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Decarboxylative borylation

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The widespread use of alkyl boronic acids and esters is frequently hampered by the challenges associated with their preparation. Herein we describe a simple and practical method to rapidly access densely functionalized alkyl boronate esters from abundant carboxylic substituents. This broad-scope Ni-catalyzed reaction uses the same activating principle as amide bond formation to replace a carboxylic acid with a boronate ester. Application to peptides allowed expedient preparations of α-amino boronic acids, often with high stereoselectivity, facilitating the synthesis of both FDA approved alkyl boronic acid drugs (Velcade and Ninlaro) as well as a boronic acid version of the iconic antibiotic vancomycin. The reaction also enabled the discovery and extensive biological characterization of potent elastase inhibitors which may have a strategic advantage due to their covalent-reversible binding properties.

Boronic acids and their esters are of paramount importance to all facets of chemical science. Although their popularization has largely been spurred by the incredible utility of the Suzuki coupling (*1*), boronic acids have, to date, found countless applications in fields far outside of cross-coupling, such as materials science (*2*), chemosensor development (*3*), and drug discovery (*4*, *5*). Their Lewis acidity, their propensity to reversibly engage various nucleophiles (*e.g.*, alcohols and amines), and their ability to form hydrogen bonds confer boronic acids unique chemical and biological properties. For example, in materials science, the reversible covalent bonding of boronic acids has enabled the development of self-assembled nanomaterials, hydrogels, and macromolecular saccharide sensors (*2*, *3*). In medicinal chemistry, boronic acids have been harnessed as bioisosteres where they replace structural motifs of similar physical and chemical properties, such as carboxylic acids (*6*), to alter the physiochemical properties of lead candidates (*4*, *5*). The reversible covalent binding properties allow tuning of the drug-target residence time in relationship to pharmacodynamic activity rather than affinity, while avoiding permanent covalent adducts with off-target proteins that could lead to associated toxicity.

Alkyl boronic acids and α-amino boronic acids in particular have attracted considerable attention as potent protease inhibitors (*7*). Currently, two alkyl boronic acids are approved by the FDA for various oncology indications: Ninlaro (**1**) (Fig. 1A) and Velcade (**49**). However, efforts to fully exploit the vast potential of these promising medicinal scaffolds are often hampered by the challenges associated with their preparation—relatively few complex alkyl boronic acids have been synthesized for biological evaluations (*4*). Unlike carboxylic acids which are ubiquitous in nature and inexpensive, boronic acids are almost entirely derived through synthesis. The retrosynthetic analysis of alkyl boronic acids can itself be a deterrent to their incorporation into drug candidates. General methods to forge alkyl C–B bonds include hydroboration of alkenes (*8*, *9*), Miyaura borylation of alkyl halides (*10*–*14*), transmetalation (*e.g.*, with alkyl organolithium species) (*15*), and conjugate addition (*16*, *17*). α-Amino boronic acids are typically accessed through metal catalyzed addition of diboron species onto imines (*18*) where elegant asymmetric variants have been reported (*19*). While these approaches have been highly enabling, few of them utilize naturally occurring or readily available starting materials; many of these methods also possess modest functional group compatibility. Path-pointing advances in metal catalyzed C–H activation highlight the possibilities of transforming C_{sp3}–H bonds directly into alkyl boronates at a late stage of a synthesis (*20*). However, presently, alkyl boronic acids are usually installed at an early stage when few reactive functionalities are present. Thus, as illustrated with **1** (Fig. 1A), the conventional approach focuses all strategic attention on the means with which the boron atom will be incorporated even though this represents <5% of the total molecular weight of **1** (*21*). The synthesis of an engineered amino acid (AA) is therefore required. To systematically probe the structure-activity relationship of lead compounds, each analog must be made individually.

In contrast, the direct transformation of the carboxylic acid containing native peptide into the corresponding boronic acid at a late stage constitutes a far easier and more logical approach. Given the sheer number of alkyl carboxylic acids in feedstock chemicals, natural products, and drug molecules, this transformation could provide the unique opportunity to expediently procure a myriad of previously difficult-to-access boronic acids as versatile building blocks, functional materials, and potent medicines.

Here we present a simple method for nickel-catalyzed decarboxylative borylation that is mild, scalable, and general across a range of primary, secondary, tertiary, peptidic, and even natural product-derived substrates. A diverse array of boronates which would otherwise require lengthy de novo synthesis was furnished directly from the corresponding carboxylic acids. This method's capacity to transform native peptides into α-amino boronic acids has led to the discovery of three potent small molecule elastase inhibitors.

Development of the decarboxylative borylation reaction

Recent efforts in our laboratory revealed redox-active esters (RAEs, *e.g.*, *N*-hydroxyphthalimide ester **2**) derived from alkyl carboxylic acids as convenient surrogates for alkyl halides in nickel or iron catalyzed cross-coupling reactions. These versatile intermediates, most commonly used in amide bond forming reactions, have enabled practical means of C–C bond formation in various modalities, including decarboxylative Negishi (*22*, *23*), Suzuki (*24*), and Kumada (*25*) couplings, as well as Giese reactions (*26*). Although RAEs have yet to be used in carbon–heteroatom cross-coupling reactions, our earlier discoveries, coupled with Fu's (*10*) pioneering work on nickel catalyzed Miyaura borylation of alkyl halides (*11–14*), prompted us to investigate the possibility of harnessing them for C–B bond formation, thereby achieving direct conversion of alkyl carboxylic acids into boronic acid derivatives.

