Versatile positional editing of diverse functional groups through radical 1,2-boron shifts

Wenwen Zhang,[+] Shuxin Mao,[+] Mengqi Peng & Yumeng Xi*

Department of Chemistry, Faculty of Science, National University of Singapore, Singapore

Functional groups are central to the property, function, and reactivity of organic molecules. Their identity, spatial orientation–and specific location–can influence a molecule's behavior and fate.[1] The direct, precise "editing" of the position of a given functional group without altering other parts of the molecule, particularly at late stages, represents a strategy that is complementary to traditional synthetic logic[2] and valuable for molecular diversification.[3,4] However, only a limited number of methods for such functional group positional editing exist, and these often lack generality as they are typically tailored to specific functional groups, often require the design of specialized substrates, or both. Here we report a general strategy for positional editing of a diverse set of functional groups through a short sequence to access a myriad of corresponding positional isomers. This approach is realized by developing a catalytic, direct 1,2-transposition of pinacolboryl group that occurs across a wide range of substrates and harnessing the well-appreciated synthetic versatility of organoboron. Key to our design is the identification of hydrogen atom transfer (HAT) catalysts possessing suitable rate constants, which control the reaction efficiency and selectivities. Our work establishes a generalized mechanistic framework for designing direct 1,2-transposition reactions of other applicable functional groups, and more broadly, has the potential to enable the positional editing of many functional groups, including those that do not undergo radical rearrangements.

Positional isomers belong to a subset of constitutional isomers that share identical carbon skeleton and functional groups but differ from each other in the location of the functional group. This subtle difference can often exert a profound influence on the physicochemical and biological properties of a given organic compound. Prior reports showed that transposing a certain functional group to a vicinal site in a molecule resulted in drastic increase of its potency towards biological targets[5-7] or led to distinct pharmacological mechanisms of action.[8] In materials chemistry, positional isomerism has been demonstrated as a viable means to tune and enhance target functions.[9-11] Despite the impact of positional isomerization across various pillars of the chemical science, achieving functional group transposition is not a trivial task, frequently requiring a multistep, low-yielding sequence[6] (**Fig. 1A**) or even de novo synthetic design to access desired isomers.

From a retrosynthetic perspective, direct transposition of functional groups is fundamentally distinct from any other strategies that manipulate functional groups, such as introduction and interconversion, allowing their installation step to be decoupled from the "location-determining" step. This process, which solely edits the position of a functional group, offers the unique opportunity to 1) access challenging target molecules unattainable by traditional means; 2) expedite molecular optimization campaigns by providing a set of analog compounds;[4,12] 3) override the intrinsic regioselectivity of a prior functionalization event at a later stage of a synthesis; 4) switch on previously unknown disconnections for synthetic planning. With the exception of alkene isomerization,[13] direct functional group transposition is largely untapped in organic chemistry.[14-20] This conspicuous lack of available techniques has limited such transformations to be explored as a general concept. Yet, positional editing processes, if made versatile, highly efficient, and tunable in selectivities, would hold broad implications for organic chemistry and allied fields.

Here we report a general strategy that allows 1,2-transposition of various functional groups enabled by the development of a catalytic, site-selective 1,2-boron shift reaction (**Fig. 1**). This approach comprises an initial, selective borylation of a functional group of interest, the boron shift protocol established in this study, and a final conversion of the migrated boron group back to the original functional group. Based on this concept, we achieved the positional isomerization of alcohols, amines, acids, alkenes, and bromides. Furthermore, the mechanistic framework established in this work should be extended to a plethora of other functional groups that undergo 1,2-radical rearrangement reactions readily, allowing single-step positional editing of these groups.

