ORGANIC
LETTERS

2002
Vol. 4, No. 25
4391−4393

Computer-Aided Design of Chiral Ligands. Part III. A Novel Ligand for Asymmetric Allylation Designed Using Computational Techniques

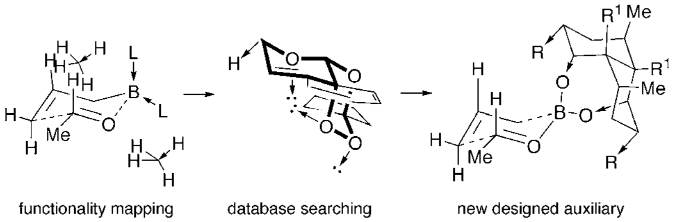
Marisa C. Kozlowski,* Stephen P. Waters, Jason W. Skudlarek, and Catherine A. Evans

Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, Philadelphia, Pennsylvania 19104

marisa@sas.upenn.edu

Received September 26, 2002

ABSTRACT



Computer-aided design protocols to identify new chiral ligands for reactions proceeding through well-defined transition states are outlined. Ligand families are discovered via computational screening of large structural databases such as the Cambridge Structural Database. Using this method, a novel *cis*-decalin ligand has been identified as a chiral auxiliary for the allylboration of aldehydes. Synthesis, resolution, and evaluation revealed that this new auxiliary provided the aldehyde facial approach upon which the design was predicated.

Diastereo- and enantioselective chemical reactions have become essential for the efficient synthesis of complex chiral targets. Much progress has been made in developing nonenzymatic asymmetric methodology; however, good stereoselective versions of many reactions remain unavailable. One driving force for the development of effective chiral auxiliaries and catalysts for asymmetric reactions is the identification of the appropriate chiral ligands. To this end, we have developed a computational method to identify new chiral ligand classes by screening large numbers of potential ligands motifs.

We chose to examine the boron allylation in this context because it has been examined extensively experimentally and theoretically.[1,2] The absence of turnover as well as elements past the second row simplifies any computational analysis. Numerous auxiliaries and catalysts have been developed for the boron allylation reaction,[1] but some variants, particularly anti crotyl additions, remain problematic.

Only a single reaction step needs to be modeled in the allylation reactions of unsubstituted alkenes; the product ratios are controlled by the free energies of the illustrated transition states (Figure 1). The rational design of asymmetric boron allylation reactions has been aided by the development of a molecular mechanics force field;[2d,e] however, prior computational efforts have been restricted to the prediction of stereoselectivity for given systems.[3] In this communication, the use of computational methods for the *generation*, as well as for the evaluation, of novel chiral auxiliaries is addressed.

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(1) For lead references: *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I. Eds.; Pergamon Press: Oxford, 1991; Vol. 2.

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(3) For examples in other systems, see: *Transition State Modeling for Catalysis;* Truhlar, D. G., Morokuma, K., Eds.; ACS Symposium Series 721; American Chemical Society: Washington, DC, 1999; and references contained therein.

10.1021/ol026971w CCC: $22.00

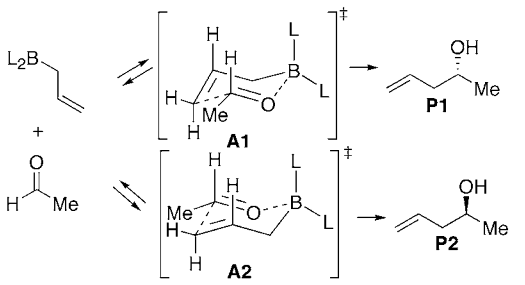

Figure 1. Boron allylation reaction.

Computational methods can aid in the generation of chiral auxiliaries and catalysts by providing increased efficiency, an improved rational basis, and leads usually available only by intuitive leaps. The multiple step design procedure for chiral ligands **2** and **3**, designed to control the absolute stereochemistry in the allylation reaction, is outlined in Figure 2 and the following paragraphs. Well-defined monomeric boat and chair transition states[2] have been postulated to account for the product distributions in boron allylation reactions. As a first step, the more stable chair **A** was chosen as a starting point.

