc00954d>

Scheme 1 Selenium- π -acid catalysis and our work.

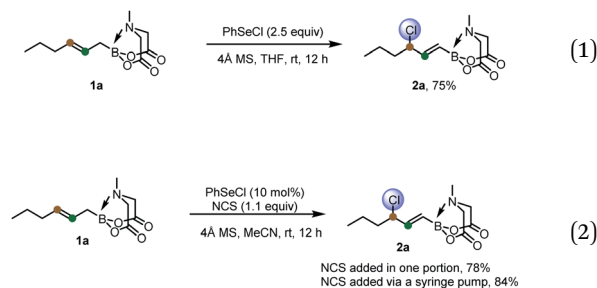
To address the regioselectivity issue, the most commonly used and fruitful strategy is to run the process intramolecularly by introducing a pendent nucleophile to the substrates.⁸ Also effective is the employment of tri-substituted alkenes as substrates, which usually leads to clean tertiary functionalized products as guided residues at the allylic position can function as a directing group by the Markovnikov's rule.⁹ A recent study from Zhao suggests that the hydroxyl group (*via* precoordination with the selenium cation) to enable a selective anti-Markovnikov aza-Wacker imidation reaction (Scheme 1c).¹⁰ A more general solution is by electronic perturbation *via* the installation of an electron-withdrawing group (EWG) at the allylic position, as firstly reported by Tunge (Scheme 1d).¹¹ Thus, by virtue of the reversibility of the chloroselenylation and oxidation processes (**A** → **C**, Scheme 1a),¹² a rate-limiting dehydrodeselenylative elimination eventually leads to an allylic chloride product. The acidity of the proton α to the EWG accounts for the profound regioselectivity by facilitating the irreversible deprotonation process. Linear alkenes bearing no allylic EWGs result in complex product mixtures. Similar strategy was later found to be applicable to the elegant selenium- π -acid catalytic amination,¹³ oxygenation^{9b,14} and fluorination^{9c,15} reactions.

On the other hand, the protection of sp^2 -B organoboron into the pyramidalized sp^3 -B MIDA (*N*-methyliminodiacetic acid) boronates brings about tremendously improved stability, which thereby offers new opportunities to the late-stage modification of organoborons.¹⁶ In this context, previous studies have showcased that in certain cases, the MIDA boron moiety is by no means a bystander, but could confer interesting reactivity to the substrates.¹⁷ For instance, independent work from Yudin¹⁸ and us¹⁹ uncovered an intriguing directing effect of MIDA boron in metal-catalyzed functionalization of alkenes and alkynes, respectively. This effect is attributed to a neighboring stereoelectronic stabilizing donation of electron density to boron, thanks to the hemilabile nature of the MIDA B–N dative bond.²⁰ In line with the selenium- π -acid catalysis, we reason the similar neighboring group effect would offer a chance for a regiocontrolled allylic functionalization reactions. Herein, we report our realization of a selenium-catalyzed double bond transpositional allylic chlorination and imidation of allyl MIDA boronates (Scheme 1e). The reaction leads to the facile synthesis of multifunctional amphoteric building blocks with both the olefin and boron functionality being preserved as valuable handles for further chemical elaboration.

Results and discussion

To start, we examined the feasibility of MIDA boron-directed allylic chlorination. The reaction of allyl MIDA boronate **1a** with stoichiometric amount of PhSeCl as both the oxidant and chlorine source was firstly investigated. A brief survey revealed that mixing **1a** with PhSeCl (2.5 equiv.) in THF in the presence of 4 Å molecular sieve provided cleanly a single allylic chlorination product **2a** in 75% yield (eqn (1)). The double bond was selectively transpositioned towards the boron moiety and only the *E* geometric isomer was formed as

expected. We also turned our attention to the catalytic version of this reaction. And was found that with 10 mol% of PhSeCl catalyst and *N*-chlorosuccinimide (NCS, 1.1 equiv.) in MeCN, a comparable yield of 78% was obtained. Considering the potential inhibition effect of NCS as observed by Tunge,¹¹ the slow addition of NCS *via* a syringe pump gives an improved yield of 84% (eqn (2)).