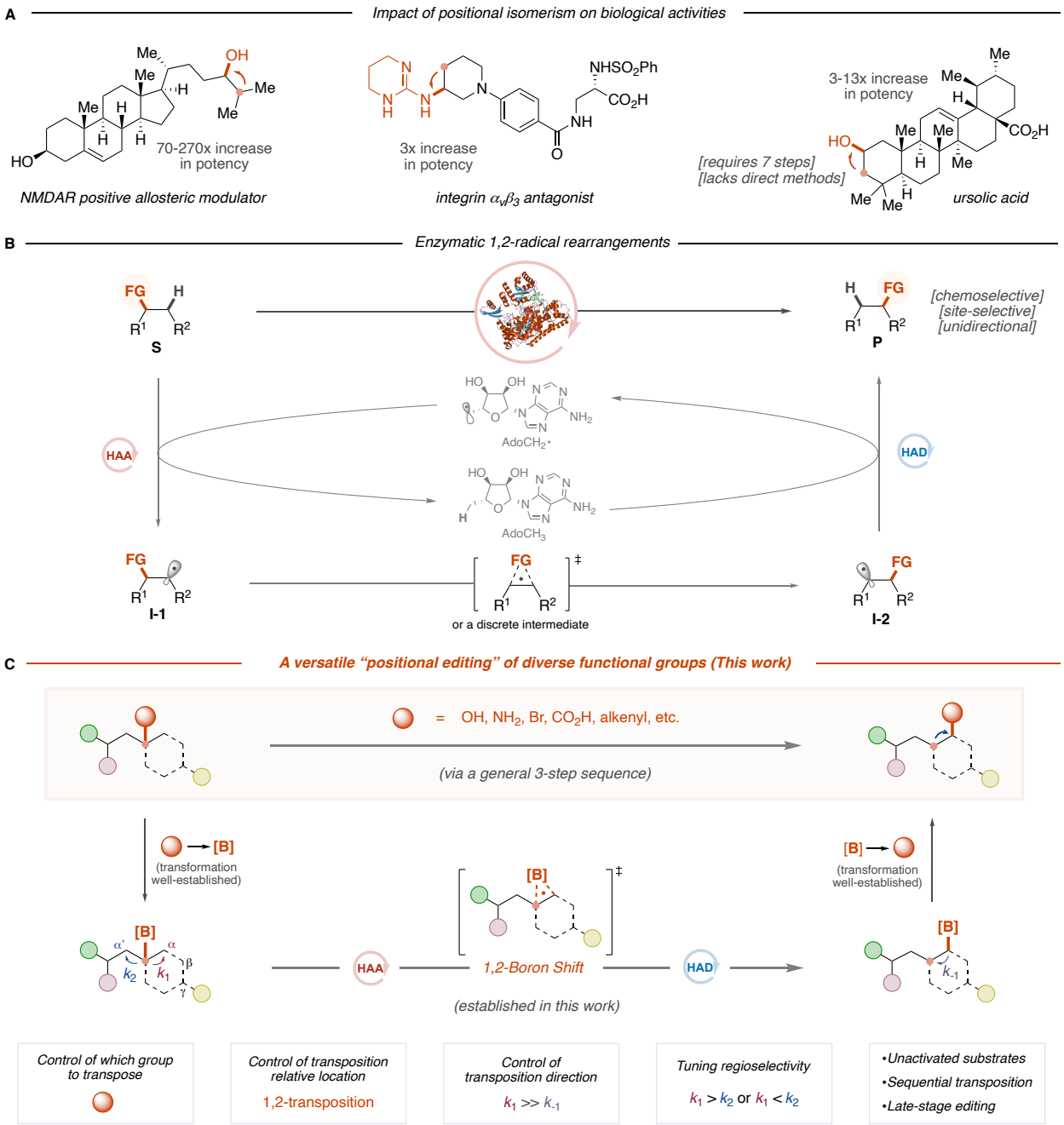


Fig. 1. Concept of versatile positional editing. a, Significance of positional isomerism to medicinal chemistry. **b,** Mechanism of enzymatic 1,2-radical rearrangements. **c,** A general strategy for positional editing of diverse functional groups through radical 1,2-boron shift. HAA, hydrogen-atom abstraction; HAD, hydrogen atom donation. k_1, k_2, and k_{-1} represent hypothetical rate constants for the corresponding transposition.

Reaction design and development

In nature, vitamin B12-dependent[21] and SAM[22] enzymes are known to promote a suite of 1,2-radical rearrangements that swap a hydrogen atom and a vicinal substituent, such as an amino, a hydroxyl, an (alkylthio)carbonyl group. In particular, aminomutases catalyze the direct conversion of several canonical amino acids into their positional isomers through 1,2-amino migration,[23] a transformation yet to be invented in chemical synthesis. The biological machinery achieved this transformation through a series of HAT events including hydrogen-atom abstraction (HAA) and hydrogen atom donation (HAD), and a radical rearrangement step, while exerting exquisite control over reaction directionality and site- and chemoselectivities (**Fig. 1B**). We wondered if a mechanistic framework resembling nature's approach along with extensive literature on radical rearrangement reactions,[24] in particular radical 1,2-boron shift,[25-27] could be harnessed to establish a general platform for functional group positional editing.

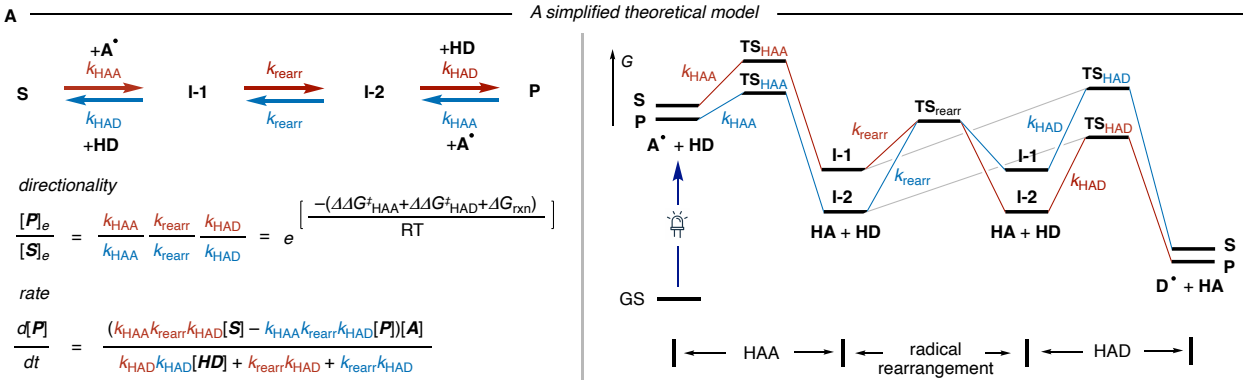
Fig. 1C illustrates the major challenges facing the development of this transposition reaction: 1) control of which substituent migrates in densely functionalized molecules; 2) control of the direction of a potentially reversible isomerization process that has minimal or unfavorable thermodynamic bias;[28-32] 3) control of the relative location of the functional group before and after transposition (i.e., 1,n-selectivity, n≥1); and 4) tuning of regioselectivity among the preferred 1,n-sites, if more than one is possible. In addition, this reaction must accommodate a broad scope of substrates in order to be general, without specific structural limitation, and tolerate diverse functionalities.

