Pinene-Derived Iminodiacetic Acid (PIDA): A Powerful Ligand for Stereoselective Synthesis and Iterative Cross-Coupling of C(sp\(^3\)) Boronate Building Blocks

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Supporting Information

ABSTRACT: Efficient access to chiral C(sp\(^3\)) boronates in stereocemically pure form is critical for realizing the substantial potential of such building blocks in complex-molecule synthesis. We herein report that a pinene-derived iminodiacetic acid (PIDA) ligand enables the highly diastereoselective synthesis of a wide range of oxiranyl C(sp\(^3\)) boronates from the corresponding olefins. These oxiranyl PIDA boronates, in turn, can be readily transformed into unprecedented stable α-boryl aldehydes via a novel 1,2-migration of the boronate group that proceeds with complete maintenance of stereocemical purity. B-Protected haloboronic acids containing dual sp\(^3\)-hybridized C centers are readily accessible via this platform, and the herein demonstrated capacity for stereocontrolled iterative C(sp\(^3\)) cross-coupling with this novel type of bifunctional reagent to access a medicinally important chiral small-molecule target in highly enantiomeriched form represents a substantial advance for the building-block-based approach to synthesis.

In an idealized form of the building-block approach for small-molecule synthesis, off-the-shelf subunits having all the required functional groups preinstalled in the correct oxidation states and with the desired stereochemical relationships are brought together using a single reaction iteratively. Toward this goal, we have developed N-methyliminodiacetic acid (MIDA) boronates as a highly versatile platform of building blocks. Recent advances in the stereocontrolled cross-coupling of C(sp\(^3\)) boronates suggest that the generality of this approach could be substantially increased. C(sp\(^3\)) boronates also represent highly versatile intermediates for a wide range of other applications. To realize all of this potential, highly stereoselective methods for accessing such intermediates are critical. We herein report the discovery of a pinene-derived iminodiacetic acid (PIDA) ligand that enables the facile synthesis of a wide range of versatile C(sp\(^3\)) boronate building blocks in a highly stereocontrolled fashion. We further demonstrate that iterative C(sp\(^3\)) cross-coupling with B-protected haloboronic acids containing dual sp\(^3\) hybridized C centers derived from this platform can substantially expand the scope of the building-block-based approach for small-molecule synthesis.

The remarkable stability of the MIDA boronate motif under a wide range of common reaction conditions enables the transformation of simple boron-containing starting materials into many types of complex boronate building blocks. Importantly, the crystal structures of many MIDA boronates have revealed that the N-methyl substituent is always closely positioned to the organic group appended to the boron atom, and variable-temperature NMR studies have demonstrated that the iminodiacetic acid framework is conformationally rigid in solution. Collectively, these observations suggested that if the N-alkyl substituent of iminodiacetic acid were chiral, highly effective transfer of stereocemical information might be achieved during functionalizations of the corresponding boronates as a result of the enforced proximity (Figure 1). In view of the exceptional versatility of epoxides in the preparation of many other chiral building blocks, we first questioned whether the epoxidation of alkenylboronates could be rendered asymmetric via such modifications of the MIDA ligand.

We surveyed a range of iminodiacetic acid ligands derived from different chiral amines and discovered that ligand 1a (PIDA), which can be easily prepared from very cheap and readily available (+)-α-pinene, is exceptionally effective. Specifically, treatment of the corresponding styrenyl PIDA boronate 2a with m-chloroperbenzoic acid (mCPBA) under standard conditions yielded oxiranyl PIDA boronate 3a with outstanding diastereoselectivity (Table 1, entry 1). Alternatively linking the pinene-derived appendage via a conformationally flexible methylene spacer (1b) or employing some other less sterically bulky chiral secondary amine (1c or 1d) resulted in substantially reduced diastereoselectivity (entries 2–4).

Single-crystal X-ray analysis of 3a (Table 1, entry 1) revealed that despite N-alkylation with a very sterically bulky substituent, the [3,3,0]-bicyclic structure of the iminodiacetic acid motif was preserved, with the chiral alkyl group positioned <2.4 Å from the newly formed epoxide. Moreover, variable-temperature NMR analysis confirmed that the iminodiacetic acid framework of the PIDA ligand was conformationally rigid in both the starting material 2a and the product 3a. Collectively, these findings are
consistent with the conclusion that highly effective transfer of stereochemical information in this system is attributable to the enforced proximity between the chiral appendage and the site of reactivity in the transition state of the epoxidation reaction.