Realization of this transformation required considerable experimentation. Figure 1B provides the optimal reaction parameters alongside an abbreviated picture of the optimization process on 2-methyl-4-phenylbutanoic acid. NHPI ester (**2**) proved to be the optimal substrate for borylation with B_2pin_2; other RAEs such as the tetrachloro-NHPI (TCNHPI) ester were less effective (entry 1). The inexpensive combination of $NiCl_2{\bullet}6H_2O$ and bipyridine ligand ***L1*** emerged as the best catalyst system after an exhaustive screening—the use of alternative catalysts (table S4) or ligands (entries 3–5; see table S5) had deleterious effects. The choice of solvent was critical: a binary mixture of tetrahydrofuran (THF) and dimethylformamide (DMF) gave the optimal result; lower yields were observed in the absence of DMF (entry 6). Pre-mixing methyl lithium with B_2pin_2 was necessary to activate the diboron species toward transmetalation; numerous other activating agents surveyed (*e.g.*, entries 7–10) were less effective, affording borylation products in lower yields, if at all. Magnesium salts were also indispensable to the reaction: in the absence of the $MgBr_2{\bullet}OEt_2$, virtually no product was obtained (entry 11) whereas other Lewis acidic additives surveyed (entries 12–13) gave lower yields. Although its precise role is unclear, it is hypothesized that $MgBr_2{\bullet}OEt_2$ promotes the transmetallation of boronate species onto the metal catalyst (*27*, *28*). Pinacol boronate ester product ***3*** could be accessed directly from the carboxylic acid in comparable yields using a one-pot procedure wherein RAE **2** was formed in situ, in a similar vein to amide coupling (entry 14). Overall, the reaction was found to proceed smoothly over the course of 2 hours (1 hour at 0°C and 1 hour at room temperature).

Scope of the decarboxylative borylation reaction

With the optimized conditions in hand, the scope of this methodology was subsequently explored. RAEs derived from a broad selection of primary, secondary, and tertiary carboxylic acids were all found to be viable substrates (Fig. 2). These encompass acyclic, cyclic, caged, bridgehead, fluoroalkyl, and benzylic acids which were transformed to the corresponding pinacol boronate esters (Bpin ester) smoothly. Scalability of the reaction is evident through the preparation of **29** on a gram scale. Additionally, 12 of the products (**3**, **4**, **7**, **11**, **12**, **13**, **16**, **19**, **25**, **29**, ***35***, **38**) were obtained in comparable yields when only 2.5 mol% of nickel catalyst (3.3 mol% of ligand) was used, further attesting to the adaptability of this method in a process setting.

As the methyl lithium was pre-mixed with B_2pin_2 to form an ate-complex, strongly nucleophilic/basic organometallic species were sequestered from the substrate: a gamut of functionalities such as ethers (**30**, **31**, ***35***, **37**, **41**), esters (**5**, **8**, **21**, **22**, **39**, **41**), carbamates/amides (**8**, **15**, **28**, **36**, ***37***, **1**), ketones (**34**, **38**, **39**, **40**), olefins (**39**, **40**, **41**), and alcohol/phenol (**40**, **41**) were left unscathed under the mild reaction conditions. Indeed, even the highly base-sensitive Fmoc group was tolerated (see **8**). The compatibility with alkyl bromides (**7**) and chlorides (***33***) points to the orthogonality of this reaction to halide-based Miyaura borylations. Enoxolone derived boronates **39** and **40** were obtained in similar yields, suggesting that the free hydroxyl group had minimal influence on the reaction. The discrete isolation of RAEs, as alluded to earlier, is not necessary. Tertiary and secondary boronate esters can be prepared directly from carboxylic acids when RAEs are generated in situ. This one-pot procedure also pertains to primary substrates, albeit in lower yields.

Although some of the products presented herein (*e.g.*, **9**, **16**, **17**, **19**, **20**, **23**) can be synthesized from the analogous halides via Miyaura borylation reactions (*10–14*), organohal-

ides are oftentimes not commercially available and require extraneous steps to prepare (usually from the corresponding alcohols). Conversely, the use of readily available carboxylic acids largely circumvents this problem. A great majority of products in Fig. 2 are derived from commercially available acids. For instance, **21** was conveniently prepared from a cubane-based carboxylic acid whereas the reported synthesis of the analogous bromide enlisted a harsh Hundsdiecker reaction (Br_2 and HgO) on the same acid (*29*). Furthermore, the scope of this borylation protocol can be extended to amino acid derivatives to furnish α-amino boronate esters such as **15**. The synthesis of **15** through halide-based Miyaura borylation is simply not feasible as the corresponding α-amino halide starting material would be unstable. In this regard, the decarboxylative borylation strategy allows explorations of previously elusive chemical space.

The prevalence of alkyl carboxylic acids is demonstrated by their presence in over 450 approved drug molecules (*30*). To this end, the impressive chemoselectivity of this reaction offers the unique opportunity to pursue late-stage modifications of bioactive molecules that are densely adorned with reactive functionalities. Over 10 carboxylate containing drug molecules or natural products have been successfully converted into pinacol boronate esters (**28**–**41**) which would otherwise only be accessible through multi-step functional group interconversions or de novo syntheses.

Synthetic applications of the decarboxylative borylation reaction

The pinacol boronate esters can be conveniently hydrolyzed into the corresponding boronic acids (*e.g.*, **4a**, **3a**, **33a**, **1**) (Fig. 2). This allows the transformation of carboxylic acids into their borono-bioisoteres to identify compounds with superior potency or pharmacokinetic properties. Alternatively, boronate esters could be diversified into a variety of structural motifs (*31*–*33*). As an illustrative example, the Lipitor derived Bpin ester (**36**) can be expediently elaborated into the corresponding carbamate (**36a**) (*34*) or alcohol (**36b**) upon treatment with appropriate oxidants (Fig. 3A). Under conditions reported by Aggarwal, **36c** and **36d** were directly accessed through reaction with aryllithium species (*35*). Decarboxylative borylation could also convert RAEs, which are electrophiles in cross-couplings, into Bpin esters that serve as nucleophiles in Suzuki reactions (*e.g.*, **36** to **36e** and **36** to **36f**) (*36*). This "umpolung" approach is particularly strategic in the case of **36e** whereby the 2-pyridylboronic acid or organozinc species are often not viable Suzuki/Negishi coupling substrates owing to a lack of stability.