To address these challenges, we established a simplied kinetic model as depicted in **Fig. 2A** to guide reaction design. By applying steady-state approximation and assuming that HAA occurs exclusively at the adjacent carbon and no side reaction is present, we obtained two rate law equations that inform the directionality and efficiency of the proposed transformation, respectively. The first equation concerns the ratio of product to substrate at equilibrium ($[\boldsymbol{P}]_e/[\boldsymbol{S}]_e$), which contains three terms–the ratio of the forward to reverse rate constants for HAA, radical arrangement, and HAD steps. This suggests that the transposition is likely dominated by the second term, as driven by the formation of a more stable rearranged radical from a less stable initial counterpart. However, it is possible to overturn this thermodynamic bias if an appropriate combination of HAA and HAD catalysts are discovered.

The secondary equation provides the rate of the product formation in this reversible reaction. Careful analysis of the resulting complex equation points to a positive correlation of HAA rate to the overall reaction efficiency. In addition, the presence of a HAD-associated term ($k_{\mathrm{HAD}}[HD]$) in the denominator indicates that the rate of HAD needs to be on the similar order of magnitude as that of the radical rearrangement in order for the overall process to be productive, because the product formation is inhibited by the HAD catalyst when HAD is significantly faster than radical rearrangement. This notion can be clearly understood by the examination of a simple reaction

profile (**Fig. 2A**, right) in which the relative energy of the transition state for HAD (in blue) and radical rearrangement determines if the initial radical proceed to form the product or revert back to the starting material. Based on these analyses (see supplementary information section IX.D for further discussions), we posited that key to our strategy is the discovery of a catalyst capable of producing reactive radicals for rapid HAA of unactivated C-H bonds, along with another catalyst that undergoes HAD in rates similar to those of radical 1,2-boron shifts.

Our investigation began with the identification of suitable HAT catalysts for the 1,2-boron transposition process. Initial optimization studies using an unactivated tertiary boronate, **1**, as the model substrate identified chlorine radical, known for the unparalleled rate constant (on the order of 10^{10} s^{-1} M^{-1}) for HAA of strong C-H bonds,[33] as a suitable candidate. This chlorine radical is facilely accessible from ligand-to-metal charge transfer (LMCT) photoexcitation[34,35] of simple metal salts. The use of other popular, potent HAA catalysts,[36] including excited-state decatungstate[37] and alkoxy radicals,[38] led to low yields of transposed products, primary boronate **2** and secondary boronate **2a** (**Fig. 2B**). In addition, examination of HAD catalysts revealed that thiophenols possess the suitable HAT rate constants,[39] likely matching those for radical 1,2-boron shifts.[27]



entry	variation	convn	yield	2:2a
1	15 mol% [TBA][$FeCl_4$], 20 mol% $TRIP_2S_2$ 390 nm LEDs (*standard condition*)	95%	85%	5.5:1
2	no Fe	0%	0%	n/a
3	no $TRIP_2S_2$	8%	0%	n/a
4	no LED	1%	0%	n/a

HAA catalyst	$Cl^{\bullet}$	$MeO^{\bullet}$		$^*[W_4O_{10}]^{4-}$
k_{HAT} ($M^{-1}s^{-1}$)	1.2×10^{10}	~9.6×10^5	1.4×10^6	4.0×10^7
yield (**2**&**2a**)	61%	9%	<1%	12%

HAD catalyst	TRIPSH	*t*BuSH	PMN
k_{HAT} ($M^{-1}s^{-1}$)	~1.4×10^8	8.0×10^6	$<10^6$
yield (**2**&**2a**)	61%	36%	17%

Fig. 2. Reaction Development. a, A simplified kinetic model for FG transposition. **b,** Development of 1,2-boron transposition for positional editing. **S**, substrate; **P**, product; **I**, intermediate; **A**·, hydrogen-atom abstractor; **HD**, hydrogen-atom donor.

Further optimization studies uncovered the combination of tetrabutylammonium ferrate ($TBAFeCl_4$) as a HAA catalyst and bis(2,4,6-triisopropylphenyl) disulfide ($TRIP_2S_2$) as a HAD catalyst as an effective system. This condition gave rise to **2** and **2a** in 85% combined assay yield

and with a ratio of 5.5:1 (**Fig. 2B**). We did not observe the formation of other isomers that would result from 1,n-transpositions (n>2). Control experiments confirmed the critical role of the iron photocatalyst, disulfide catalyst, and light irradiation. When subjecting the product **2** to the reaction condition, we did not detect starting material **1** or minor product **2a**, even in trace amounts.

Preliminary mechanistic study

The realization of site-selective, unidirectional transposition in unactivated boronates suggests that this reaction has the potential to become a general positional editing method. The free energy for the isomerization of **1** to **2** and **2a** is computed by density functional theory (DFT) to be –1.4 and 0.3 kcal/mol, respectively, indicating that the thermodynamic driving force is weak. Our success in using unactivated substrates contrasts previous work[20] in which substrates are specific as radical-stabilizing substituents α to the translocating group are a key requirement. This feature caused the thermodynamic driving force to be substantial (exergonic by 10 kcal/mol, see supplementary information) and the reverse reaction to be kinetically unfeasible due to a polarity-mismatched HAA in most cases.[40]

To reveal the origin of the reaction directionality, we conducted deuterium labeling experiments using **S5** and **5** as the starting material, respectively (**Extended Data Fig. 1**). ^{1}H and ^{2}H NMR analysis of the recovered **S5-d** and **5-d** revealed that the deuterium scrambling occurred non-selectively across all possible sp^3-carbon sites. The observation of deuterium incorporation in both cases supports that HAA is operative in either direction and that subsequent steps (i.e., boron shift and HAD) instead control the reaction directionality.

