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Concatenated Catalytic Asymmetric Allene Diboration/Allylation/ Functionalization

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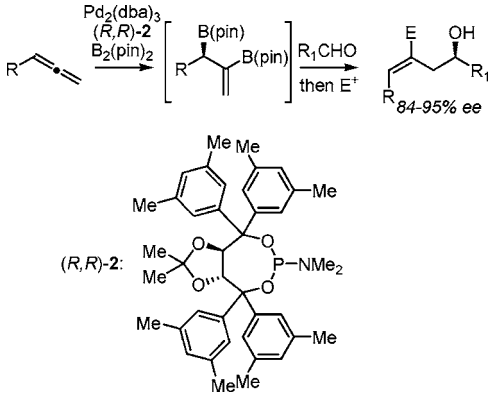
ABSTRACT



Palladium-catalyzed enantioselective diboration of prochiral allenes generates a reactive chiral allylboron intermediate which is a versatile reagent for the allylation of carbonyls. Experiments that improve the enantioselectivity of this process, examine the substrate scope, and are directed toward functionalization of the allylation intermediate are described.

Methods for the stereoselective allylation of carbonyl compounds have been aggressively developed by many groups and are of substantial importance in synthetic organic chemistry.[1] The products that arise from these processes contain versatile alkene functionality that renders the homoallylic alcohol an important building block for asymmetric synthesis. Recent advances in this area of investigation are impressive; however, there are few stereoselective reactions that result in homoallylic alcohols bearing functionalized alkenes.[2,3] Along these lines, we have recently developed an asymmetric diboration of prochiral allenes[4] with the expectation that the resulting diboron compound (**A**, Scheme 1) might prove to be a versatile intermediate for allylation reactions. It was expected that the in situ-generated chiral type I allyl metal reagent would provide predictable and high levels of chirality transfer in reactions with prochiral electrophiles.[5] Initial studies suggested that carbonyl allylation reactions proceed through transition structure **C** to give vinyl boronates **B** in an enantioenriched fashion. As depicted in Scheme 1, the allylation product contains a malleable vinyl boronic ester that might be used in concatenated reaction sequences. While the precursor diboron reagents are relatively inexpensive[6] and allenes are readily available,[7] our initial report suggested that the level of chirality transfer in the allylation is not perfect (i.e., 88% ee **A** → 82% ee **B**), thereby diminishing the overall enantioselectivity, and the

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(2) (a) Hoffmann, R. W.; Landmann, B. *Chem. Ber.* **1986**, *119*, 2013. (b) Hoffmann, R. W.; Dresley, S. *Chem. Ber.* **1989**, *122*, 903. (c) Corey, E. J.; Yu, C. M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495. (d) Evans, D. A.; Hu, E.; Burch, J. D.; Jaeschke, G. *J. Am. Chem. Soc.* **2002**, *124*, 5654. (e) Denmark, S. E.; Beutner, G. L. *J. Am. Chem. Soc.* **2003**, *125*, 7800. (f) Patterson, I.; Davies, R. D.; Marquez, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 603.

(3) For allene-derived bis(stannanes) in synthesis, see: (a) Williams, D. R.; Meyer, K. G. *J. Am. Chem. Soc.* **2001**, *123*, 765. (b) Williams, D. R.; Fultz, M. W. *J. Am. Chem. Soc.* **2005**, *127*, 14550.

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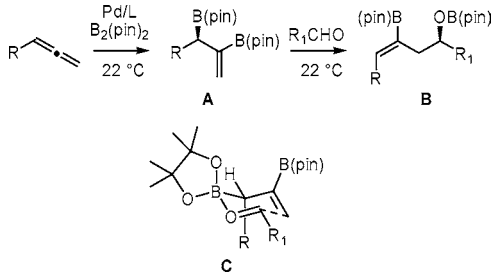
corresponding synthetic utility, of the reaction sequence. To address the shortcomings of this synthesis strategy, we have undertaken a study of the catalytic diboration reaction and have developed significantly improved catalysts that improve the overall utility of the sequence depicted in Scheme 1.

Scheme 1

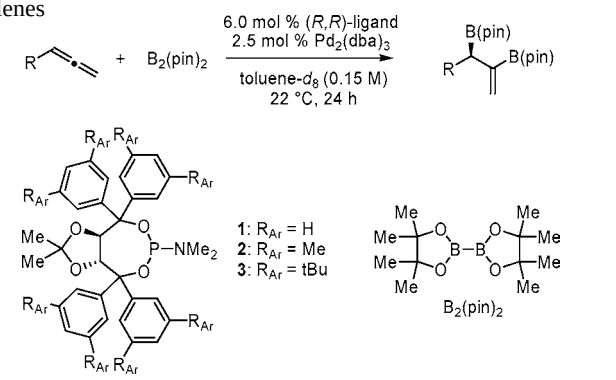


Described herein are studies that probe the potential of tandem diboration/allylation/functionalization sequences for the efficient preparation of enantiomerically enriched substructures.

Tunable TADDOL-derived phosphoramidite[8] ligand **1** (Table 1) provides significant rate enhancement and good enantioselectivity in the palladium-catalyzed diboration of both aliphatic and aromatic monosubstituted allenes. In an effort to improve the enantioselectivity of the allene diboration reaction, the components of the ligand structure were systematically evaluated. Whereas variation of the nitrogen substituents and the glycol protecting group was not rewarding (data not shown), modification of the aryl rings had a significant positive impact on asymmetric induction (Table 1). The enantioselectivity of the reaction run in the presence of xylyl-derived ligand **2** was substantially improved compared to the selectivity obtained with the parent phenyl-derived ligand **1**. When the xylyl group was replaced by the more sterically demanding 3,5-di-*tert*-butylphenyl group, both the conversion and the enantioselectivity suffered.