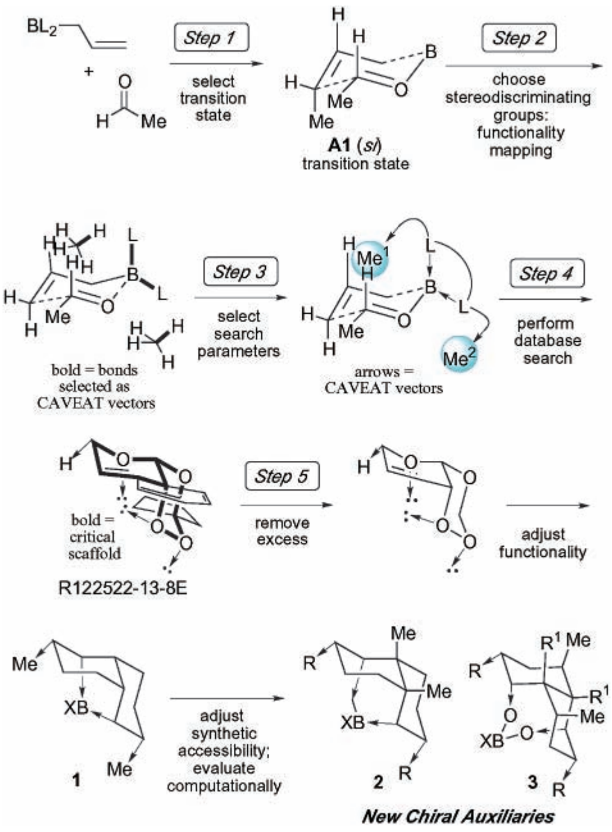

Figure 2. Design procedure illustrated for ligands **2** and **3**.

In the second step, stereodiscriminating groups are selected from models of previously successful chiral ligands or are generated around the desired transition state by functionality mapping. The intent is to design ligands that place a key stereodiscriminating moiety to incur favorable (or at least no disfavorable) nonbonded interactions in one enantiomeric transition state and to incur disfavorable nonbonded interactions in the other enantiomeric transition state. The positions of these “stereodiscriminating groups” (in this case, methanes that stand in for a methyl substituent on a ligand) were determined by functionality mapping[4] of the enantiomeric transition states (**A1** and **A2**). This allowed the selection of methane positions (Me^1 and Me^2) that would disfavor **A2** sterically and complement **A1** (Figure 3).

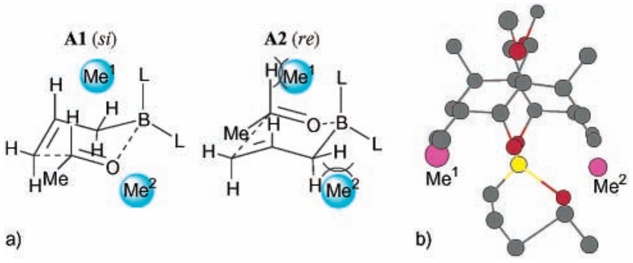

Figure 3. (a) Step 2 in the design procedure. Illustration of the Me^1 and Me^2 groups selected from the functionality mapping. (b) Overlay of the Me^1 and Me^2 groups used in the CAVEAT search (purple spheres) with the new ligand **3** appended to the A1 transition state.

In the third and fourth steps, three-dimensional databases such as the Cambridge Structural Database and the Chemical Abstracts Service (CAS) three-dimensional database are searched using CAVEAT[5,6] for molecules that can position the two methanes and the boron with the indicated placement and orientation. This methodology could also be applied to other databases such as the Fine Chemicals Directory or corporate databases allowing for selection of *readily available* ligands. The resultant lead compounds are classified into structural subgroups and then analyzed. The enantiomer of CAS structure 122522-13-8 represents a typical lead that satisfies the design criteria. This lead could not be used directly, but the basic scaffold (*cis*-decalin) provided the insight for the design of decalin-based ligand **1** (step 5). Since ligand **1** is not readily synthesized, several modifications were incorporated resulting in analogues **2** and **3**. The resultant compounds **1**−**3** were examined with respect to the initial search parameters used, namely, the initial methane groups Me^1 and Me^2. Overall, ligand **3** places the two methyl groups very close to the desired positions (Figure 3b).

In an encouraging affirmation of the validity of this strategy, lead structures corresponding to the Masamune dimethyl-borolane[7] and the Corey stein reagent[8] were also

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(5) Kozlowski, M. C.; Panda, M. *J. Mol. Graphics Model.* **2002**, *20*, 399−409.

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(7) Short, R. P.; Masamune, S. *J. Am. Chem. Soc.* **1989**, *111*, 1892−1894.

found when a different set of input stereodiscriminating groups was used.[5]

The decalin ligands could have been envisioned as a ligand for boron allylation reactions without the intervention of this design protocol. However, the benefit of this method lies in the large number of potential scaffolds that can be rapidly and efficiently screened by the end user. Furthermore, the databases of compounds employed allow the user to identify structure types with which the user may not necessarily be familiar.