DFT computational studies provided further insights into the observed reaction directionality. The analysis of the DFT data presented in **Extended Data Fig. 2A** revealed that the preference for the forward reaction (**S** to **P1**) arises from the difference in HAD transition states, whereby the energy of the HAD transition state (**TS3-1**) leading to the formation of **P1** involving tertiary radical **Int2-1** is 7.3 kcal/mol lower than that (**TS4-1**) leading to the formation of **S** involving primary radical **Int1-1**. This large difference is primarily contributed by the energy difference of the initial primary radical and the rearranged tertiary radical (5.4 kcal/mol). These results are consistent with our kinetic model (**Fig. 2A**).

In addition, our calculations revealed the origin of site-selectivity. The energies of the transition states of 1,2-boron shift are significantly lower (by at least 8.6 kcal/mol) than those of 1,3-, 1,4-, and 1,5-boron shifts. In the latter cases, such migrations necessitate overcoming a substantial activation barrier (**Extended Data Fig. 2B&C**), causing radicals **Int1-3, Int1-4**, and **Int1-5** to favor reacting with the thiol HAD catalyst to regenerate the starting material. By contrast, radicals **Int1-1** and **Int1-2**, once formed, undergo 1,2-boron shifts to form rearranged radicals **Int2-1** and **Int2-2**, respectively, without reverting to the starting material. This distinction arises because the energy of the transition states of 1,2-boron shift (**TS2-1, TS2-2**) is lower than that of HAD (**TS4-1, TS4-2**). Thus, the observed site-selectivity is governed by the favorable 1,2-boron shift over other 1,n-boron shifts and multiple reversible, unselective HAA and HAD steps in a “pseudo”-Curtin-Hammett scenario.[41]

Substrate scope

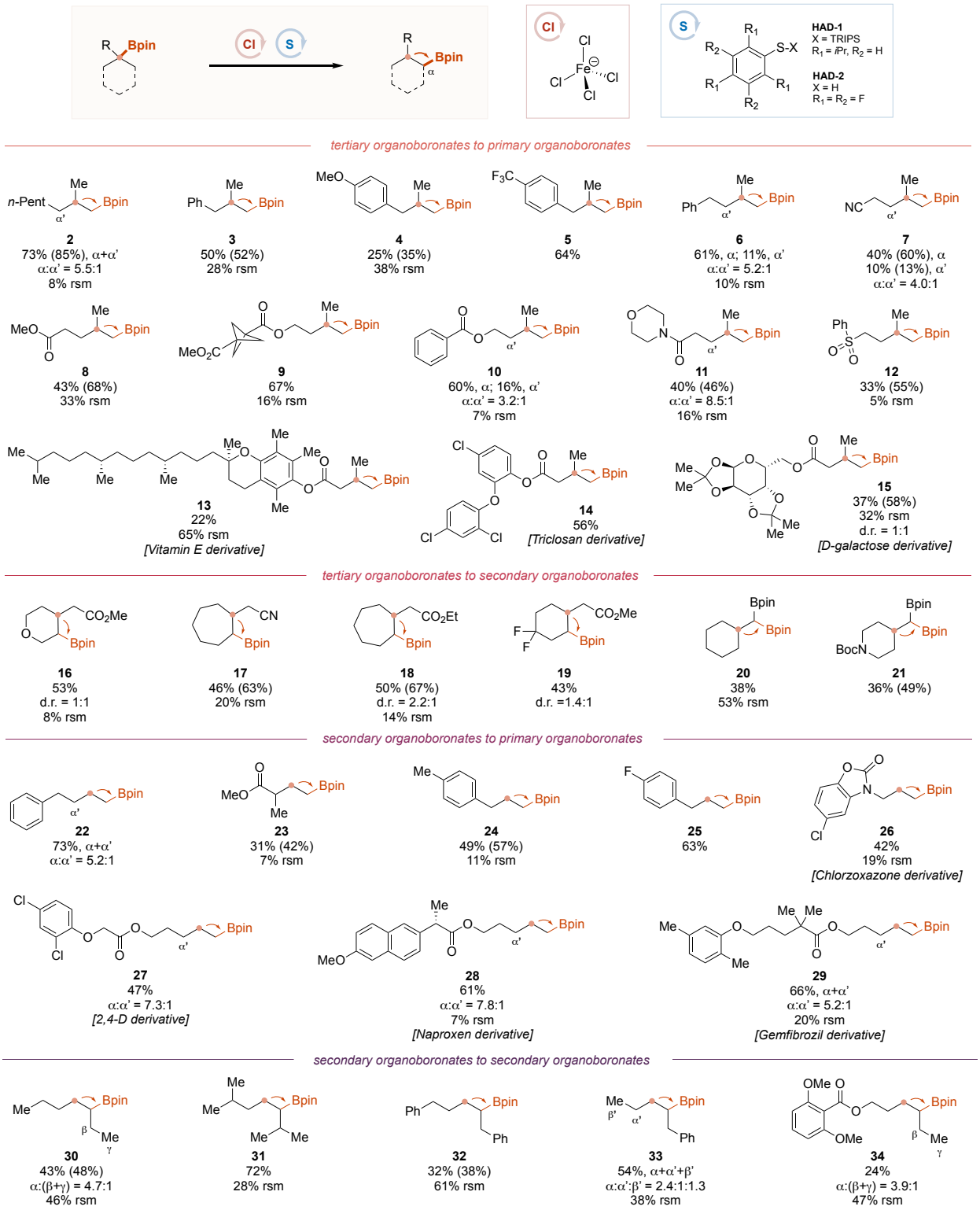


Fig. 3. Scope of the 1,2-boron transposition. See supplementary materials for detailed conditions. Yields refer to those of the isolated compounds. Assay yields are given in parenthesis.