Moreover, selective decarboxylative borylation at the C-terminus of native peptides allowed rapid access to coveted α-amino boronic acids which are privileged medicinal chemistry motifs (*18*, *37*). Ninlaro (**1**), for example, was obtained in three steps from a simple peptide (Fig. 2). This opens up a distinct dimension to the study of peptide-based therapeutics: in perhaps the most striking example, vancomycin was converted into a boronic acid analog (**44**) through the decarboxylative borylation of **42** (Fig. 3B) (*38*). This process proceeded smoothly in the presence of four methylated phenoxy groups, two TBS-protected hydroxyls, two aryl chlorides, six secondary amides, one primary amide, one secondary amine, and seven epimerizable stereocenters. Although **44** showed less activity compared to the parent acid **43** (Fig. 3B and table S12), such remarkable chemoselectivity still attests to the potential utility of this reaction.

Unpredictable stereoselectivity of radical processes oftentimes presents a hurdle to their broad adoption in late-stage modifications of drug leads or natural products. Complex α-amino boronic acid **44** was obtained as a single diastereomer in this radical-based decarboxylative borylation reaction. This result prompted us to investigate the stereoselectivity of the decarboxylative borylation on several dipeptides (Fig. 3C). We found that increased steric bulk on the N-terminal residue resulted in better diastereoselectivity: though both diastereomers were furnished in almost equal quantities for **45**, higher selectivities were observed for **46** and **47**. Meanwhile, **46** was obtained in the same diastereomeric ratio from Boc-L-Val-L-Val and Boc-L-Val-D-Val. Lower reaction temperatures could also be used to enhance the stereoselectivity. At –15°C, **48** was furnished in greater than 5 to 1 *d.r.*, enabling a stereoselective synthesis of Velcade (**49**) in a short sequence.

Discovery of potent human neutrophil elastase inhibitors

By wedding the rich medicinal potential of boronates to the ubiquity of alkyl carboxylic acids, the decarboxylative borylation reaction has the potential to open up new vistas in drug development. For example, application of the decarboxylative borylation reaction to readily available tripeptides allowed the expedient preparations of **50**–**52** which were formed as single diastereomers and found to be potent inhibitors of human neutrophil elastase (HNE) (Fig. 4, A and B). Notably, the carboxylic acid precursor to **50** (**50b**) was found to be devoid of any inhibitory activities while **50** and **51** displayed substantially enhanced potency compared to their trifluoromethyl ketone congeners (**50a** and **51a**) which have been examined in phase II clinical trials for lung diseases such as cystic fibrosis (*39*–*45*). HNE, a highly active serine protease, plays a pivotal role in the immune response, tissue remodeling, and the onset/resolution of inflammation by breaking down mechanically important structures of the body's cellular matrix as well as proteins of foreign origin (*46*). While five generations of HNE inhibitors have been

evaluated clinically in multiple inflammatory lung diseases (*e.g.*, cystic fibrosis, emphysema, and bronchiectasis), none have been overwhelmingly efficacious in humans to make a significant impact in these conditions (*46*).

Toward this end, **52** exhibited an IC_{50} = 15 pM (K_i = 3.7 pM) while **51** exhibited an IC_{50} = 30 pM (K_i = 34 pM) against purified HNE (Fig. 4B). The IC_{50} values were determined head-to-head with other pre-clinically and clinically validated HNE inhibitors (**53**–**57**), including BAY 85-8501 (**54**, a leading clinical candidate with reported K_i = 80 pM) (*47*), **55** (POL6014, a phase I peptide-based clinical candidate for cystic fibrosis) (*48*) as well as **56** and **57** (reported by Chiesi Pharmaceuticals) (*49*). Additionally, **51** and **52** retained much of their inhibitory activities in sputum samples of cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD) patients, underscoring their potency in the context of a more patho-physiologically relevant environment than the traditional biochemical assay. Conversely, while dimeric compound **58** from AstraZeneca (IC_{50} = 11 pM, K_i = 2.7 pM) (*50*) and BAY 85-8501 (**54**) showcased low IC_{50} values, their potencies diminished in CF patient sputum. Comparison of the LipE values in COPD sputum revealed that the superior potency of **52** is not driven by increased lipophilicity (10.2 versus 9.46 for **57**) (*51*).

Additionally, the IC_{50} value of **52** was found to remain unchanged with increasing incubation times (5–60 min) while that of **58**, a non-covalent inhibitor, exhibited a 55-fold increase in potency under the same conditions. These data retain the profile that is expected: compound **52** is behaving like a partial mechanism-based inhibitor (or a covalent reversible inhibitor) likely due to the potentially slow off-rate of the α-amino boronic acid. This correlates with tighter binding and potentially long residence time as seen in other amino boronic acid compounds and unlike the many reversible elastase inhibitors (*e.g.*, **58**) (*52*). Clinically, this mechanism has been proven successfully through Velcade (**49**), which inhibits the catalytic site of the 26S proteasome. In this example, covalent reversible bonding between the boronate and the nucleophilic oxygen results in a slow disassociation rate (*53*, *54*). As most clinical elastase inhibitors (such as **54**, BAY 85-8501, one of the most potent HNE inhibitors reported to date) are non-reactive, reversible, transition state inhibitors, the high potency of **52** and the inherent mechanism of the amino boronic acids could help address these limitations. Through this "hybrid" enzymatic inhibitory approach (based upon Fischer's Lock and Key model/Ehrlich's Pharmacophore Model), boronic acids such as **52**, which combine a rapid, potent binding with a slow off-rate, may effectively restore the protease versus anti-protease balance in a clinical setting. They could therefore be tuned rapidly toward lung-specific clinical applications.