Finally, the ligands are evaluated theoretically for potential selectivity. Analysis of simple stereochemical models based on six-membered transition states reveals that these compounds possess asymmetric environments (Figure 4). Furthermore, transition states in which the prochiral aldehyde is approached from the *re* face contained disfavorable nonbonded interactions between the ligand and the six-membered transition state core, which are largely absent in transition states involving approach from the *si* face.

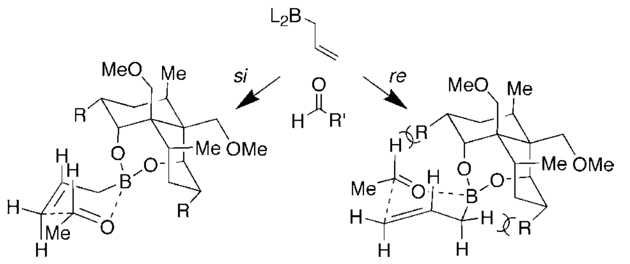

Figure 4. Stereochemical boron allylation models of **3**.

To determine if ligands such as **2** and **3** can control the stereochemical course of these reactions as envisioned, the synthesis of compound **3** was undertaken.[9] The synthesis of diol **3** is straightforward and employs the strategy of Lautens[10] for the nucleophilic ring-opening of oxabicyclic compound **4** (Figure 5). Directed hydrogenation of **5** provided the requisite diols **3**, which were resolved using chiral chromatography. An X-ray crystal structure indicated that **3b** adopted the indicated conformation with axially disposed hydroxyls. From the ^{1}H NMR spectra, this conformation persisted in solution.

Treatment of **3** with trisallylborane provided the requisite allylboronates **6** cleanly as judged by ^{1}H and ^{11}B NMR spectroscopy (Figure 5). These reagents were anticipated to display *si* facial selectivity (≥85:15 *si:re*) in additions to aldehydes on the basis of the stereochemical models depicted in Figure 4 and transition state calculations (MM2*, AM1, HF). Upon treatment of **6a** and **6b** with dihydrocinnamaldehyde, *si* facial selectivity was indeed observed (55:45 and 71:29 *si:re*, respectively). The lower selectivity of **6a** compared to **6b** likely arises from a lower degree of occupancy of the positions indicated in Figure 3 by the pendant ethyl substituents compared to the *n*-butyl substituents. Nevertheless, the designed ligands fulfilled the basic criteria stipulated in the design process: favoring one reactive pathway (*si* facial attack) over another (*re* facial attack). Furthermore, the observed selectivity (71:29 *si:re*, $\Delta\Delta G = 0.36$ kcal/mol) is within the error (0.2−0.5 kcal/mol) of the transition structure calculations (85:15 *si:re*, $\Delta\Delta G = 0.68$ kcal/mol). As such, refinements in these calculations will be instrumental in expanding the utility of this approach.

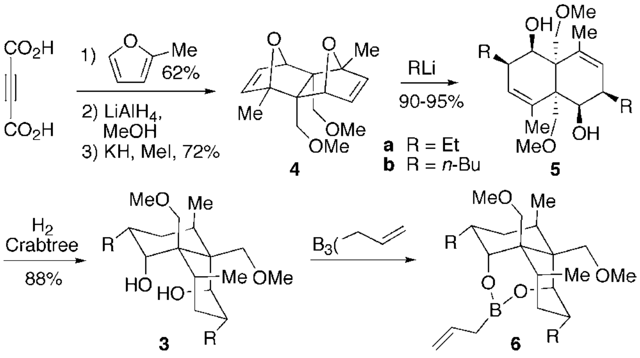

Figure 5. Synthesis of allyl boronates **6**.

In summary, a protocol for the design of new chiral ligands has been identified that uses transition structures as the starting input. In the particular case described above, ligands **1**−**3** were identified for boron allylation reactions. The designed compounds were anticipated to impart *si* selectivity in these reactions, which has been corroborated experimentally. Although the selectivity observed was only modest, a new ligand motif with a well-defined chiral environment has been identified that is finding utility in a variety of contexts.[11]

In addition to identifying new ligands, several other applications of the functionality mapping and database screening are possible. The functionality mapping can be used to determine which groups/interactions in stereoselective reactions are important. The database screening can be used to find alternate scaffolds for ligands that either perform well or are costly. Similarly, many ligand variants can be rapidly identified for reaction optimization if there is a lead in hand. Efforts are currently underway to examine such applications.

Acknowledgment. Financial support was provided by the National Institutes of Health (GM-59945), Merck Research Laboratories, and DuPont. Computing support was provided by the NCSA in the form of a supercomputing grant. The invaluable assistance of Dr. Patrick Carroll in obtaining the X-ray structure is gratefully acknowledged.

Supporting Information Available: Experimental details and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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