PIEF-GA-2010-274783. Final report / proposal acronym “TASTE”.
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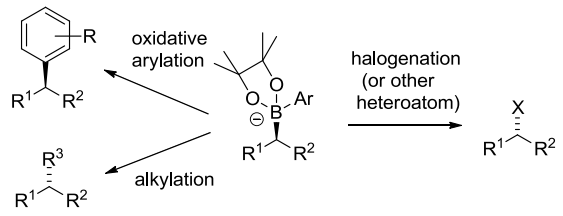
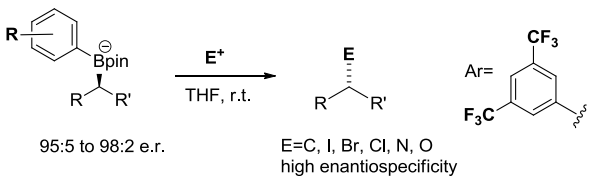
The carbon-boron bond is a highly useful synthetic handle in organic synthesis since there are numerous methods for its introduction with high enantioselectivity. Amongst these methods, the Aggarwal group has reported that boronic esters can be homologated using stereodefined Hoppe’s lithiated carbamate to generate chiral secondary and tertiary boronic esters with very high ee. Our proposal for the Fellowship was focused on expanding the synthetic utility of the newly created chiral boronic esters through further ground-breaking transformations for which there were no current precedents including: a) the stereoselective replacement of boron to halides and other heteroatoms, b) the reaction of boronic esters with carbon electrophiles and c) their oxidative arylation as a conceptually novel approach to (metal-free) cross coupling of secondary organometallics. We have progressed significantly with regard to a) and b) during the course of the fellowship. In particular, since the mid-term report we have been able to extend the chemistry of boron-ate complexes to include additions to N-containing heterocycles, such as quinolone and pyridine. This chemistry has now been developed and a manuscript is under preparation for a peer-reviewed publication.



Scheme 1. New transformations of secondary alkylboronic esters

Stereoselective replacement of boron to halides and other heteroatoms and reaction with carbon electrophiles. Extension of the chemistry to new C-electrophiles.

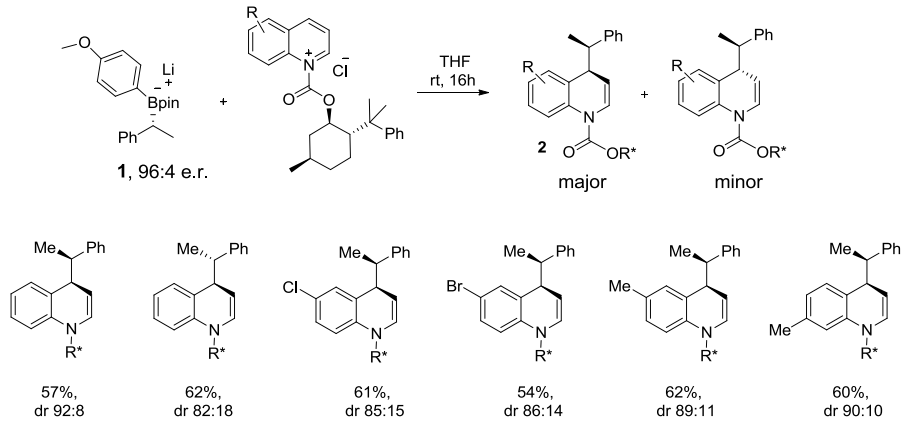
Recently we published our progress in realizing some of these endeavors in a manuscript that described the stereodefined reaction of boron-ate complexes with a variety of electrophiles including carbon, nitrogen, oxygen and halide-based ones (*J. Am. Chem. Soc*. **2011**, *133*, 16794-16797). Within our efforts towards the development of new configurationally stable chiral organometallics, we discovered that boron-ate complexes of chiral boronic esters can react with electrophiles always with inversion of configuration. Thus, indeed the addition of an aryllithium to a chiral secondary pinacol boronic ester produces a boron-ate complex that transfers its chiral organic component with complete enantiospecificity to electrophilic carbon, nitrogen atoms and halides.



We next turned our attention to expanding on carbon-based electrophiles, since our initial report only contained two of them, namely tropylium tetrafluoroborate and dimethylmethylene ammonium iodide. Inspired from our promising result of dimethylmethylene ammonium iodide, we thought to elaborate on this chemistry and try to achieve other transformations involving imine or iminium-type electrophiles, and thus we employed pyridinium and quinolinium ions. In our mid-term report we mentioned some initial progress and preliminary results from these studies. We had identified optimum conditions and chiral auxiliaries that would render these reactions diastereoselective. During the rest of the fellowship period (second year) the fellow has developed a substrate scope for the reactions with quinoline, a method for auxiliary deprotection as well as studied and developed an unprecedented auxiliary-free asymmetric addition methodology, as a collaborative project with a PhD student of the Aggarwal group.

