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Diastereo- and Enantioselective Reactions of Bis(pinacolato)diboron, 1,3-Enynes, and Aldehydes Catalyzed by an Easily Accessible Bisphosphine–Cu Complex

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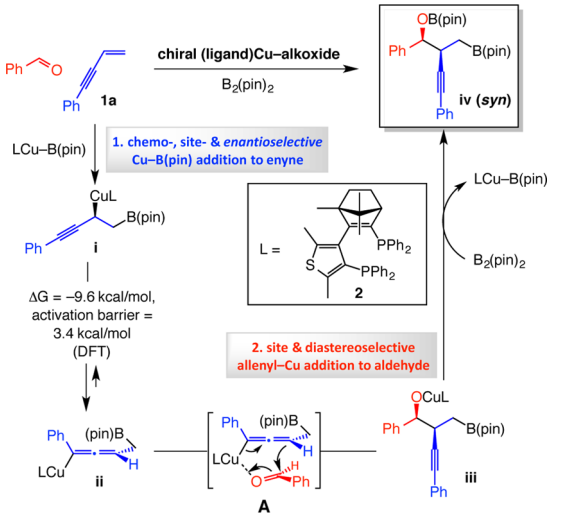
Supporting Information

ABSTRACT: Catalytic enantioselective multicomponent processes involving bis(pinacolato)diboron [$B_2(pin)_2$], 1,3-enynes, and aldehydes are disclosed; the resulting compounds contain a primary C–B(pin) bond, as well as alkyne- and hydroxyl-substituted tertiary carbon stereogenic centers. A critical feature is the initial enantioselective Cu–B(pin) addition to an alkyne-substituted terminal alkene. This and other key mechanistic issues have been investigated by DFT calculations. Reactions are promoted by the Cu complex of a commercially available enantiomerically pure bis-phosphine and are complete in 8 h at ambient temperature; products are generated in 66–94% yield (after oxidation or catalytic cross-coupling), 90:10 to >98:2 diastereomeric ratio, and 85:15–99:1 enantiomeric ratio. Aryl-, heteroaryl-, alkenyl-, and alkyl-substituted aldehydes and enynes can be used. Utility is illustrated through catalytic alkylation and arylation of the organoboron products as well as applications to synthesis of fragments of tylonolide and mycinolide IV.

Homopropargyl alcohols are used frequently in organic chemistry, and their enantioselective synthesis through addition of appropriate C-based nucleophiles to aldehydes is a critical transformation in chemical synthesis.[1] Pioneering studies have led to the development of enantiomerically enriched allenylmetal compounds (Sn-, Zn-, B-, Si-, or In-based) that provide access to homopropargylic products with excellent diastereoselectivity.[2] Groundbreaking investigations have identified chiral catalysts for additions of Sn-, Cr-, or B-based allenyl reagents to aldehydes.[3] In the majority of the above transformations, products contain a single stereogenic center; in a limited number of cases,[2d,h] an additional propargylic methyl-substituted stereogenic center is generated. A compelling recent advance entails phosphine–Ir-catalyzed transfer hydrogenation coupling of an enyne with a variety of aldehydes.[4] Homopropargylic alcohols containing a methyl-substituted stereogenic carbon were obtained efficiently and with impressive diastereo- and enantioselectivity. A notable attribute of the latter study is that initial preparation of an organometallic reagent was obviated.

We envisioned a catalytic process commencing with site- and enantioselective addition of an in situ-generated (ligand)Cu–B(pin) [from (ligand)Cu–alkoxide and $B_2(pin)_2$] species to the alkene[5] of a 1,3-enyne.[6] DFT calculations[7] indicated that the propargylcopper species **i** (Scheme 1), formed by reaction of the

Scheme 1. Principal Strategy for Reaction Development[a]



[a]B(pin) = (pinacolato)boron.