Fortunately, both enantiomers of \( \alpha \)-pinene are cheap and readily available on a very large scale, so PIDA has the potential to serve as a very practical chiral auxiliary. 11 We therefore explored the capacity of this ligand to enable the diastereoselective epoxidation of a variety of alkenylboronates. As shown in Table 2, the series of trans-1,2-disubstituted olefins \( 2a \) and \( 2e–i \) all were efficiently epoxidized in good yields and with outstanding stereosecontrol (entries 1–6). PIDA boronate \( 2a \) could also be epoxidized on a 15 mmol scale and isolated via simple crystallization (entry 1). Cis-1,2-disubstituted and trisubstituted olefins were also very effective substrates (entries 7 and 8). Somewhat diminished but still synthetically useful diastereoselectivities were observed with 1,1-disubstituted olefins \( 12 \) (entries 9 and 10). Strikingly, even the smallest olefin, vinyl PIDA boronate \( 2n \), was epoxidized with outstanding diastereoselectivity (entry 11). Importantly, all of the oxiranyl PIDA boronates \( 3 \) were produced as crystalline free-flowing solids that were completely stable toward silica gel chromatography and benchtop storage under air, making them highly desirable chiral building blocks for many applications in complex-molecule synthesis.

In this vein, preliminary studies also revealed that oxiranyl PIDA boronates can be transformed into previously inaccessible C(sp\(^3\)) boronate building blocks. For example, Mg(ClO\(_4\))\(_2\) promotes a very interesting Meinwald rearrangement\(^{13}\) of \( 3a \) to generate air-stable \( \alpha \)-boryl aldehyde \( 4 \) (Scheme 1). To the best of

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Table 1. Diastereoselective Epoxidations of Various Iminodiacetic Acid-Based Alkenylboronates

| Entry | Product | \( \alpha \)-pinene SIDA (PIDA) | Oxiranyl PIDA (3) | Diastereomeric ratio |
|-------|---------|--------------------------------|-------------------|---------------------|
| 1     | ![Structure 1](image) | ![Structure 2](image) | ![Structure 3](image) | >20:1 |
| 2     | ![Structure 4](image) | ![Structure 5](image) | ![Structure 6](image) | 2.1:1 |
| 3     | ![Structure 7](image) | ![Structure 8](image) | ![Structure 9](image) | 2.7:1 |
| 4     | ![Structure 10](image) | ![Structure 11](image) | ![Structure 12](image) | 1.6:1 |

\( ^{a} \) Diastereomeric ratios determined via 500 MHz \(^1\)H NMR analysis of the unpurified reaction mixtures.

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Table 2. Highly Diastereoselective Epoxidations of a Wide Range of Alkenyl PIDA Boronates

| Entry | Product | Oxiranyl PIDA (3) | Diastereomeric ratio |
|-------|---------|-------------------|---------------------|
| 1     | ![Structure 13](image) | ![Structure 14](image) | >20:1 |
| 2     | ![Structure 15](image) | ![Structure 16](image) | 20:1 |
| 3     | ![Structure 17](image) | ![Structure 18](image) | 20:1 |
| 4     | ![Structure 19](image) | ![Structure 20](image) | 20:1 |
| 5     | ![Structure 21](image) | ![Structure 22](image) | 20:1 |
| 6     | ![Structure 23](image) | ![Structure 24](image) | 20:1 |
| 7     | ![Structure 25](image) | ![Structure 26](image) | 17:1 |
| 8     | ![Structure 27](image) | ![Structure 28](image) | 20:1 |
| 9     | ![Structure 29](image) | ![Structure 30](image) | 11:1 |
| 10    | ![Structure 31](image) | ![Structure 32](image) | 5:1 |
| 11    | ![Structure 33](image) | ![Structure 34](image) | 20:1 |

\( ^{a} \) Isolated yields after silica gel chromatography. \( ^{b} \) The stereochemistries of epoxides \( 3a, 3g, \) and \( 3n \) were all determined unambiguously via single-crystal X-ray analysis. The remaining product configurations were assigned by analogy. \( ^{c} \) Diastereomeric ratios determined via 500 MHz \(^1\)H NMR analysis of the unpurified reaction mixtures. \( ^{d} \) Conducted on a 15 mmol scale and isolated by crystallization."
Scheme 2

containing dual sp³-hybridized C termini into a medicinally important chiral small-molecule target via highly efficient and flexible iterative C(sp³) cross-coupling represents a major step toward generalizing this building-block approach to synthesis.

ASSOCIATED CONTENT

Supporting Information. Procedures, spectral data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Information for details.

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recent reports by Crudden and co-workers.4a,4b