To further evaluate the therapeutic potential of **51** and **52**, the in vitro adsorption, distribution metabolism, and excretion properties (ADME properties) were probed to determine if any deleterious effects of the boronate replacements of the trifluoromethyl ketone would be revealed (Fig. 4C). These amino boronic acids displayed comparable kinetic solubility to the trifluoromethyl ketone analog (**51a**). A substantial portion (90.3% and 79.2% respectively) of **51** and **52** were found to be intact in CD-1 mouse plasma after 2 hours. **51** and **52** exhibited similar metabolic stability as the trifluoromethyl ketone **51a**. **51** and **51a** also demonstrated similar levels of permeability in *Caco-2* cells (see table S19). These data suggest that the novel boronates simply improve potency without changing the drug-like properties of their ketone congeners.

Method summary

Procedurally, the conversion of redox-active esters into boronate esters was achieved in three stages: namely, the preparation of catalyst mixture, the preparation of $[B_2pin_2Me]Li$ complex, and the nickel catalyzed decarboxylative borylation reaction. An abbreviated experimental protocol is presented herein with a graphical guide (Fig. 5, from the gram-scale decarboxylative borylation of ibuprofen-derived RAE). Comprehensive information on the commercial source and purity of chemicals or variations in experimental details for different substrate classes can be found in the supplementary materials.

Preparation of $NiCl_2•6H_2O$/ligand stock solution or suspension

A flask charged with $NiCl_2•6H_2O$ (1.0 equiv.) and ligand (***L1*** or ***L2***, 1.3 equiv.) was evacuated and backfilled with argon for three times. Following the addition of THF (the concentration of $NiCl_2•6H_2O$ was 0.025 M) or DMF (the concentration of $NiCl_2•6H_2O$ was 0.050 M), the resulting mixture was stirred at room temperature overnight (or until no granular $NiCl_2•6H_2O$ was observed) to afford a green solution or suspension (for an example, see Fig. 5A, center left).

Preparation of $[B_2pin_2Me]Li$ complex

To a solution of B_2pin_2 (1.1 equiv.) in THF (the concentration of B_2pin_2 was 1.1 M) was added MeLi (1.6 M in Et_2O, 1.0 equiv.) at 0°C under argon. The reaction mixture was warmed to room temperature and stirred for 1 hour to afford a milky white suspension (Fig. 5A, center right).

Ni-catalyzed decarboxylative borylation

A flask charged with the redox-active ester (1.0 equiv.) and $MgBr_2•OEt_2$ (1.5 equiv.) was evacuated and backfilled with argon for three times (Fig. 5A, left). Catalyst solution or

suspension (containing 10 mol% of $NiCl_2 \bullet 6H_2O$ and 13 mol% of ligand) was added via a syringe (Fig. 5B, left). When a catalyst suspension/solution in DMF was used, an additional portion of THF (twice the volume of the DMF suspension/solution needed) was added to the reaction vessel prior to the addition of the catalyst mixture [this process can be exothermic on large scales and cooling (with ice/water bath) may be necessary]. The resulting mixture was stirred vigorously until no visible solid was observed at the bottom of the reaction vessel (Fig. 5B, center) [this was found to be accelerated by sonication]. This mixture was cooled to 0°C before a suspension of $[B_2pin_2Me]Li$ in THF (3 equiv.) was added in one portion (Fig. 5B, right). After stirring for 1 hour at 0°C (Fig. 5C, left), the reaction was warmed to room temperature and stirred for another 1 hour (Fig. 5C, center). When thin layer chromatography (TLC) analysis indicated the completion of the reaction (Fig. 5C, right), the reaction was quenched with aqueous HCl (0.1 M) or saturated aqueous NH_4Cl and extracted with diethyl ether (Et_2O) or ethyl acetate (EtOAc). Alternatively, on larger scales, as is the case shown in Fig. 5, the reaction mixture was directly poured onto Et_2O (Fig. 5D, left) and the resulting suspension was filtered through a pad of silica gel and celite (Fig. 5D, center). Purification by flash column chromatography (Fig. 5D, right) afforded the desired pinacol boronate ester.

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Supplementary Text
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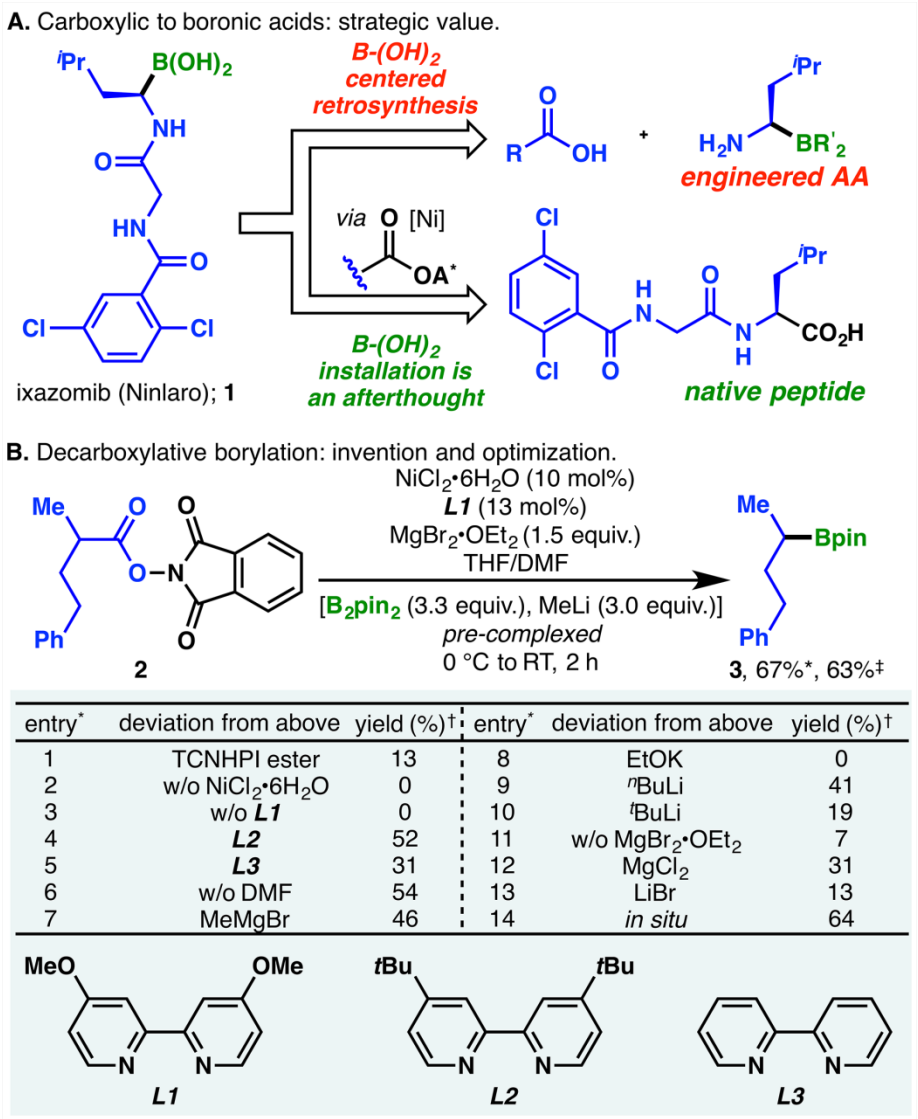