Cu species derived from bis-phosphine **2**,[8] would readily collapse to the more energetically favorable trisubstituted allenyl complex **ii**, which might then add diastereoselectively to an aldehyde (via **A**). Accordingly, versatile boron-containing propargylic addition products (**iv** via **iii**) would be formed that contain easily modifiable functional units and cannot be accessed by an alternative protocol (catalytic or otherwise). The main obstacle in the proposed sequence is that the initial Cu–B(pin) addition must occur enantioselectively. This represents an intriguing challenge, since monosubstituted alkenes are likely the most difficult sets of reactants for enantioselective catalysis,[9] particularly when attached to a relatively small alkynyl substituent. Such a sequence would be markedly distinct from the recently disclosed transformations that involve allenyl substrates.[10] Here we detail the development of a multicomponent catalytic enantioselective process that combines $B_2(pin)_2$, a 1,3-enyne, and an aldehyde. The reactions are facilitated by a chiral catalyst that can be conveniently generated in situ from inexpensive CuCl and a commercially available chiral bis-phosphine.

We first examined the ability of the Cu complex derived from commercially available **2**, which had emerged as the optimal

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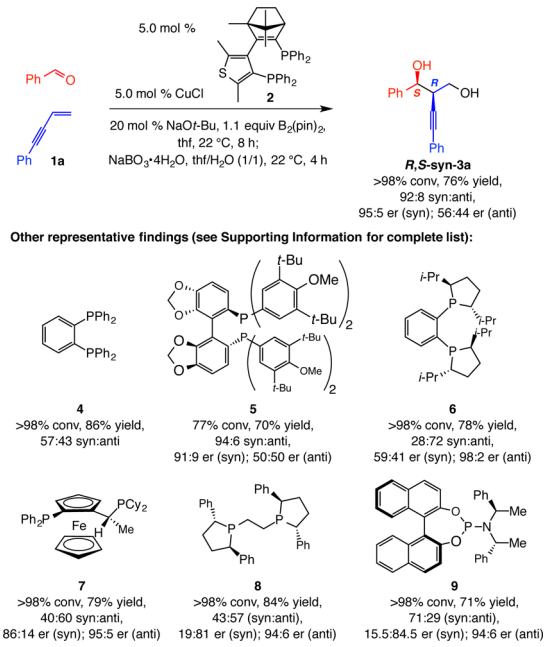
choice in reactions involving monosubstituted allenes[10] (Scheme 2). We found that, with 5.0 mol% bis-phosphine–Cu complex,

Scheme 2. Initial Examination of Chiral Cu Complexes[a]

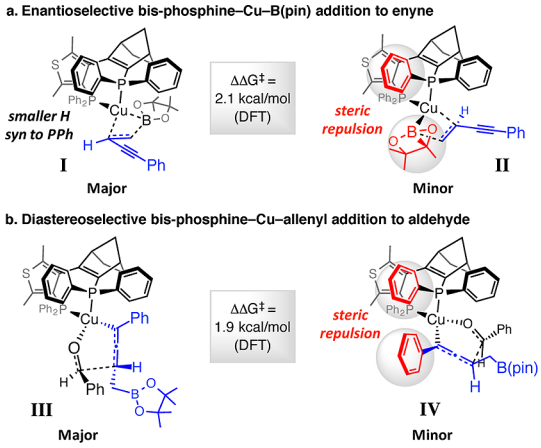


[a]Conversion (±2%) was determined by analysis of 400 MHz ^{1}H NMR spectra of the unpurified mixtures; dr and er were determined by HPLC analysis (±1%). Yields correspond to isolated and purified products (±5%). See the SI for details.