With a mechanistic understanding of the reaction and development of suitable conditions, we examined the scope of organoboronates that underwent the 1,2-boron transpositions (**Fig. 3**). An

array of tertiary boronates were converted to the corresponding primary boronates in modest to good yields and with exclusive 1,2-selectivity. The regioselectivity among two or more 1,2-migration sites in many cases was >20:1, higher than with the reaction of **1**. This is because the secondary C-H bonds (α' site) are electronically deactivated due to the close proximity to an electron-withdrawing group.[40] The boron migration to benzylic sites was not observed presumably due to an energetically uphill boron shift. Our conditions are tolerant of various functional groups and substituents, including substituted aryl groups (**4**,**5**,**13**), a cyano group (**7**), alkoxycarbonyl groups (**8**,**9**,**10**,**13**,**14**,**15**), bicyclo[1.1.1]cyclopentane (**9**), an aminocarbonyl group (**11**), a sulfonyl group (**12**), ethers (**13**,**14**), and acetals (**15**), and are effective towards complex targets (**13**,**14**,**15**).

This boron transposition was extended to the isomerization of tertiary cycloalkyl boronates to furnish the corresponding secondary boronates. The regioselectivity could be tuned by the neighboring substituents. The reactions of tertiary boronates containing an exocyclic electron-withdrawing group β to the boron yielded endocyclic products exclusively (**16-19**) due to a polarity-mismatched HAA at the site α to an electron-withdrawing group. On the contrary, the reactions of tertiary boronates containing exocyclic Bpin groups β to the boron formed exocyclic products exclusively (**20-21**). The observation that no endocyclic product formed in the latter case implies that the activation barrier of an exocyclic 1,2-boron shift is lower than that of an endocyclic 1,2-boron shift because HAA of unactivated C-H bonds and of those α to a Bpin group should be unselective.[42]

By analogy, our 1,2-boron migration could be applied to the modification of secondary boronates. An electron-deficient thiol, pentafluorothiophenol, was utilized as the HAD catalyst in place of $TRIP_2S_2$ because both reaction yield and mass balance were improved. We suspected that a faster HAD with pentafluorothiophenol[43] would decrease the concentration of carbon-centered radical intermediates formed by HAA, thereby limiting their participation in non-productive side reactions. The isomerization of secondary boronates to primary boronates occurred smoothly in high yields (**22-29**) and is applicable to the modification of several drug-like molecules (**27-29**). However, the conversion of secondary boronate substrates to the transposed secondary boronate products was challenging to achieve due to a lack of intrinsic thermodynamic bias (**30-34**). These reactions generally proceeded in lower yields and in some cases formed multiple positional isomers.

Synthetic applications

Next, we sought to investigate potential strategic implementations of our positional editing method at more intricate synthetic settings. The 1,2-boron transposition conducted on a complex molecule (**35**) derived from cholestane-3-one provided the boron-migrated product (**36**), in 44% isolated yield and with exclusive regio- and diastereoselectivity (**Fig. 4A**). The structure of **36** was unequivocally established by single-crystal crystallography, which confirmed that no epimerization had occurred. This example underscores the utility of our method towards accessing positional isomers in late-stage settings and it should prove particularly significant in scenarios where synthetic campaigns are hindered by the access to various isomers, making the production of even small quantities of an isomer highly valuable.

The regioselectivity of our 1,2-boron transposition could be tuned by the reaction condition. Based on the kinetic framework described in **Fig. 2A** (see supplementary information section IX.D for further details), the formation of a primary boronate (e.g., **2**) would be preferred over that of a

secondary boronate (e.g., **2a**) in the isomerization of **1** provided that the HAD step is fast and the concentration of HAD catalyst is high, and *vice versa*. We found that using a HAD catalyst that possesses a much larger rate constant than thiophenol, benzeneselenol,[44] led to an intrinsic regioselectivity of 4.3:1 (**2**:**2a**), whereas diluting the reaction concentration and employing much reduced HAD catalyst loading (2%) led to an inverted intrinsic regioselectivity of 1:3.8 (**2**:**2a**). Although these selectivities are modest, this tunable regioselectivity allows the access to all possible positional isomers as the major product by simply switching the reaction condition, which would be beneficial especially for late-stage diversifications.

