Catalytic Enantioselective Protoboration of Disubstituted Allenes. Access to Alkenylboron Compounds in High Enantiomeric Purity

Hwanjong Jang,† Byunghyuck Jung,† and Amir H. Hoveyda*

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, United States

ABSTRACT: Proto-boryl additions to 1,1-disubstituted allenes in the presence of 1.0−5.0 mol % of chiral NHC−Cu complexes, B2(pin)2, and t-BuOH proceed to alkenyl−B(pin) products in up to 98% yield, >98:2 site selectivity, and 98:2 er. The enantiomerically enriched alkenylboron products can be converted to otherwise difficult-to-access alkenyl bromides, methyl ketones or carboxylic acids. What’s more, the corresponding boronic acids may be used in highly stereoselective NHC−Cu-catalyzed allylic substitution reactions.

Allylmetal complexes occupy a prominent position in organic chemistry; reactions of these nucleophilic agents with carbonyl- and imine-containing compounds are a cornerstone of chemical synthesis. Nonetheless, methods for enantioselective protonation of allylmetal species are scarce. The difficulty in designing a catalytic enantioselective allyl anion protonation arises from the identification of a Bronsted acid that is compatible with the reaction conditions and contains a counterion component that allows proper acidity to be maintained while imparting sufficient bulk to cause stereochemical differentiation. We envisioned that if a 1,1-disubstituted allene (i, Scheme 1) were to undergo selective reaction with a chiral Cu−B(pin) complex (pin = pinacolato), and the resulting allylcopper (ii) were to be γ-selectively and enantioselectively protonated via iii, a Cu-catalyzed route to versatile unsaturated organoboron compounds (iv) would be in hand. The enantioselective C−H bond forming step would be distinct from other catalytic protoborations (i.e., γ proton transfer vs direct Cu−C bond protonation), affording entities that cannot be accessed by traditional hydroboration procedures. Herein, we report the realization of the above plan.

We first established a practical method for preparation of 1,1-disubstituted allenes (Scheme 2). Treatment of a propargylic phosphate, prepared in one step from the corresponding alcohol, with 5.0 mol % CuCl and an arylaluminum compound, accessed in situ by reaction of an aryllithium reagent and AlMe2Cl, furnishes the desired allenes typically in >60% yield with complete control of SN2′ selectivity. Transformations proceed to completion in 5 min to 1 h (depending on the scale).

We began by investigating the possibility of a chiral Cu catalyst promoting protoboration of 1a in a site-selective (2a vs 3a or 4a) and enantioselective fashion (Table 1). In our previous studies involving Cu−B(pin) additions to monosubstituted allenes in the presence of aldehydes and ketones, a chiral phosphine proved to be most effective (vs nonselective chiral NHCs). Accordingly, we first examined the representative protoboration process under the same parameters, Reaction with bis-phosphine 5 (R-SEGPHOS) generated 2a in 88:12 er along with 9% of 4a (entry 1, Table 1). Consistent with earlier investigations, the reaction with imidazolium salt 6a was much less enantioselective (63:37 er; entry 2), affording 14% of 3a as the byproduct. We reasoned that use of a more sizable alcohol might exacerbate the steric interactions within
the competing transition states for enantioselective protonation, leading to a rise in enantioselectivity. We therefore examined protoboration of 1a with t-BuOH (entries 3−4, Table 1); this resulted in a substantial improvement in enantioselectivity with bis-phosphine 5 (93:7 er). To our surprise, catalytic protoboration promoted by the NHC−Cu complex derived from 6a delivered the desired product not only in a similarly high er but also in a significantly improved yield (77% vs 53%) with superior site selectivity (98% vs 91% 2a and 3% 3a).

To account for the selectivity trends observed with the NHC−Cu complex derived from 6a, as well as the positive influence of a large alcohol reagent, we arrived at the stereochemical models depicted in Scheme 3. We surmised that two interactions could render III less favorable (vs II). One is engendered by the tilt of the NAr, causing the ortho unit of the NAr (blue sphere) to interact with the alcohol substituent (R); III might be less favored because of steric repulsion between the NAr’s para unit (red sphere) and the aryl group of the allene. The latter point led us to prepare and study imidazolinium salt 6b, which delivered some increase in enantioselectivity (95:5 vs 93:7 er). As will be demonstrated below, 6b, while requiring a longer synthesis route (6 vs 3 steps), in some cases delivers a better stereoselectivity profile.

