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Tandem Metal-Mediated Synthesis

R. Tom Baker*

Abstract

This is the final report of a one-year, Laboratory Directed Research and Development (LDRD) project at Los Alamos National Laboratory (LANL). Boronic acids $\text{RB}(\text{OH})_2$ are currently of interest for applications involving molecular recognition such as amine and sugar sensors and selective transport of biomolecules. They have also been shown to be powerful enzyme inhibitors and alpha-aminoboronic acids (ABAs) are particularly selective inhibitors of serine proteases. Unfortunately, current multistep synthetic routes to the latter compounds do not allow for the incorporation of a wide variety of organic substituents R^{1-3} that may lead to new, more selective enzyme inhibitors. In this work we describe several direct routes to ABAs based on metal-catalyzed addition of diboron compounds to imines and nitriles. Several other applications of diboron additions to heteroatom-containing unsaturated organics are also described.

Background and Research Objectives

Boronic acids $\text{RB}(\text{OH})_2$ are currently of interest for applications involving molecular recognition such as amine and sugar sensors,¹ and selective transport of biomolecules.² They have also been shown to be powerful enzyme inhibitors and alpha-aminoboronic acids (ABAs—see Figure 1) are particularly selective inhibitors of serine proteases.³

Figure 1. Structure of alpha-aminoboronic acids.

Unfortunately, current multi-step synthetic routes⁴ to the latter compounds do not allow for the incorporation of a wide variety of organic substituents R^{1-3} that may lead to new, more selective enzyme inhibitors. We and others have recently shown that addition of tetraalkoxydiboron compounds to unsaturated organics such as alkenes⁵ and alkynes⁶ can be catalyzed by transition metal complexes. We also demonstrated previously the metal-

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catalyzed hydroboration of imines to give N-borylamines.⁷ Extension of the catalyzed diboron addition to imines as shown in Figure 2 provides a direct, one-step route to a variety of ABAs, which will be tested for biological activity by our pharmaceutical company partner.

Figure 2. Proposed direct route to alpha-aminoboronic acids.

As this project proceeded we discovered the metal-catalyzed diboration of nitriles, which can provide alternative direct routes to ABAs. In addition, we found that the uncatalyzed addition of diboron compounds to imines affords N-boryl diamines stereoselectively (i.e. no meso diastereomer is formed). Hydrolysis of these compounds gives the *racemo* diamines, which are useful ligands for homogeneous catalysis. In fact, these ligands were a major factor in attracting Akzo Nobel and Caltech to participate in a joint research project on homogeneous alkane activation, recently funded by DOE-EE-OIT.

Importance to LANL's Science and Technology Base and National R&D Needs

Production of high value chemicals to be sold as drugs or agrochemicals by the chemical and pharmaceutical industries often involves multistep preparations that generate significant amounts of chemical waste. One of the goals of our research is the discovery of new types of *tandem catalysis*, which will allow several synthesis steps to be performed in the same pot and will significantly reduce the production of chemical waste. The discovery of new catalytic reactions also enhances the LDRD initiative in Catalysis Science, which encompasses a multidisciplinary effort (chemistry, engineering, computation, neutron

scattering, solid state NMR, and surface characterization) at the interface of homogeneous and heterogeneous catalysis.

Scientific Approach and Accomplishments

We have initiated studies to prepare alpha-aminoboronic acids by direct routes that rely on metal-catalyzed diboration of imines and nitriles. In the course of these studies we discovered that the diboron compound also promotes the uncatalyzed, stereospecific reductive coupling of imine substrates to give N-boryldiamines with a two-carbon backbone (Figure 3). The efficiency of this coupling can be controlled by changing the dialkoxy substituents on the diboron compound (i.e. for R = alkyl, the phenylethanediol-derived diboron compound gives higher yields of the diamine) and we are filing for patent protection of this work.

Figure 3. Stereoselective imine coupling using diboron compounds.