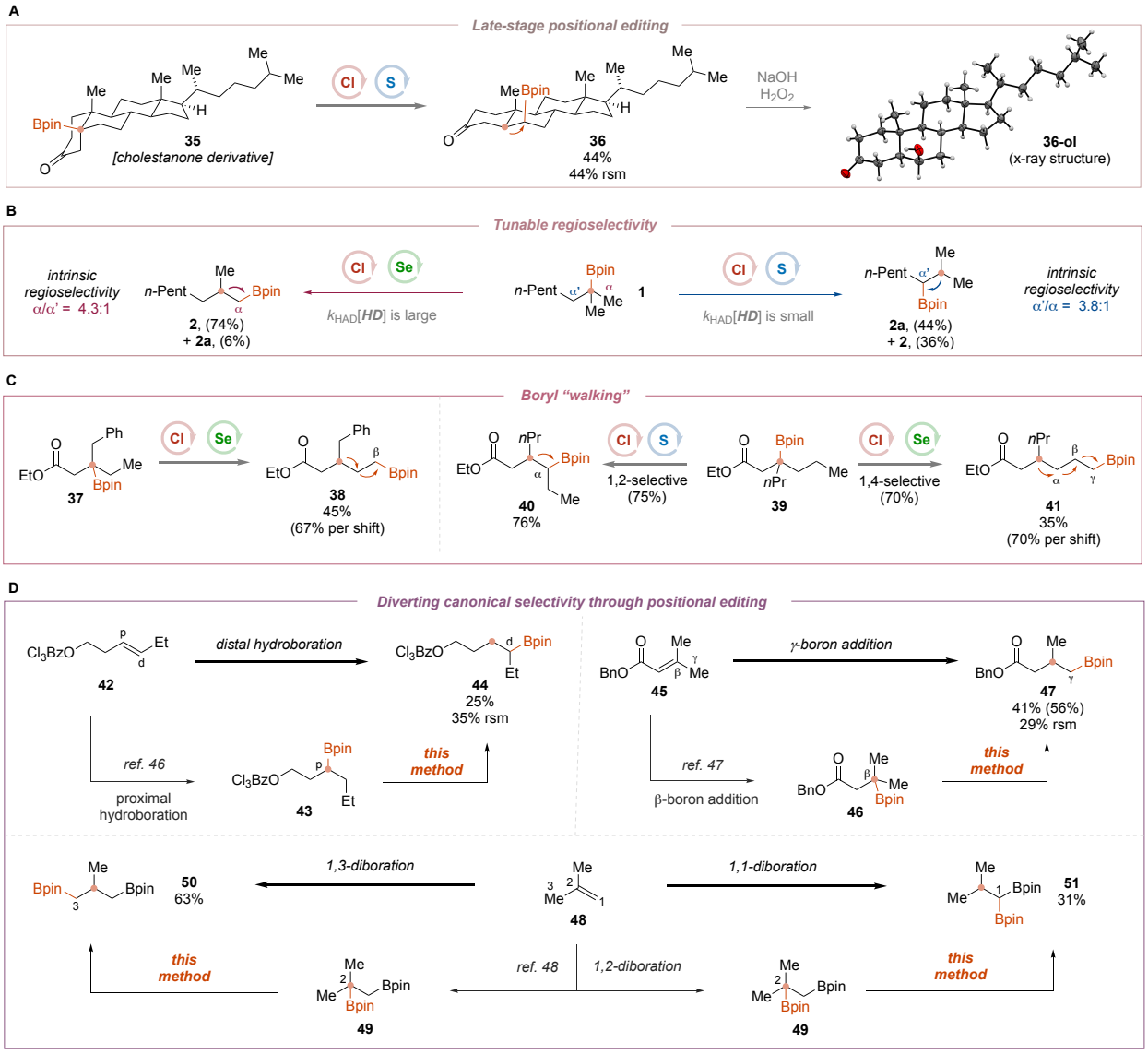


Fig. 4. Synthetic application of the 1,2-boron transposition. a, Late-stage positional editing conducted on a complex molecule. **b,** Regioselectivity of positional isomerization can be tuned by reaction conditions. **c,** Consecutive boron shifts for direct "chain-walking" of boryl groups along a carbon chain. **d,** Utilization of positional editing to divert the regioselectivity of several classic transformations. See supplementary information for detailed conditions.

A hallmark of our method is the 1,2-selectivity which allows access to products with the functional group migrated to an adjacent position. Arguably, this selectivity is the most valuable and synthetically useful over other 1,n-selecitivities (n>2) because the latter could be potentially realized by a series of 1,2-transpositions but the reverse is not possible. To demonstrate such possibilities of boron migration to a remote site, we presented examples in which formal 1,3- and 1,4-boron transpositions (**37,39**) could be indeed achieved by successive 1,2-boron shifts (**Fig. 4B**), reminiscent of the classic chain walking process in organometallic chemistry. In both cases, the starting tertiary boronates (**37,39**) were converted to terminal boronates with high yields per boron shift. Good selectivities towards the terminal products were obtained by using a selenol-based HAD catalyst, but the exact origin of this observation remains unclear at this time. In the reaction of **39**, the preference for the formation of 1,2- or 1,4-transposed products could be tuned by the choice of reaction conditions.

The development of positional editing techniques allows the regioselectivity of a reaction to be revised in subsequent steps of a synthesis and provides a strategy to achieve non-canonical selectivities of classic organic transformations (**Fig. 4C**). For example, copper-catalyzed hydroboration of unsymmetrical internal alkenes bearing electron-withdrawing groups (**42**) at the homoallylic position usually occurred with >10:1 proximal-to-distal regioselectivities.[45] By utilizing the 1,2-boron transposition, we accessed the product (**44**) resulting from a distal-selective hydroboration of the same alkene, which could be otherwise difficult to access by other means. Similarly, the classic boron conjugate additions generate β-boryl carbonyl compounds,[46] and through our approach such additions could be diverted to a γ-boron addition (**47**). In addition, diboration of alkenes occurs in a 1,2-addition fashion to afford 1,2-diboron compounds.[47] Our 1,2-boron transposition reaction enabled direct access to products that would formally result from 1,1- and 1,3-diboration of alkenes (**50,51**).