the transformation is complete within 8 h at 22 °C, affording **3a** in 76% yield, 92:8 diastereomeric ratio (dr), and 95:5 enantiomeric ratio (er). Examination of a number of other ligand systems did not yield an alternative that was superior to **2** but led to noteworthy findings; representative cases are shown in Scheme 2. With the exception of the reaction with **5** (94:6 dr), other achiral or chiral bis-phosphine ligands generated significantly lower diastereoselectivity (40:60–28:72; see the Supporting Information (SI) for a complete list). These observations have two important implications: (1) Aldehyde addition is influenced by the nature of the phosphine–Cu catalyst and is not merely subject to substrate control. (2) The changes in er and dr values observed with different chiral Cu complexes point to variations in the selectivity preferences of the stereochemistry-generating steps (Cu–B addition to enyne and allenyl–Cu addition to aldehyde). Formation of one diastereomer in higher er indicates that isomeric Cu–allenyl complexes react with distinct stereochemical preferences (syn vs anti diastereomer formation), causing a certain degree of "enantioselectivity refinement".[11] That is, the final er for the major diastereomer reflects an improvement of the enantiomeric purity derived from the initial Cu–B(pin) addition. One example is the high selectivity for the syn diastereomer but nearly racemic anti isomer formation in the transformations with **2** or **5**. This is likely because the small amount of *R,R-anti*-**3a** produced by the major Cu–allenyl intermediate is similar in quantity to *S,S-anti*-**3a** generated preferentially by the minor Cu-allenyl species.[12] In turn, the smaller enantiomeric component of *syn*-**3a** is probably due to reaction of the less favored allenyl–Cu complex with the aldehyde.[12] The preference for the anti diastereomer might originate from an extended transition structure (vs synclinal **A**, Scheme 1).

To gain insight regarding the origins of high selectivities, DFT calculations were performed (Scheme 3). These investigations

Scheme 3. Transition State Models Derived from DFT Calculations[a]



[a]For 3-D representations and other details, see the SI.

revealed that the chiral catalyst can promote Cu–B(pin) additions to the 1,3-enynes that energetically favor the formation of one enantiomer (via **I** vs **II**, Scheme 3a), followed by reaction with the aldehyde partner that proceeds with appreciable stereoselectivity (via **III** vs **IV**, Scheme 3b). Inspection of DFT-optimized geometries revealed that, in transition complexes **II** and **IV**, unfavorable steric interactions, as highlighted in Scheme 3, lead to a significant rise in energy.

A range of aryl- and heteroaryl-substituted aldehydes can be used (**3b–f**, Scheme 4), including those containing sterically demanding ortho substituents (**3b–d**). Oxidative workup afforded the desired 1,3-diols in 66–94% yield and 92.5:7.5–99:1 er. *α,β*-Unsaturated aldehydes are effective substrates (**3g–i**; precursor to **3i** is enantiomerically pure and can be purchased). The catalytic protocol can be extended to aliphatic aldehydes, as illustrated by the synthesis of **3j** (see below for more examples). In certain instances, simple recrystallization can be used to access materials of higher diastereo- and enantiomeric purity; the case that furnishes **3i** in >98:2 dr and 98:2 er (vs 98:2 dr and 92.5:7.5 er) is representative. The two examples involving commercially available alkyl-substituted aldehydes (Scheme 4) demonstrate that, when enantiomerically pure substrates are used, either diastereomeric form can be obtained efficiently and with exceptional stereoselectivity (**3k–l**). It merits note that, although the same allenyl–Cu species is involved in the reactions illustrated in Scheme 4, variations in the identity of the aldehydes and the resulting changes in the selectivity of the second stereochemistry-determining step can lead to different dr and er values for the major isomer.[12]

Substrate diversity extends to enynes as well (Scheme 5). The requisite reaction components were prepared in 80–96% yield through a single catalytic cross-coupling involving a terminal alkyne and vinyl bromide.[7] 1,3-Enynes that contain an electron-donating or electron-deficient aryl unit undergo reaction with high selectivity (**3m,n**). Transformations with a heteroaryl- (**3o**) and an alkenyl-substituted enyne (**3p**) were similarly effective. Two enynes with different removable groups were examined, and