entry*	deviation from above	yield (%)†	entry*	deviation from above	yield (%)†
1	TCNHPI ester	13	8	EtOK	0
2	w/o $NiCl_2•6H_2O$	0	9	^{n}BuLi	41
3	w/o ***L1***	0	10	^{t}BuLi	19
4	***L2***	52	11	w/o $MgBr_2•OEt_2$	7
5	***L3***	31	12	$MgCl_2$	31
6	w/o DMF	54	13	LiBr	13
7	MeMgBr	46	14	*in situ*	64

Fig. 1. Development of the decarboxylative borylation reaction. (A) Strategic value of the decarboxylative borylation illustrated through the retrosynthetic analysis of Ninlaro (1). (B) Development and optimization of the decarboxylative borylation reaction. Footnotes: * Reaction conducted on 0.10 mmol scale. † Yield by gas chromatography (GC). ‡ Isolated yield.

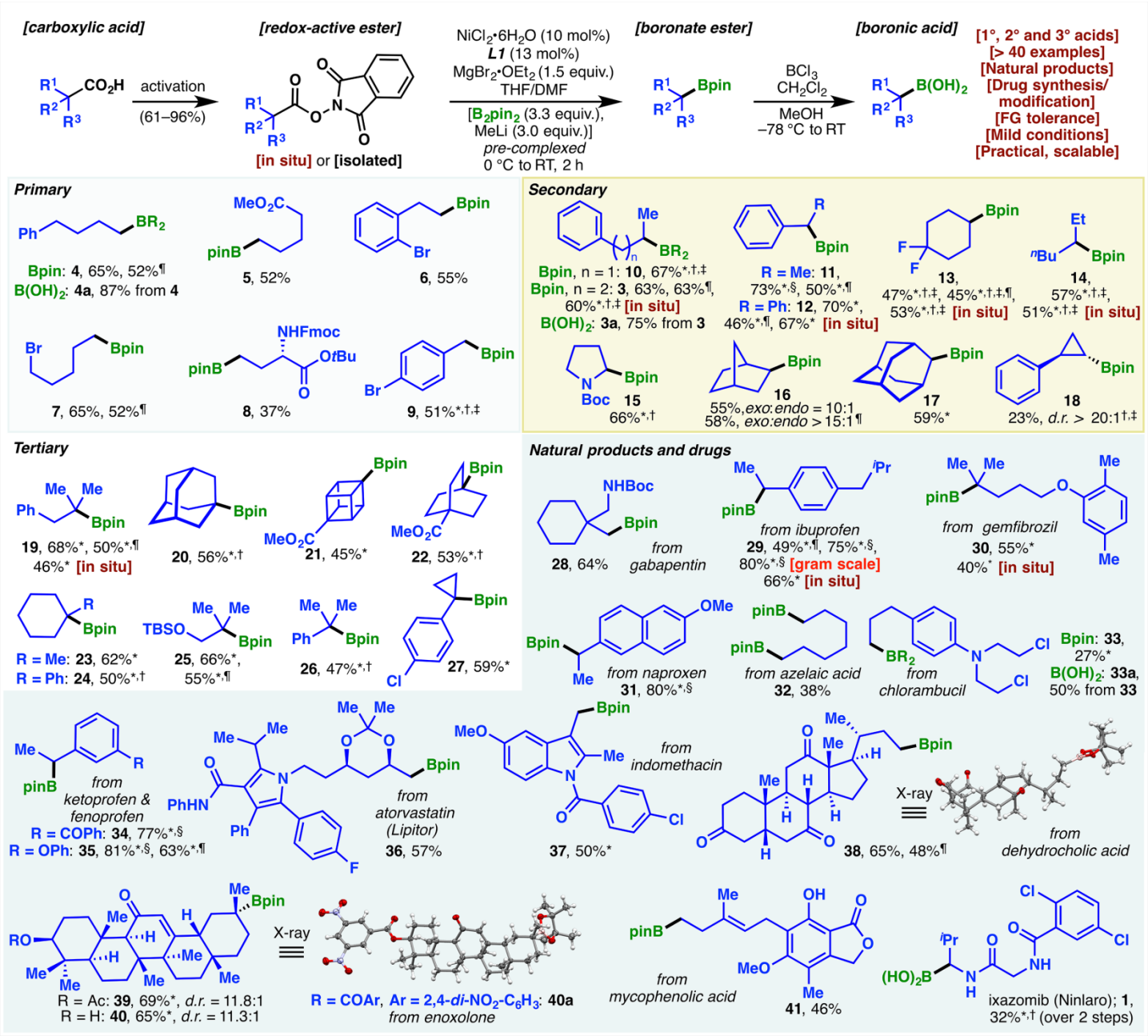
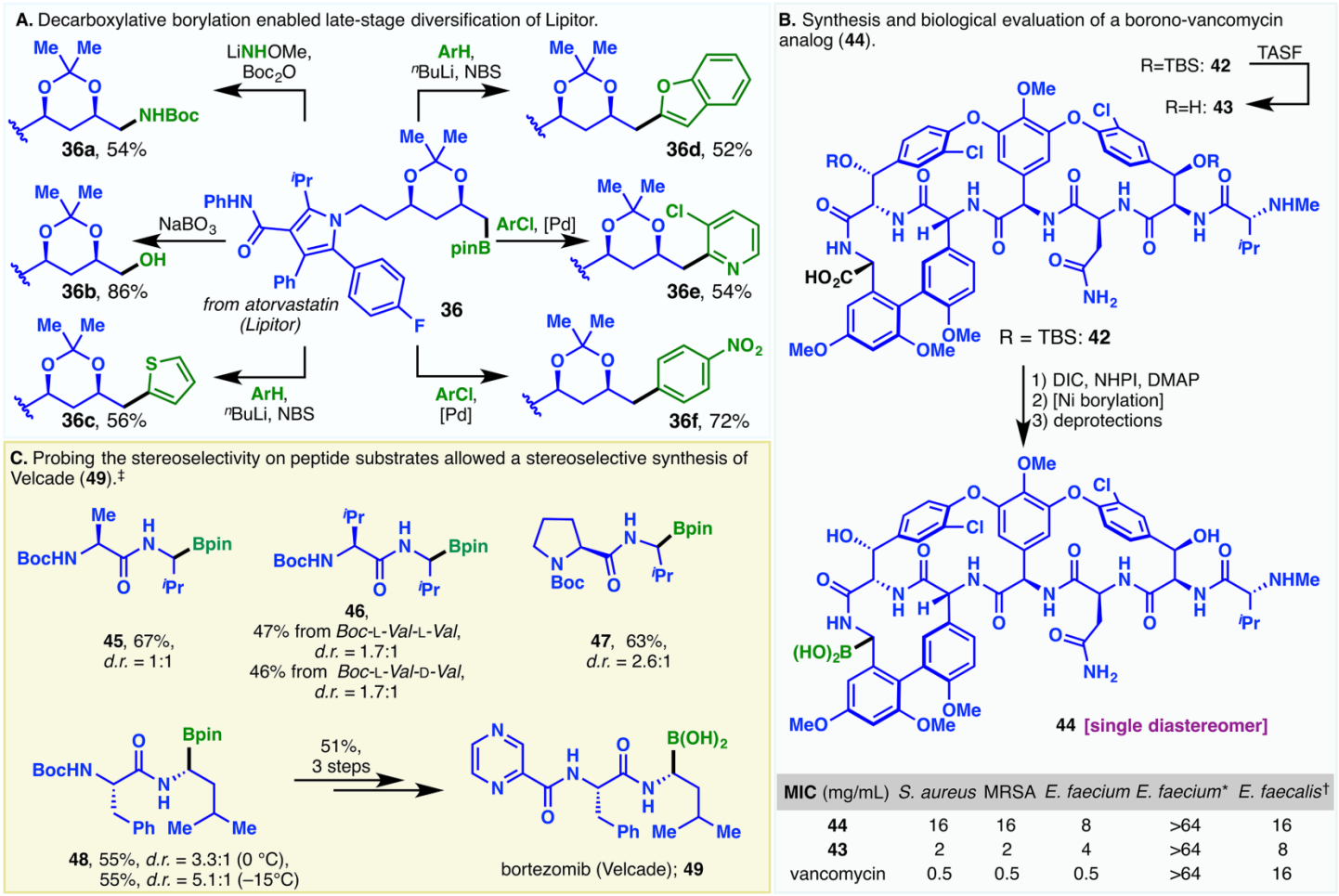