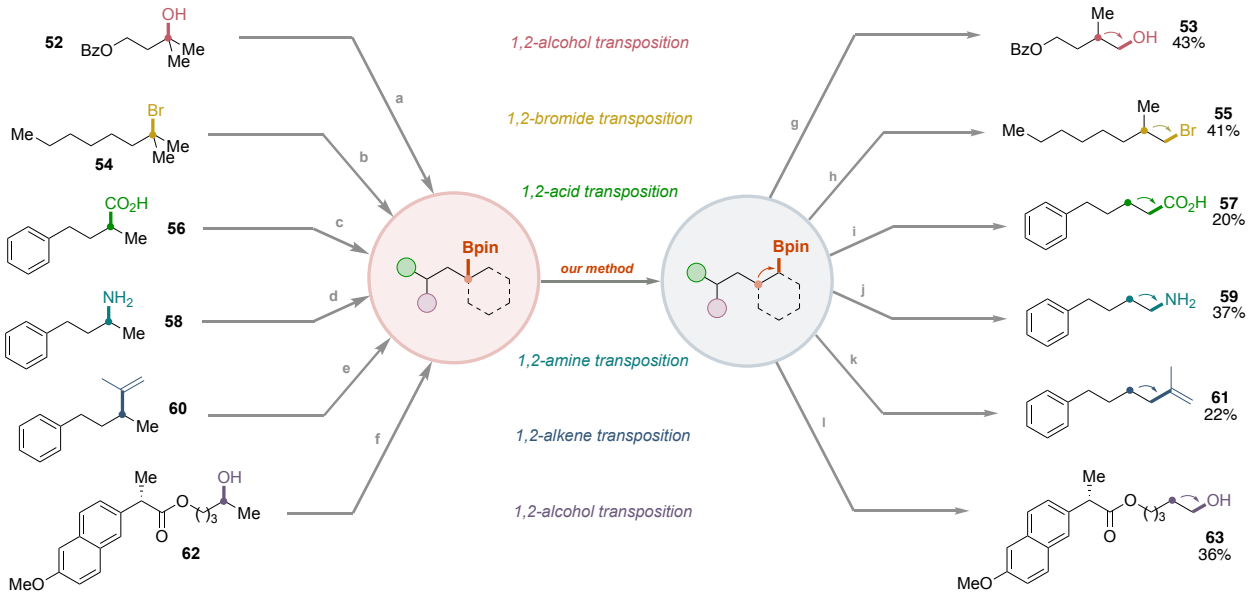


Fig. 5. Positional editing of diverse functional groups enabled by 1,2-boron shifts. Reaction condition: **a**, ref. 51. **b**, $NiBr_2$•diglyme, pybox, KOEt, B_2pin_2. **c**, ref. 49. **d**, ref. 50. **e**, 1) $Co(acac)_2$, Et_3SiH, DTBP, O_2; 2) $Ir(ppy)_3$, B_2cat_2, then pinacol, Et_3N. **f**, 1) pyridine, *o*-iodophenyl chloro thionoformate; 2) $Ir(ppy)_3$, B_2cat_2, then pinacol, Et_3N. **g**, $NaBO_3$•$4H_2O$. **h**, 1-bromo-3,5-

bis(trifluoromethyl)benzene, *n*-BuLi, then NBS. **i**, IPrCuCl, NaOtBu, CsF, CO_2. **j**, $MeONH_2$, KO*t*Bu. **k**, Isopropenyl magnesium bromide; then I_2, NaOMe. **l**, $NaBO_3 \bullet 4H_2O$.

Finally, we demonstrate the positional editing of a diverse set of functional groups through a three-step sequence that employs the 1,2-boron transposition reported herein and an array of known transformations that convert a functional group to and back from pinacolboryl group (**Fig. 1C**).[48-51] Following this workflow, we showcased this positional editing concept with various functional groups, including those in alcohols (**52, 62**), a halide (**54**), a carboxylic acid (**56**), an amine (**58**), and an olefin (**60**), all accomplished in satisfactory overall yields. Our approach is advantageous and general because many native functional groups, such as hydroxyl, amino, and carboxyl, are unable to participate in radical rearrangements directly.[24] As a consequence, two additional steps that interconvert between the native group and another group amenable to radical rearrangement (e.g., alcohol⇄alkanoate, amine⇄imine) are required and specific conditions need to be developed for each distinct transposition. We anticipate that the positional editing logic outlined here will significantly contribute to molecular diversification and expand access to uncharted chemical space, which should prove valuable for research in various fields including medicinal chemistry.

Data Availability

The data that support the findings of this study are available within the article and its Supplementary Information.

Acknowledgements

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Author contributions

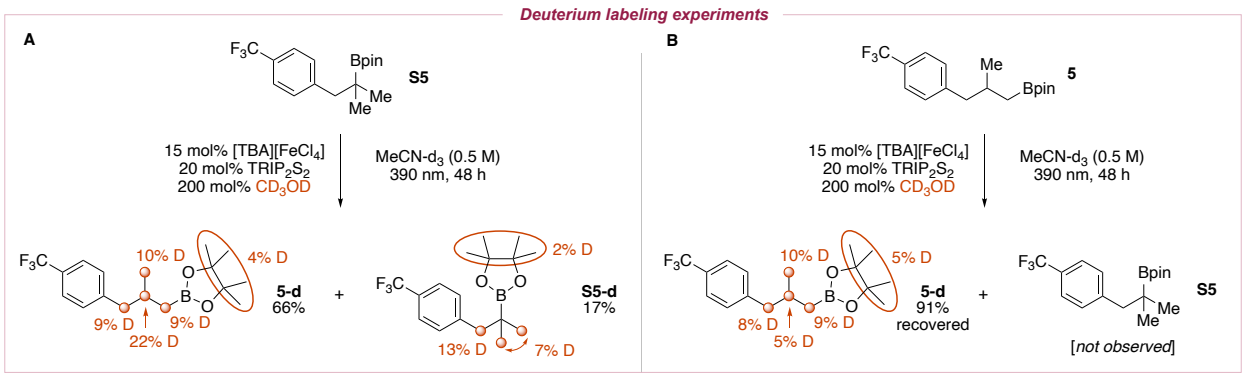
Y.X. conceived of and directed the study. W.Z., S.M., M.P., and Y.X. conducted the experiments. Y.X. performed DFT computational studies and wrote the manuscript with the input of all authors. All authors have approved the final version of this manuscript. W.Z. and S.M. contributed equally to this work.