Encouraged by these results and considering the importance of allyl amines, we further attempted to explore the applicability of this concept to allylic functionalization imidation reactions. With *N*-fluorobenzenesulfonimide (NFSI, 1.0 equiv.) as oxidant and diphenyl diselane (5 mol%) as catalyst in THF at room temperature, an allylic imidation product (25% yield) was indeed formed with most of the starting materials being untouched (Table 1, entry 1). The site and stereoselectivity were in accordance with the above chlorination protocol, confirming the versatility of boron-directing effect. A higher yield was obtained by changing the solvent to MeCN (entries 2 and 3). Further improvements were achieved by introducing the molecular sieve (entry 4), increasing the oxidant dosage (entry 5), and slightly raising the reaction temperature (entry 6). And finally, the use of DCE as solvent in associated with 10 mol% of catalyst were able to reduce the oxidant (to 1.5 equiv.) while enhancing the yield to 68% (entries 7–9).

Table 1 Reaction optimization of allylic imidation^a

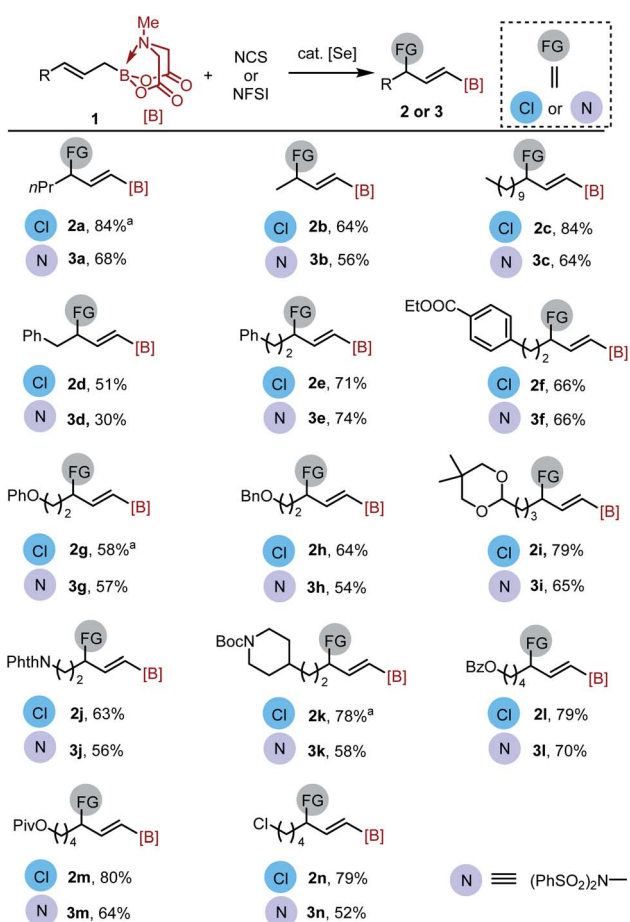
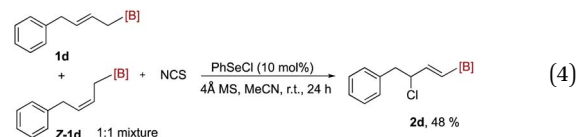
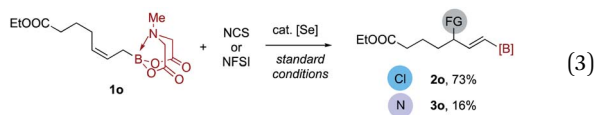
Entry	<i>x</i>	<i>y</i>	Solvent	Temp.	4 Å MS	% yield
1	1	5	THF	25	0	25
2	1	5	1,4-Dioxane	25	0	21
3	1	5	MeCN	25	0	29
4	2	5	MeCN	25	10	32
5	2	5	MeCN	25	20	43
6	2	5	MeCN	35	20	55
7	2	5	DCE	35	20	67
8	1.5	5	DCE	35	20	61
9	1.5	10	DCE	35	20	68

^a Reaction condition: **1a** (0.2 mmol), NFSI (*x* equiv.), (PhSe)₂ (*y* mol%), 4 Å MS (mg), temp. (°C), solvent, under Ar, 12 h.



With the optimized conditions in hand, the substrate scopes for both the oxidation allylic chlorination and imidation reactions were explored. As shown in Scheme 2, a wide variety of alkyl-substituted allyl MIDA boronates were well applicable, generating the γ -chlorinated/imidized alkenyl boronates both as single regio- and *E*-geometric isomers in moderate to good yields. Some commonly encountered functional groups, such as ester (**1f**, **1l**, **1m**), phenoxy (**1g**), alkoxy (**1h**), acetal (**1i**), amide (**1j**), carbamate (**1k**), halogen (**1n**) were all well tolerated, indicating the mildness of the protocols. Secondary allyl MIDA boronates showed no reactivity in this reaction, probably for steric reasons.