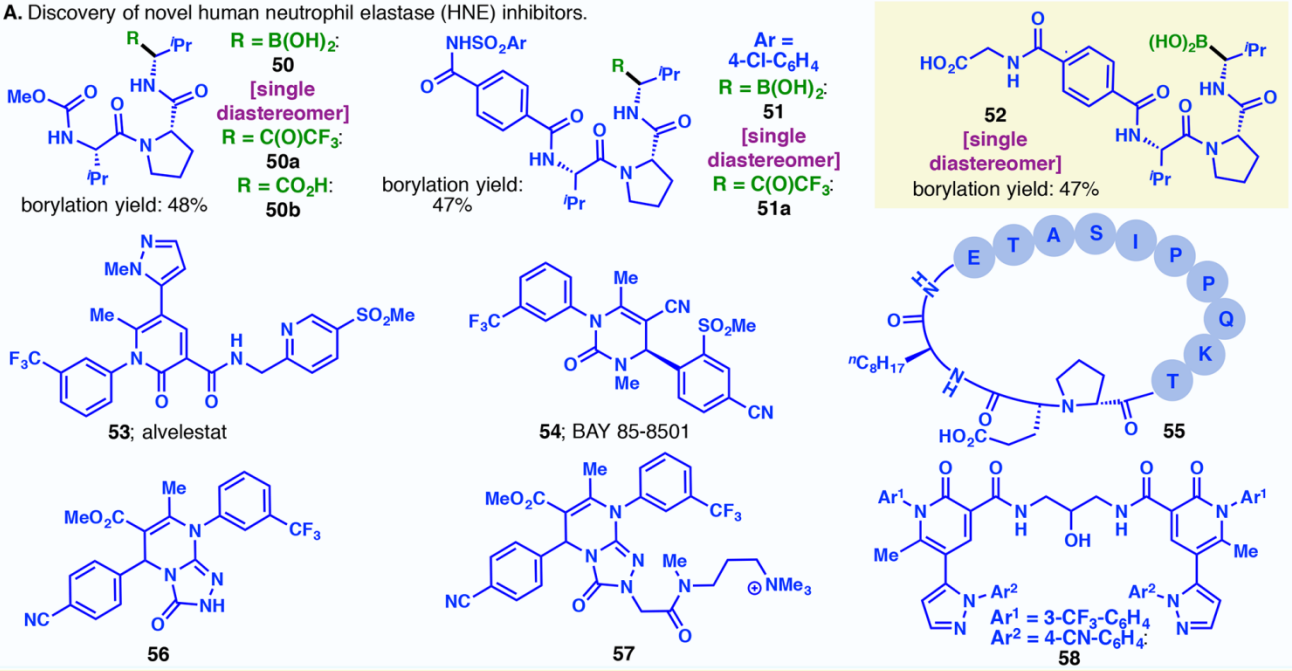
Fig. 2. Scope of the Ni-catalyzed decarboxylative borylation reaction of redox-active esters. *Standard reaction conditions*: Redox-active NHPI ester (1.0 equiv.), $NiCl_2$•$6H_2O$ (10 mol%), ***L1*** (13 mol%), $MgBr_2$•OEt_2 (1.5 equiv.), [B_2pin_2 (3.3 equiv.), MeLi (3.0 equiv.)] *pre-complexed*, THF/DMF (2.5: 1), 0°C to room temperature (RT), 2 hours. Footnotes: * Using THF as the solvent. † Using ***L2*** as the ligand. ‡ Using tetrachloro-*N*-hydroxyphthalimide (TCNHPI) ester. § Using 1.0 equiv. of $MgBr_2$•OEt_2. ¶ Using 2.5 mol% of $NiCl_2$•$6H_2O$ and 3.3 mol% of ligand (***L1*** or ***L2***). See the supplementary materials for experimental details.



MIC (mg/mL)	*S. aureus*	MRSA	*E. faecium*	*E. faecium**	*E. faecalis*†
44	16	16	8	>64	16
43	2	2	4	>64	8
vancomycin	0.5	0.5	0.5	>64	16

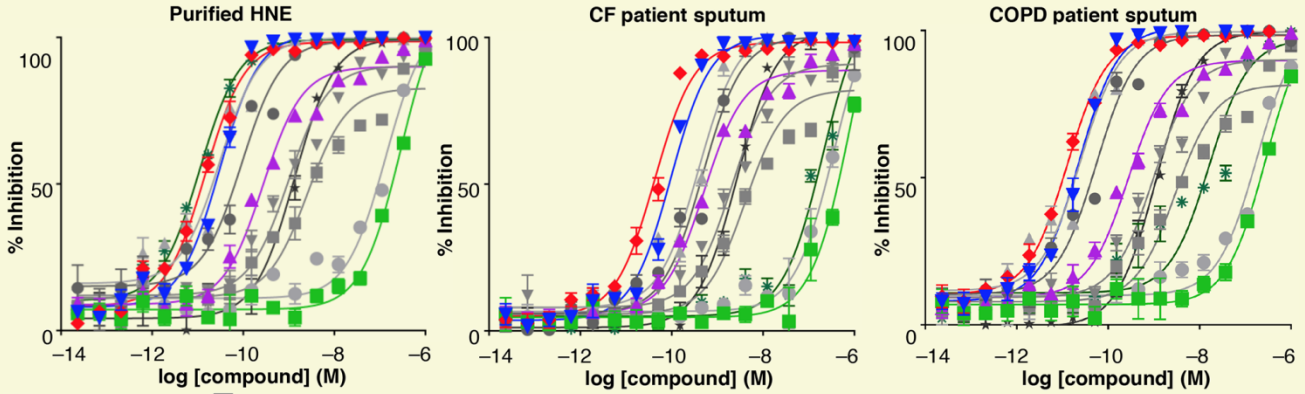
Fig. 3. Applications of the decarboxylative borylation reaction. (A) Late-stage diversification of Lipitor. (B) Synthesis and biological evaluation of **44**, a boronic acid analog of vancomycin. (C) Probing the stereoselectivity of peptide substrates and the ensuing stereoselective synthesis of velcade (**49**). Footnotes: * VRE(VanA). † VRE(VanB). ‡ Yield and diastereoselectivity refer to the decarboxylative borylation of the corresponding RAE. See the supplementary materials for experimental details.

A. Discovery of novel human neutrophil elastase (HNE) inhibitors.



B. Inhibitory activites of HNE inhibitors.

Compound	*Purified NHE*		*CF sputum*		*COPD sputum*	
	IC_{50}/nM	LipE	IC_{50}/nM	LipE	IC_{50}/nM	LipE
50–$B(OH)_2$	0.27±0.02	8.37	0.51±0.04	8.09	0.274±0.004	8.36
50a–$C(O)CF_3$	135±12	4.57	358±55	4.15	179±15	4.45
50b–CO_2H	Not Active	N.A.	N.A.	N.A	N.A.	N.A.
51–$B(OH)_2$	0.030±0.002	7.33	0.096±0.002	6.83	0.0223±0.0006	7.46
51a–$C(O)CF_3$	290±32	1.95	833±221	1.49	282±23	1.96
52–$B(OH)_2$	0.015±0.001	10.1	0.043±0.002	9.62	0.0127±0.0008	10.2
53	2.62±0.39	7.32	4.08±0.39	7.11	2.98±0.82	7.22
54	0.031±0.002	6.76	0.40±0.04	5.87	0.024±0.003	6.85
55	0.093±0.008	18.6	0.48±0.03	17.8	0.051±0.004	18.8
56	1.34±0.13	4.59	2.68±0.04	4.29	1.12±0.04	4.67
57	0.99±0.13	9.46	2.04±0.08	9.16	0.97±0.14	9.45
58	0.0111±0.0002	5.04	203±31	0.77	16.2±2.1	1.87