Competing interests

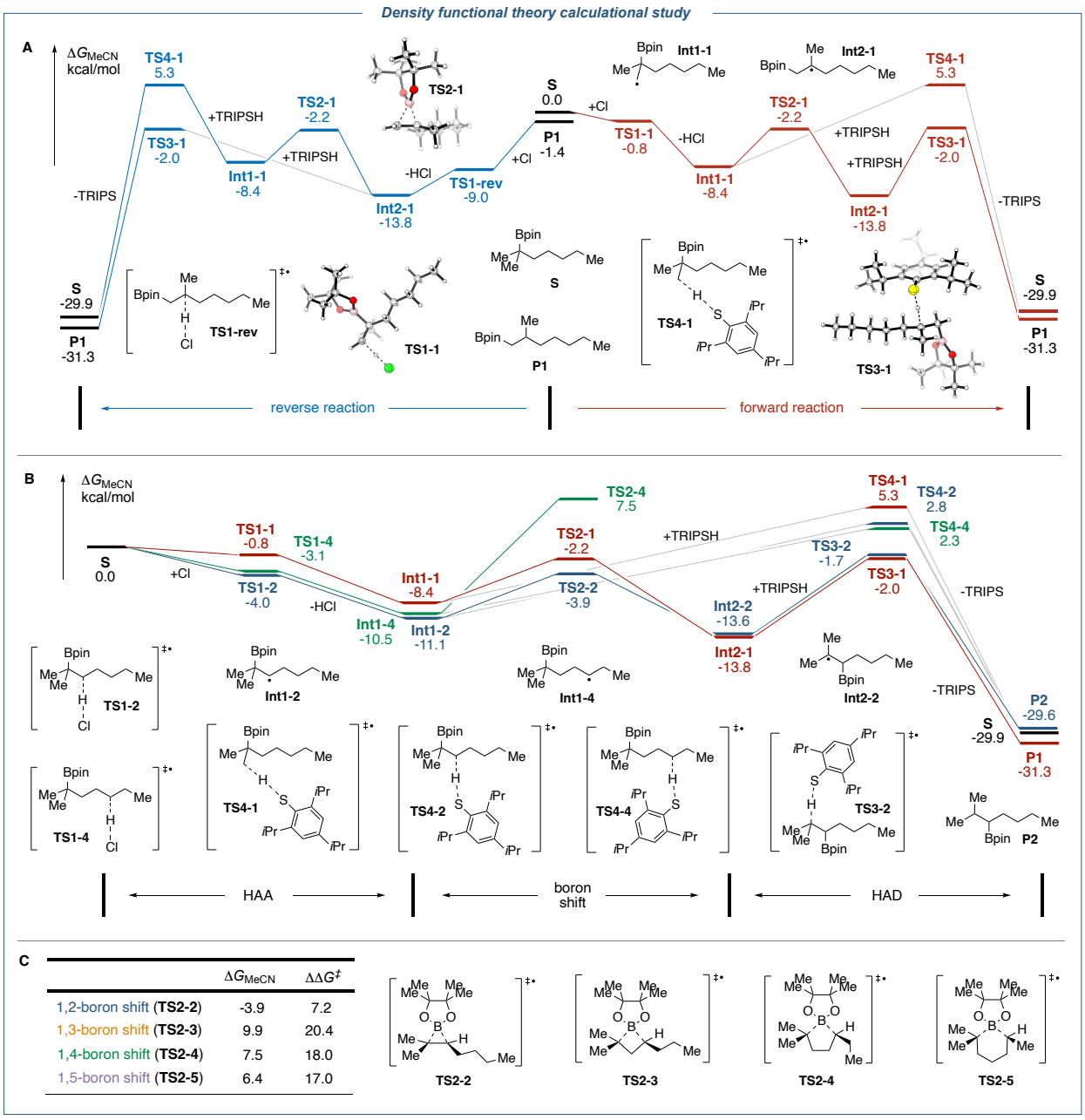
Authors declare that they have no competing interests.

Author Information

Correspondence and requests for materials should be addressed to Y.X. (yumengxi@nus.edu.sg).



Extended Data Fig. 1. Mechanistic studies of the 1,2-boron transposition. a, Deuterium labeling experiments with **S5**. **b,** Deuterium labeling experiments with **5**.



Extended Data Fig. 2. Density functional theory computational studies of the 1,2-boron transposition. a, Reaction profiles of the forward and reverse reactions. **b,** Computed reaction profiles of the overall reaction. **c,** Energies of 1,n-boron shifts. Single-point energies were computed at the UM06-2X/def2-QZVPP/SMD(MeCN) level of theory with structures optimized at the UM06-2X/6-311G(d,p) level.

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