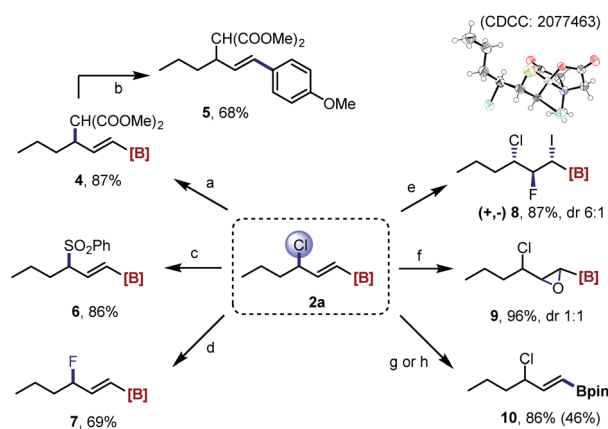
Substrate **1o** with a *Z* geometry also successfully delivered the desired chlorination product **2o** with *E* configuration in good yield (eqn (3)). However, the imidation product **3o** was formed in low yield, probably due to the greater steric hindrance of nitrogen-centered nucleophile. The reaction of a 1 : 1 mixture of **1d** and **Z-1d** produced *E* product **2d** stereo-convergently (eqn (4)).



Scheme 2 Substrate scope. Chlorination: **1a** (0.2 mmol), NCS (1.1 equiv.), PhSeCl (10 mol%), 4 Å MS, MeCN, rt. ^aNCS (dissolved in MeCN) was added via syringe pump. Imidation: **1a** (0.2 mmol), NFSI (1.5 equiv.), PhSeSePh (10 mol%), 4 Å MS, DCE, 35 °C, under Ar, 12 h.

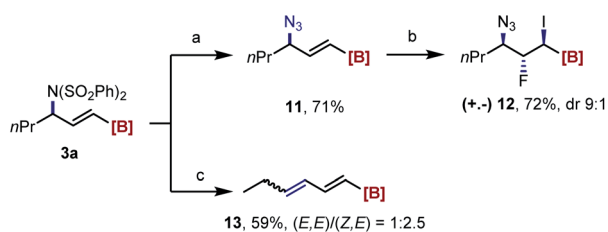
The utility of the formed products was then investigated (Scheme 3). The allylic C–Cl bond in **2a** provided the valuable handle for follow-up functional group manipulations. For examples, subjecting **2a** to palladium-catalyzed Tsuji–Trost reactions using malonate and sulfinate as nucleophiles delivered the corresponding allylic alkylation (**4**) and sulfonylation (**6**) products, respectively, in good yields. A copper-catalyzed displacement of chloride furnished an allyl fluoride **7** without difficulty.²¹ In addition, the iodofluorination of the double bond in **2a** following our previous protocol²² produced the α -iodo- β -fluoro- γ -chloroalkyl MIDA boronate **8** (confirmed by X-ray single crystal diffraction analysis)²³ with good regio- and stereoselectivity. And the epoxidation reaction gave efficiently a highly functionalized amphoteric epoxide **9**. Finally, the transesterification reaction of the B(MIDA) moiety with pinacol allowed the efficient synthesis of alkenyl Bpin **10**. And under a slow-release reaction conditions, the palladium-catalyzed Suzuki–Miyaura coupling with aryl iodide was successful to provide the styrenyl product **5**.

Interestingly, reacting the imidation product **3a** with NaN₃ provided the γ -azidated alkenyl MIDA boronate **11**, which can then be applicable to the iodofluorination reaction as well (**12**). A E2 elimination occurred by heating **3a** with NaI under



Scheme 3 Synthetic derivatizations of **2a**. Reaction condition: [a] dimethyl malonate, NaH, Pd(OAc)₂, PPh₃, THF, rt.; [b] Pd(OAc)₂, Sphos, *p*-iodoanisole, 1 M NaOH, THF, rt.; [c] sodium benzenesulfinate, Pd(PPh₃)₄, THF/DMSO, 50 °C; [d] AgF, CuBr, MeCN, rt.; [e] DIH, Et₃N·HF, DCM, rt.; [f] mCPBA, DCM, 30 °C; [g] pinacol, 2 M H₂SO₄, THF, rt.; ¹H NMR yield; [h] isolated yield. For more details, see the ESI. † DIH = 1,3-diiodo-5,5-dimethylhydantoin.





Scheme 4 Synthetic derivatizations of **3a**. Reaction condition: [a] NaN_3 , NaI, DMF, 100 °C; [b] DIH, $\text{Et}_3\text{N}\cdot\text{HF}$, DCM, rt.; [c] NaI, DMF, 140 °C (microwave). For more details, see the ESI.†

microwave irradiation to give a boryl-substituted diene **13** (Scheme 4).