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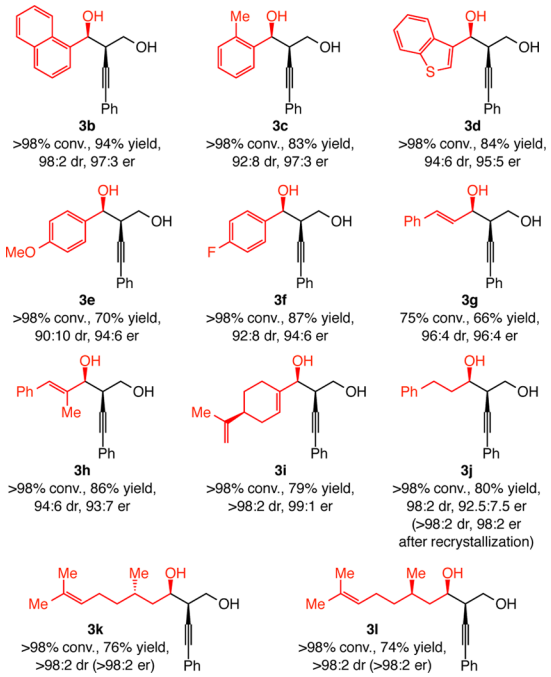
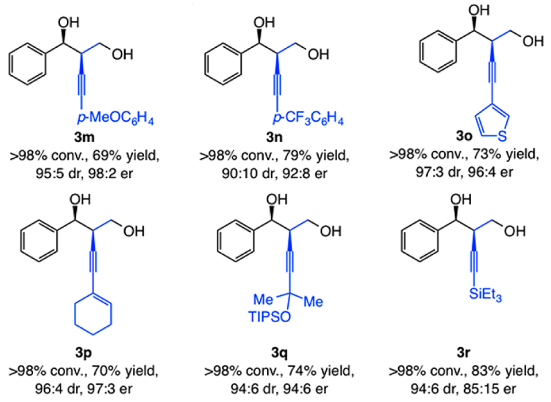
Scheme 4. Scope of Aldehyde Component[a]



[a]Same conditions and analytical methods as in Scheme 2; see the SI for details.

Scheme 5. Scope of Enyne Component[a]

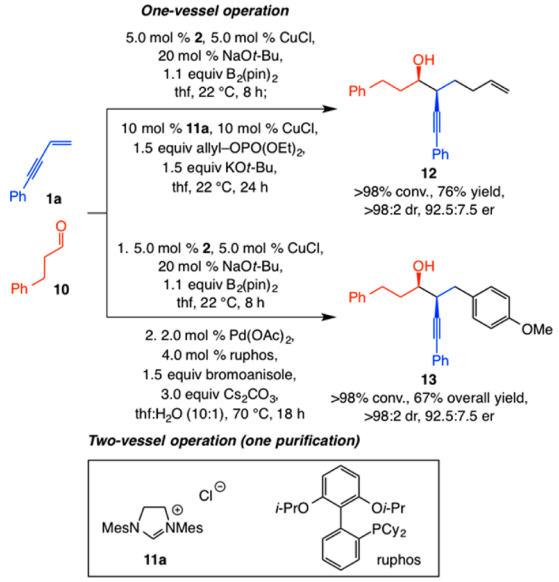


[a]Same conditions and analytical methods as in Scheme 2; see the SI for details. TIPS = $(i\text{-Pr})_3$Si.

the product with a tertiary alkyl group (**3q**) was generated with higher enantioselectivity (94:6 er vs **3r** in 85:15 er).