Different 1,1-disubstituted allenes underwent catalytic protoboration efficiently and with high enantioselectivity (Scheme 4; for additional cases, see the Supporting Information). Allenes containing an ortho-, meta-, or para-substituted aryl group (2b−f) and those that bear a heteroaromatic moiety (e.g., 2g) were suitable substrates. Synthesis of 2h−j illustrates that reactions of allenes with larger alkyl units (vs Me) are facile. The data for the Cu complexes derived from bis-phosphine 5 as well as NHC ligands obtained from 6a−b highlight the characteristics of each system and illustrate that in all cases the NHCs are the ligands of choice. In many instances, the phosphine−Cu complex generated substantial amounts of inseparable isomeric products (e.g., 3 and 4); with methoxy-substituted 2c, the desired product constituted only 5% of the mixture, and in reactions to generate 2h−j, the corresponding allylboron compounds (4h−j) were formed. On several occasions, use of bis-phosphine 5 resulted in low to moderate enantioselectivity (e.g., 33:67 er for 2c, 16:84 er for 2f, 21:79 er for 2g and 2j). While 6a−b were often

Table 1. Evaluation of Chiral Complexes

| entry | ligand; alcohol | conv (%) | yield (%) | 2a/3a or 4a | er (%) |
|-------|----------------|----------|-----------|--------------|-------|
| 1     | 5; MeOH        | >88      | 71        | 8:2         | 12.68 |
| 2     | 6a; MeOH       | 89       | 90.14     | <2          | 63.37 |
| 3     | 6b; t-BuOH     | 97       | 91.29     | <2          | 7.90  |
| 4     | 6a; t-BuOH     | >88      | 77        | <2          | 99.7  |
| 5     | 6b; t-BuOH     | 89       | 78        | <2          | 95.5  |

a Reactions performed under a N2 atmosphere. b By analysis of 1H NMR spectra of the unpurified (for conv) or purified (for selectivity) mixtures (±2%). c Yields of purified products (±5%). d By GC analysis.
similarly effective, in some cases, the latter afforded significantly higher site selectivities in favor of 3 (cf. 2e and 2g). The general effectiveness of the NHC–Cu species is in stark contrast to additions of allylcopper species derived from Cu–B(pin) additions to aldehydes and ketones, where bis-phosphines such as 5 are optimal. These results underline the fundamental steric and geometric distinctions between the transition states involved in the reactions of B(pin)-substituted allylcopper species with aldehydes or ketones vs those involving proton addition.

The examples in Scheme 5 show that reactions of exocyclic 1,1-disubstituted allenes are efficient as well as site selective and stereoselective (cf. 7a–b).10 Similar efficiency and stereoselectivity levels were observed with substrates with an alkyl and a silyl substituent (cf. 8).11

The alkynyl–B(pin) products are versatile, as underscored by the transformations in Scheme 6. The first category deals with synthesis of alkenyl bromides (cf. 9a–b), precursors to many catalytic or noncatalytic C–C bond forming reactions; such entities cannot be easily accessed by alternative protocols.12 Exceptional enantiospecificity (es) was observed for reactions performed with CuBr2. The second set entails preparation of enantioselectively enriched α,α′-disubstituted ketones (cf. 10a–b).13 The mild oxidation process is complete in 30 min, furnishing ketones with >97% es. The alternative catalytic strategies (e.g., enantioselective allylations) have not been employed to prepare this type of α-substituted enantioselectively enriched methyl ketones.14 We have also developed a catalytic method15 for direct oxidation of enantioselectively enriched alkynyl–B(pin) products to carboxylic acids (Scheme 6).16 Enantioselective synthesis of nonsteroidal anti-inflammatory agent (S)-naproxen was carried out on 2.0 mmol scale with 1.0 mol % of 6b, affording the acid in 75% overall yield and 95:5 or (94% es).

We then investigated the possibility of directly using the alkenylboron compounds in stereoselective C–C bond formation. We selected allylic substitutions, partly because, to the best of our knowledge, chiral nucleophiles (enantioselectively enriched or otherwise) have not been utilized in this reaction class.17 However, our attempts to effect allylic substitutions involving 2a with various Cu-based complexes (achiral or chiral) led to <2% conversion (Scheme 7). Neopentyl glycol ester 12 and the trifluoroborate 13 were equally ineffective.

We subsequently prepared the less congested boronic acid R-14 (NaIO4, NH4OAc;18 83% yield) and determined that, with 5.0 mol % NH–Cu complex derived from 6c, it reacts to be 24.6-(i-Pr)C6H4.
afford 1,4-diene 15 in 62% yield with 98% S₉₂' selectivity and in 96:4 dr (>98% stereoselectivity). Cross-coupling with S-14 gave anti isomer 16 with similar site selectivity and efficiency (i.e., nearly complete catalyst control); here, 6d proved to be the more effective ligand. By comparison, when an achiral NHC−Cu complex, such as that derived from 17, was used, site selectivity (76:24 S₂₋₂:Sn₂) and stereoselectivity (80:20 dr) were substantially diminished.

Development of other catalytic proto-boryl additions and further mechanistic investigations are in progress.

■ ASSOCIATED CONTENT

Supporting Information
Experimental procedures and spectral data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

 ■ AUTHOR INFORMATION

Corresponding Author
*E-mail: amir.hoveyda@bc.edu.

Author Contributions
†H.J. and B.J. contributed equally.

Notes
The authors declare no competing financial interest.

 ■ ACKNOWLEDGMENTS

Financial support was provided by the NSF (CHE-136273) and the NIH (GM-47480).

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tetrasubstituted alkynyl-B(pin), 2% of the allyl-B(pin), and 46:54 er for the first isomer (>98% conv, 47% yield, 22:76:2 and 48:32 er with 6b).
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dx.doi.org/10.1021/ol5022417 | Org. Lett. 2014, 16, 4658–4661