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Direct Stereoconvergent Allylation of Chiral Alkylcopper Nucleophiles with Racemic Allylic Phosphates

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Abstract: Copper-catalyzed stereoconvergent allylation of chiral sp³hybridized carbon nucleophiles with a racemic mixture of acyclic secondary allylic phosphates is reported. In the presence of a coppercatalyst complexed with chiral BenzP* ligand, tandem coupling reaction of vinyl arenes, bis(pinacolato)diboron, and racemic allylic phosphates provided β -chiral alkylboronates possessing (*E*)-alkenyl moiety through a direct stereoconvergent allylic coupling with concomitant generation of a C(sp³)-stereogenic center. A range of vinyl (hetero)arenes and secondary allylic phosphates bearing 1°,2°,3° alkyl and phenyl α -substituent were suitable for the reaction, forming product with high enantioselectivities up to 95% ee. Density functional theory calculations were conducted in detail to elucidate the origin of the observed regioselectivity of borylcupration and stereoconvergent (*E*)-olefin formation from racemic allylic phosphates.

The development of synthetic strategies to obtain stereochemically well-defined, enantioenriched products is an ongoing pursuit in organic chemistry. In this regard, transitionmetal catalyzed allylic substitution has been considered as a powerful synthetic tool due to easy incorporation of a versatile allyl functionality with creation of a stereogenic center from prochiral allylic electrophiles.^[1] While the use of stabilized carbon nucleophiles is prevalent in the Tsuji-Trost-type allylation using palladium or iridium catalyst,^[2] the copper-catalyzed allylic substitution is distinguished by the use of non-stabilized carbon nucleophiles. The generation of organocopper nucleophiles from strongly basic organometallic reagents including Grignard, and organolithium reagents in earlier research^[3] had greatly advanced to the use of relatively benign organoboron and orgnozirconium compounds,^[4] and further to in-situ generation from alkenes or alkynes by organocupration.^[5]

Chiral alkylmetal species containing a sp³-carbon stereogenic center attached to metal are attractive reagents as nucleophiles in C–C bond forming reactions.^[6] Despite of their potential utilities, their synthetic applications were limited by use of very low temperatures due to intrinsic configurational lability of the α -metal stereogenic center;^[7] recently, chiral secondary alkylcopper intermediates in-situ generated from alkenes were

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successfully used in the C–C bond forming reactions with various electrophiles including carbonyl compounds, imines, and other reagents.^[8,9] Especially, few examples of allylic substitutions of chiral alkylcopper species were reported with simple allyl electrophiles in respective reports by other groups^[10] and our group (Scheme 1a).^[11] Although these methods were highly efficient, the reactions accommodated only simple allyl electrophiles, and the reaction with a racemic secondary allylic electrophile resulted in a mixture of E/Z stereoisomers.^[11a]

Controlling *E*/*Z* selectivity in the copper-catalyzed allylic substitution has been an important issue as it creates an additional stereocomponent and thus, stereochemically welldefined prochiral allylic electrophiles or cyclic electrophiles had to be used for high stereocontrol.^[4b,12] Secondary acyclic allylic electrophiles were less successful due to their conformatioal flexibility, often leading to kinetic resolution of electrophiles^[12b] or to production of *E*/*Z* mixtures (Scheme 1b).^[11a,13] To the best of our knowledge, stereoconvergent coupling between a chiral alkylcopper intermediate and a racemic allylic eletrophiles has not been reported. In this article, we report a copper-catalyzed borylative coupling of vinyl arenes and vinyl silanes with racemic allylic phosphates to form β -chiral alkylboronates having wellcontrolled, two stereo-components (Scheme 1c).







Scheme 1. Allylation of chiral alkylcopper species.