The assortment of organoboron compounds formed by the catalytic protocol can be functionalized in a number of ways (other than oxidative procedures employed above) to deliver valuable and otherwise difficult-to-access diastereo- and enantiomerically enriched fragments; two examples are presented in Scheme 6. The first is a one-vessel operation that couples the catalytic multicomponent process with an NHC–Cu-catalyzed alkylation, affording enyne **12** in 76% yield, >98:2 dr, and 92.5:7.5 er. A phosphine–Pd-catalyzed cross-coupling[13] was used to generate aryl-substituted **13** in 67% overall yield, >98:2 dr, and 92.5:7.5 er. These catalytic protocols, which involve the use of commercially available ligands (**2**, **11a**, and ruphos), constitute net diastereo- and enantioselective double

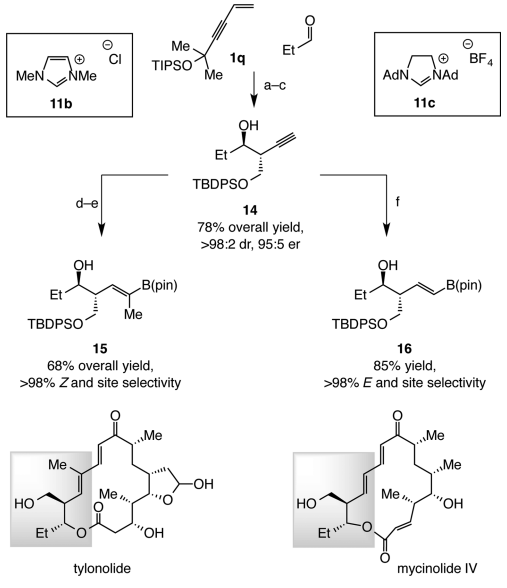
Scheme 6. Site-Selective and Enantioselective Double Alkylation and Alkylation/Arylation of an Enyne



alkylation and alkylation/arylation of a terminal olefin of an enyne, respectively.

The utility of the products is further enhanced by the presence of an alkyne group. Applications to the preparation of fragments of macrolide antibiotic natural products tylonolide[14] and mycinolide IV[15] illustrate this point (Scheme 7). Bisphosphine–Cu-catalyzed fusion of $B_2(pin)_2$, enyne **1q**, and propionaldehyde, followed by C–B oxidation, alkyne depro-

Scheme 7. Application to Fragments of Tylonolide and Mycinolide IV[a]



[a]Conditions: (a) See Scheme 2. (b) $(n\text{-Bu})_4$NF, thf, 22 °C, 12 h; NaOH, tol, 110 °C, 1 h. (c) (*t*-Bu)Ph_2SiCl, imidazole, CH_2Cl_2, 22 °C, 2 h. (d) 30 mol% CuBr, *i*-Pr_2NH, $(CH_2O)_n$, dioxane, reflux, 14 h. (e) 5.0 mol% **11b**, 5.0 mol% CuCl, 40 mol% NaO*t*-Bu, 1.1 equiv $B_2(pin)_2$, 6.0 equiv MeOH, dioxane, 22 °C, 6 h. (f) 5.0 mol% **11c**, 5.0 mol% CuCl, 20 mol% NaO*t*-Bu, 1.1 equiv $B_2(pin)_2$, 2.0 equiv MeOH, thf, 22 °C, 12 h. See the SI for details.

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tection, and generation of the corresponding silyl ether, afforded **14** in 78% overall yield, >98:2 dr, and 95:5 er. Cu-catalyzed conversion of **14** to the corresponding monosubstituted allene, followed by NHC−Cu-catalyzed site- and diastereoselective protoboration[16] involving commercially available **11b**, delivered **15** in 68% overall yield and >98% site- and *Z*-selectivity. The trisubstituted alkenylboron compound can be incorporated, in a catalytic cross-coupling process with an alkenyl halide,[17] in a route leading to tylonolide. Alternatively, site- and *E*-selective protoboration of the terminal alkyne,[18] promoted by an NHC−Cu complex derived from CuCl and **11c**, which can also be purchased, generated *E*-alkenyl−B(pin) **16**; this fragment might be utilized for enantioselective total synthesis of mycinolide IV.

Further mechanistic and computational studies as well as the development of additional catalytic and stereoselective multicomponent processes are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details; spectral and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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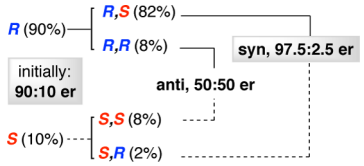

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