The use of chiral dialkoxy substituents on boron also offers the possibility of preparing optically pure diamines. The wide variety of imines readily available from aldehydes and amines make this a powerful route to a range of C_2 -symmetric diamines, which will be useful for other applications within the LANL Catalysis Science initiative.

Metal-catalyzed diboration of aldimines gives a mixture of diboration and borylation depending on the regiochemistry of imine insertion into the M-B bond (Figure 4). We are developing a hydrolysis/hydrogenation work-up procedure to obtain the desired alpha-aminoboronic acids.

Figure 4. Metal-catalyzed addition of diboron compound to aldimines.

Ketimines give N-boryl enamines resulting from beta-hydrogen elimination of the methyl C-H bond (Figure 5). Metal-catalyzed hydroboration of the resulting activated enamines is currently being pursued.

Figure 5. Metal-catalyzed addition of diboron compound to ketimines.

Rh-catalyzed diboration of nitriles gives the desired addition of the B-B bond across the $\text{C}\equiv\text{N}$ triple bond to give diborylimines (Figure 6). Subsequent hydroboration or hydrogenation of

Figure 6. Metal-catalyzed addition of diboron compound to nitriles.

these diborylimines should provide a direct route to alpha-aminoboronic acids (Figure 7), which also has potential for controlling the stereochemistry using a Corey borane reduction with a chiral auxiliary or an asymmetric hydrogenation using the Novartis iridium phosphine catalyst.

Figure 7. Hydroboration or hydrogenation of diborylimines should give primary ABAs.

Preliminary studies (Figure 8) with carbonyl compounds such as acetophenone indicate that Pd-catalyzed diboration forms diborylether and a metal carbene, which subsequently inserts into the enolizable C-H bond of another substrate, followed by β -H elimination to give the enone. The Ru-catalyzed reaction gives the α -styryl ether, presumably by reaction of the metal carbene with the enol form of acetophenone. We will attempt to use this unique reactivity to construct medium-sized rings from inexpensive aliphatic precursors.

Figure 8. Metal-catalyzed deoxyoligomerization of acetophenone using diboron compound.

Publications

1. "Metal-Catalyzed Multiple Boration of Enamines", R. T. Baker,* T. M. Cameron, S. A. Westcott,* submitted to *Chem. Commun.*, **1998**.
2. "Process for the Stereoselective Coupling of Imines using Diboron Compounds," R. T. Baker, T. M. Cameron, S. A. Westcott, U.S. Patent application, in progress.
3. "Metal-Catalyzed Deoxyoligomerization of Carbonyl Compounds," R. T. Baker, T. M. Cameron, J. M. Boncella, in preparation for submission to *J. Am. Chem. Soc.*, **1998**.

Invited Presentations

"Metal-Catalyzed Diboration of Imines: One-Step Preparation of α -Aminoboronic Acids," R. T. Baker,* T. M. Cameron, S. A. Westcott,* Canadian Society of Chemistry National Meeting, Windsor, ON, Canada, June **1997**.

"Metal-Catalyzed Hydroboration and Diboration of Functionalized Alkenes and Multiple C-X Bonds (X = N, O, S)," R. T. Baker, 5th Chemical Congress of North America, Cancun, Mexico, November, **1997**.

"Metal-Catalyzed Diboration of Imines: Applications to Enzyme Inhibitors and Chiral Diamines," R. T. Baker, University of Alberta and University of Calgary, October, **1997**.

"Metal-Catalyzed Addition of Diboron Compounds to Heteroatom-Containing Unsaturated Organics," R. T. Baker, Organometallic Chemistry Gordon Research Conference, Newport, RI, July, **1998**.

"Tandem Catalysis And Novel Reaction Media For Addition Of B-X Bonds To Unsaturated Organics," M. B. Abrams, R. T. Baker, T. M. Cameron, C. A. Carter, S. A. Nolan, W. Tumas, S. A. Westcott, Symposium on Catalysis by Design, Catalysis Secretariat, ACS National Meeting, Boston, MA, August, **1998**.

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