C. Pharmacokinetic profile of selected HNE inhibitors.

Compound	Kinetic solubility (pH 6.8) [μM]	CD-1 Mouse Plasma % remaining after 2 hours [%]	Microsomal stability (mouse extraction ratio)
51–$B(OH)_2$	>200	90.3%	<0.3
51a–$C(O)CF_3$	174.28	106.6%	0.5
52–$B(OH)_2$	>200	79.2%	<0.3

Fig. 4 (preceding page). Discovery of novel human neutrophil elastase (HNE) inhibitors. (**A**) Structures of selected elastase inhibitors. (**B**) IC_{50} values (nM) of selected elastase inhibitors (Average ± SD, n=3 plotted, representative of 3 independent, triplicate experiments). A non-linear, 3-parameter log inhibitor curve was used to calculate the IC_{50} values. Curve fit statistics: purified HNE, $R^2 \geq 0.95$, CF patient sputum, $R^2 \geq 0.93$, COPD patient sputum, $R^2 \geq 0.93$. (**C**) ADME profile of **51**, **51a**, and **52**.

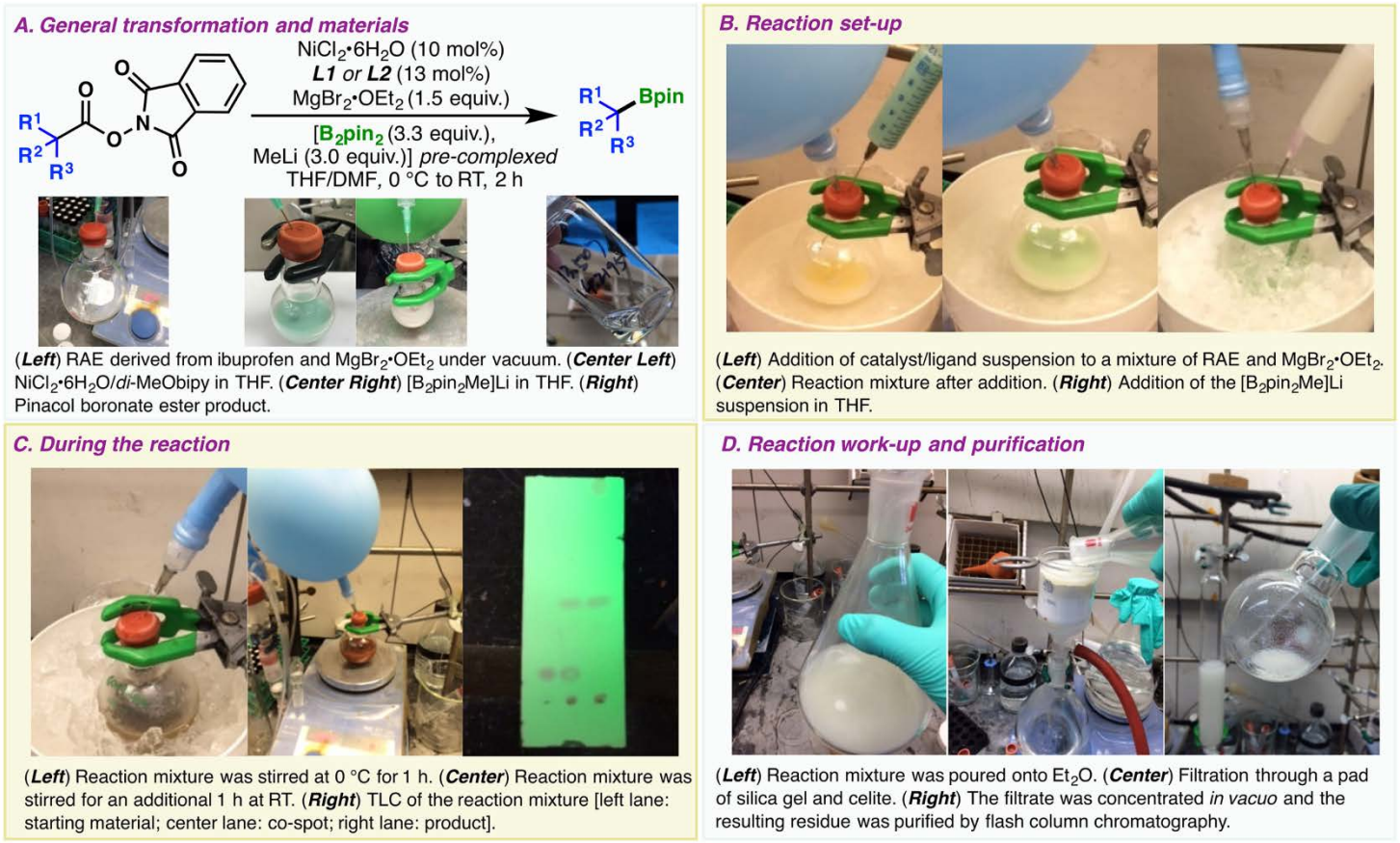


Fig. 5. A graphical guide to the decarboxylative borylation reaction. (A) General transformation and materials for the reaction. (B) Addition of reagents. (C) Observations during the reaction. (D) Work-up and purification of the reaction mixture.

Decarboxylative borylation

Chao Li, Jie Wang, Lisa M. Barton, Shan Yu, Maoqun Tian, David S. Peters, Manoj Kumar, Anthony W. Yu, Kristen A. Johnson, Arnab K. Chatterjee, Ming Yan and Phil S. Baran (April 13, 2017)

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