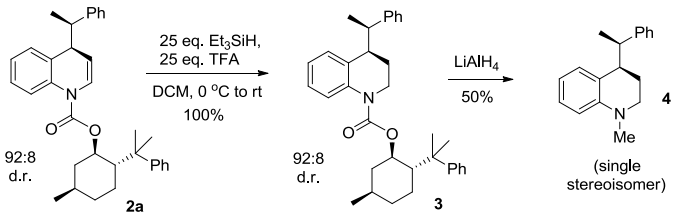
Concerning the auxiliary-controlled addition to quinoline, sequential addition of quinoline and the chloroformate of (-)-8-phenyl menthol to the boron-ate complex affords the dihydroquinoline [1,4]-adduct in a 57% yield and 92:8 diastereomeric ratio (Scheme 2). The ratio refers to the two diastereomers derived from the addition of the (*R*)-enantiomer boronic ester to the two sides of the

quinolinium ion (face selectivity). Two more isomers coming from the minor enantiomer boronic ester could sometimes be detected as well, but of course in very minor amounts. A number of differently substituted quinolines were used and the results are summarized in Scheme 2. The diastereoselectivity (or face selectivity) of the products was determined by HPLC analysis. Overall, the methodology was quite effective in terms of regio- and stereocontrol.



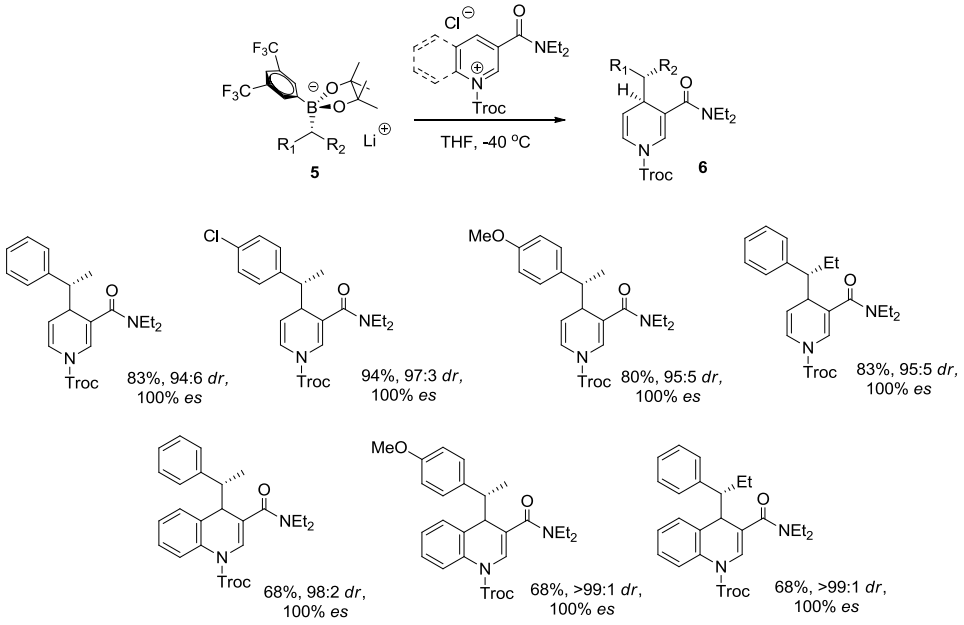
Scheme 2. Addition of boron ate complex 4 to quinoline activated by (-)-8-phenyl menthyl chloroformate

The products in Scheme 2 can be easily deprotected through reduction to give the corresponding methylamines. Product **2a** (d.r. 92:8) can be subjected to ionic reduction of the double bond using triethylsilane and trifluoroacetic acid to furnish tetrahydroquinoline **3** (d.r. 92:8). The major diastereomer of **3** then can be completely separated and subjected to $LiAlH_4$ reduction to afford chiral tetrahydro-*N*-methylquinoline **4** as a single enantiomer while *N*-(8)-phenylmenthol can be completely recovered.



Scheme 3. Deprotection of diastereoenriched dihydroquinoline **2a**

After completing this work, the fellow worked in collaboration with a first-year PhD student, Maziar Mohiti, on the identification of improved systems for steroselective additions of ate complexes without the need for chiral auxiliaries. In this vein, it was discovered that the use of 3-carboxamide substituted quinolines and pyridines can afford this type of additions, yielding dihydroquinoline and



Scheme 4. Auxiliary-free assymetric addition of boron ate complex to quinolines and pyridines

dihydropyridine products in very high diastereo- and enatioselectivities (the relative configuration is under investigation). This reaction has been developed with the use of various substituted boronic esters and the summary of our results can be seen in Scheme 4. The reaction represents a big step forward compared to most heterocyclic additions in the literature in the sense that it is a highly efficient asymmetric transformation without the need for chiral auxiliaries. A manuscript for this work is under preparation.

Conclusion: During the course of the Fellowship significant progress has been achieved towards our proposal goals. Our main objective in the proposal was the development of alkylations of boron-ate complexes, and this has been successfully addressed with the development of stereoselective additions to N-heterocycles. The milestones planned at the mid-term report were achieved and the proposal overall was realized to a good extent.