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From our earlier report on the borylative coupling of vinyl arenes with primary allylic electrophiles,^[11b] we found that the use of allyl phosphates and *N*,*N*-dimethylacetylamide (DMA) solvent were crucial for good yield of product in the presence of a catalytic amount of CuCl and a chiral bisphosphine ligand. However,

application of the previous reaction conditions to secondary allylic phosphate (*rac*-**2a**) resulted in moderate yield and enantioselectivity despite promising E/Z selectivity. Therefore, we screened a series of chiral bisphosphine ligands^[14] and discovered that the short-tethered BenzP* ligand is most effective.





^[a] E/Z ratios were determined by ¹H NMR analysis of the crude reaction mixture; ee values were determined by HPLC analysis.

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The scope of the direct stereoconvergent coupling of various vinyl arenes (1) with $B_2 pin_2$ and allylic phosphates (2) using the catalytic combination of CuCl/ BenzP* was examined (Table 1). In general, reactions of racemic secondary allylic phosphates (rac-2a-e) with the R group being a primary or secondary substituent afforded the desired products (3) after oxidation with good to excellent E/Z selectivities (88:12 to >99:1) and good enantiomeric excess (84%-90%). The E/Z selectivity increased as the steric bulk of the R group increases from methyl (2a: 88:12), 1° alkyl (2b: 92:8) to 2°, 3° alkyl, and phenyl (>99:1). A higher E/Z selectivity (3ia: >99:1) was obtained even with 2a, when an indole-derived organocopper was used as the nucleophile. However, an allylic phosphate (2f) with the sterically demanding tert-butyl group led to product (3af) in decreased enantioselectivity (66%) despite high E/Z selectivity. While vinyl arenes (1b-1e) with an ortho-, electron-donating, or halogen substituent were suitable substrates for the reaction, vinvl arene (1f) with a strongly electron-withdrawing CF_3 group provided the desired product in poor yield and ee (40% ee). Vinyl arenes (1g and 1h) bearing a naphthyl or piperonyl group were accommodated under the standard reaction conditions. Vinyl heterocycles (1i-1k) including indole, thiophene, and benzofuran were also suitable for the reaction, affording the corresponding products in excellent E/Z selectivity and high enantioselectivity. Furthermore, the reaction of vinyl ferrocene (11) and vinyl silane (1m) proceeded smoothly to yield products in 90% and 84% ee, respectively.

A proposed catalytic cycle for the coupling reaction is shown in Scheme 2 with the following three steps: (1) Insertion of a vinyl arene into a chiral ligand-bound copper–boryl complex to generate the enantiomerically-enriched β -boryl benzylcopper species I; (2) direct stereoconvergent C–C bond formation from I with the racemic secondary allylic electrophile to yield the desired coupling product; and (3) regeneration of the L*Cu–Bpin species to complete the catalytic cycle.



A series of experiments were conducted to obtain mechanistic insights into the reaction (Scheme 3). Hydrogenation of a mixture of (E)-**3aa** and (Z)-**3aa** obtained from the reaction afforded a single enantiomeric product **4aa** with the

same ee, revealing that the absolute configurations of the benzylic carbons of (*E*)-**3aa** and (*Z*)-**3aa** were the same (Scheme 3a). Reactions of enantiomerically pure starting allylic phosphates, (*R*)-**2b** and (*S*)-**2b** yielded the same enantiomeric product (*E*)-**3ab** with similar reactivities and same enantioselectivity (90% ee for (*R*)-**2b** and 90% ee for (*S*)-**2b**) (Scheme 3b and 3c). These results suggest that each of the two enantiomers of the racemic allylic phosphate is transformed into the same enantiomeric product at similar reaction rates.