Based on the previous observations on the electron-withdrawing group (EWG)-directed allylic functionalization^{11–14,15b} and the notion on the capacity of B(MIDA) to accept adjacent electron density,^{18–20} a possible reaction mechanism was proposed (Scheme 5a). The reversible olefin coordination/nucleophilic substitution/selenide oxidation forms two regioisomeric intermediates **A** and **B**. Both are prone to undergo dehydrodeselenylation or nucleophilic displacement of the selenium moiety. However, the activation effect from B(MIDA) by stabilizing the developing negative charge in the transition state TS-C would facilitate a regioselective *syn*-dehydrodeselenylation, thereby shifting the equilibrium towards the alkenyl MIDA boronate formation.²⁴ Interestingly, previous evidence from Tunge has suggested that the

dehydrodeselenylation elimination is the rate-limiting step.²⁵ However, kinetic isotope effect studies in our case by using deuterated allyl MIDA boronate revealed a small KIE value of 1.2 (Scheme 5b). This result indicates that the C–H cleavage is no longer involved in the rate-limiting step, in accordance with an activation effect of B(MIDA) (by lowering the energy of TS-C) in this reaction. Interestingly, allyl MIDA boronate **14** with an electron-withdrawing ester group on the other side produced α,β -unsaturated ester **15**, suggesting the ester group showed a greater directing ability (Scheme 5c). And the use of pinacol boronate only led to the formation of protodeborylation products (69% yield as a mixture, Scheme 5d).

Conclusions

In summary, a selenium- π -acid-catalyzed regiocontrolled olefin transpositional allylic chlorination and imidation were developed. The reaction outcome benefits from a B(MIDA) substitution. And the stabilization of α -anion from a hemilabile B(MIDA) moiety was believed to be the key factor for selectivity, which facilitates the irreversible selenium-mediated *syn*-H elimination. The protocol led to the synthesis of a wide array of multifunctional amphoteric building blocks with both the olefin and boron functionality being preserved as valuable handles for further chemical elaboration. The utilities of the products were demonstrated. The unique effect of B(MIDA) revealed in this protocol may inspire more interesting boron chemistry from the synthetic community.

Data availability

Experimental data has been provided as ESI.†

Author contributions

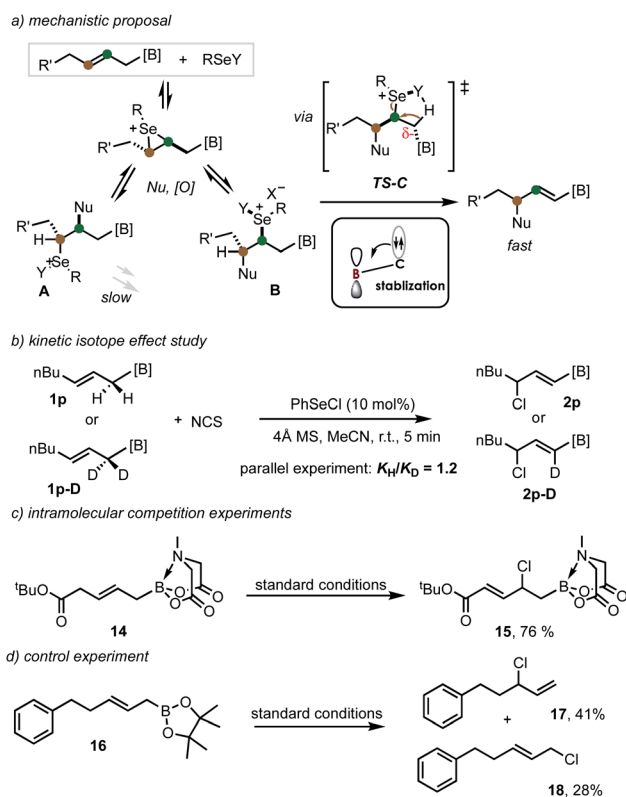
L. Y. discovered the reaction, performed the experiments and analysed the data. H. W. conceived and directed the project. H. W. and L. Y. wrote the manuscript. Y. L. and W. F. synthesized some raw materials. All authors discussed the experimental results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (22022114, 21971261), the Guangdong Basic and Applied Basic Research Foundation (2020A1515010624), the Fundamental Research Funds for the Central Universities (20ykzd12) and the Local Innovative and Research Teams Project of Guangdong Pearl River Talents Program (2017BT01Y093).



Scheme 5 Proposed mechanism and mechanistic study.



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