Hammett studies were conducted to investigate the relationship between electronic variation of the vinyl arene substrate and enantiomeric ratio of the product (Scheme 4).^[15] In reactions of para-substituted vinyl arenes 1 with allylic phosphate rac-2d, a linear correlation with negative slope ($\rho = -1.64$) was observed between the Hammett substituent constant, σ_{para} and log(er), demonstrating that electronic variation of the vinyl arene substrate has a significant impact on the enantioselectivity of the product. These results indicate that less nucleophilic benzylcopper species derived from electron-deficient vinyl arenes such as 1f (-CF₃) are not efficient for the allylic substitution, which can be ascribed to fast racemization^[10c,16] of electron-deficient organocopper intermediates (I) during C-C bond formation. In contrast, more nucleophilic benzylcopper species derived from electron-rich vinyl arenes such 1d and 1h would react smoothly with the allylic electrophile, preserving enantiopurity at the benzylic stereocenter, which are in agreement with our proposed catalytic mechanism.



Scheme 3. Experimental studies.

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Scheme 4. Hammett studies.



Figure 1. Three possible reaction pathways for allylic substitution of ${\rm I}$ with allylic phosphate.

Density functional theory (DFT) calculations were carried out using the (R,R)-BenzP* ligand, styrene, and *rac*-2d as the model substrates and provided a reasonable model of the full

mechanism and the exact origin of the stereoconvergence in the tandem coupling process (see Figure S1 in the Supporting Information for details). Among three plausible reaction pathways considered for the allylic substitution of the organocopper intermediate (I), pathway 1 in which oxidative addition of I toward the allyl phosphate with simultaneous leaving group displacement (S_N2'-oxidative addition) to form a copper(III) intermediate is favored over oxidative addition of I, ligand dissociation and reductive elimination (pathway 2) or a stepwise organocupration followed by β -elimination of a copper complex (pathway 3) (Figure 1). Interestingly, pathway 3 was often suggested as a plausible catalytic mechanism of coppercatalyzed allylic substitution reactions with possible syn or anti-Cu-LG elimination.^[12b,17] Furthermore, calculated reaction energy profiles with enantiomeric (R)-2d and (S)-2d and structural examination of possible transition states revealed that the transition states leading to (E)-intermediate were more facile than competing (Z)-transition states with less steric hindrance respectively, which is in good agreement with the experimentally observed E/Z selectivity. (See Figure S2 in the Supporting Information for details).

In summary, we have described a copper-catalyzed direct stereoconvergent coupling of vinyl arenes and racemic acyclic allylphosphates with a diboron reagent that affords β -chiral alkylboronates with an (*E*)-alkenyl moiety. Our catalytic systems enabled the use of elusive racemic acyclic substrates in a tandem process that employed chiral organocopper nucleophiles containing a stereogenic sp³-carbon center in a stereoselective C–C bond formation. Mechanistic studies and DFT calculations were conducted to elucidate the reaction mechanism and the origin of direct stereoconvergence in the tandem coupling protocol. We anticipate that our strategy will be applicable to access a variety of chiral molecules.

Experimental Section

Experimental Details. A mixture of CuCl (2.5mg, 0.025 mmol), (*R*,*R*)-BenzP* (7.8 mg, 0.0275 mmol), bis(pinacolato)diboron (190.5 mg, 0.75 mmol) and LiOMe (38.0 mg, 0.75 mmol) in DMA (0.5 mL) were stirred for 15 min in a Schlenk tube under an atmosphere of nitrogen. **1a** (0.5 mmol) dissolved in DMA (0.5mL) and *rac*-**2a** (0.75 mmol) were added to the reaction mixture. The reaction mixture was stirred at 40 °C and monitored by TLC. Upon completion of the reaction, the reaction mixture was diluted with diethyl ether (10 mL). The aqueous layer was extracted with diethyl ether, and the combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. To the mixture in THF (2 mL) and water (2 mL) was added sodium perborate (1.5 mmol). The reaction mixture was vigorously stirred for 5 h at room temperature. After the reaction was quenched with water and then, extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The product **3aa** was purified by silica gel chromatography.

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Direct stereoconvergent coupling of chiral alkylcopper species with racemic allylic phosphates was developed. Mechanistic studies and DFT calculations explain the origin of direct stereoconvergence in the tandem coupling process.

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