The performance of ligand **2** in the single-pot diboration/allylboration/oxidation cascade process renders the reaction

Table 1. Effect of Ligand Modification on the Diboration of Allenes

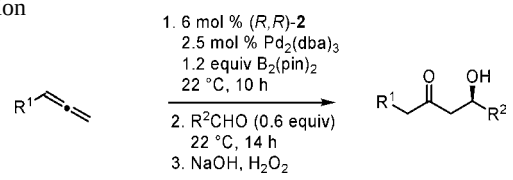


	ligand **1** % yield[a] (ee)[b]	ligand **2** % yield (ee)	ligand **3** % yield (ee)
R = decyl[c]	61 (91)	72 (98)	34 (63)
Cy	62 (89)	92 (93)	39 (66)
Ph	75 (87)	72 (97)	26 (51)

[a] Yield of diboration product isolated after silica gel chromatography. Average of two experiments with <10% difference in yield and ee in each case. [b] Enantiomeric excess determined by chiral GLC analysis of the diol obtained from hydrogenation (dimide) of the vinylboronate followed by oxidation (NaOH, H_2O_2). [c] Reaction time of 12 h.

suitable for the consistent generation of β-hydroxyketones with good levels of enantiocontrol (Table 2).[9] Unless

Table 2. Sequential Diboration/Allylboration/Oxidation Reaction



entry	R^1	R^2	% yield[a]	% ee[b]
1	Ph	*n*-Pr	85	94
2	Ph	*i*-Pr	89	95
3[c]	Ph	*i*-Pr	70	91
4[d]	Ph	*i*-Pr	80	92
5	Ph	Ph	81	93
6	decyl	*n*-Pr	88	91
7	decyl	*i*-Pr	96	91
8[d]	decyl	*i*-Pr	68	88
9	decyl	Ph	96	87
10	cyclohexyl	*n*-Pr	89	86
11	cyclohexyl	*i*-Pr	83	87
12	cyclohexyl	Ph	83	84

[a] Isolated yield of purified β-hydroxyketone product based on equivalents of aldehyde. Average of two experiments with a difference in yield of <10%. [b] Enantiomeric excess determined by chiral SFC analysis of β-hydroxyketone or benzoate derivative. [c] Conditions: 4 mol % $Pd_2(dba)_3$, 10 mol % **2**, 1.2 equiv of allene, 1.2 equiv of $B_2(pin)_2$, 1.0 equiv of aldehyde. [d] Aldehyde and allene were added together, and the reaction was allowed to stir for 14 h before oxidation.

otherwise noted, these experiments were performed by executing a Pd-catalyzed allene diboration for 10 h at room temperature prior to the introduction of the aldehyde substrate. After allowing the allylation to proceed at room temperature for 14 h, the mixture was subjected to oxidative workup. Several observations are noteworthy. While an

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(5) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 2.

(6) Bis(pinacolato)diboron is commercially available for $1500/kg from AllyChem, Co., Ltd (www.allychem.com).

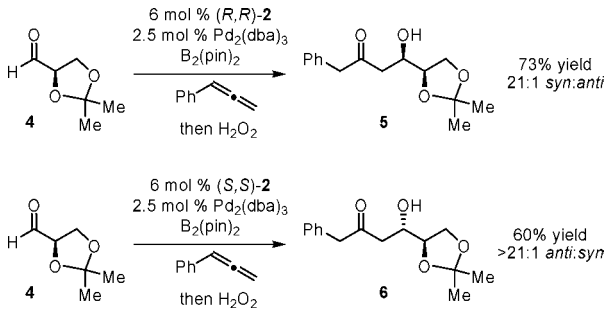
(7) Allenes are conveniently prepared by copper-catalyzed addition of Grignard reagents to propargyl tosylate or by rearrangement of propargylic alcohols. See: (a) Vermeer, P.; Meijer, J.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 112. (b) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492.

(8) Review: (a) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346. Examples: (b) ven den Berg, M.; Minnard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539. (c) Hydrosilation: Jensen, J. F.; Svendsen, B. Y.; la Cour, T. V.; Pedersen, H. L.; Johannsen, M. *J. Am. Chem. Soc.* **2002**, *124*, 4558. (d) Hydroboration: Ma, M. F. P.; Li, K.; Zhou, Z.; Tang, C.; Chan. A. S. C. *Tetrahedron: Asymmetry* **1999**, *10*, 3259.

excess of diboron intermediate was employed in these reactions, near-stoichiometric amounts of organometallic reagent are sufficient for acceptable, albeit slightly eroded, yield and enantioselectivity (entry 3). Additionally, the aldehyde may be added concomitantly with the allene (entries 4 and 8), reducing the overall reaction time and simplifying the procedure. In this case as well, enantioselectivity and yield are slightly diminished.

With chiral substrates, high levels of asymmetric induction can occur if a stereocenter is situated adjacent to a reacting carbonyl. As such, it was of interest to ascertain whether the stereoinduction arising from the chiral allylboron intermediate would dominate Felkin selectivity that may arise from the substrate stereocenter. Along these lines, glyceraldehyde derivative (*R*)-**4** was examined with both enantiomers of allene diboration adduct (Scheme 2). Depending on

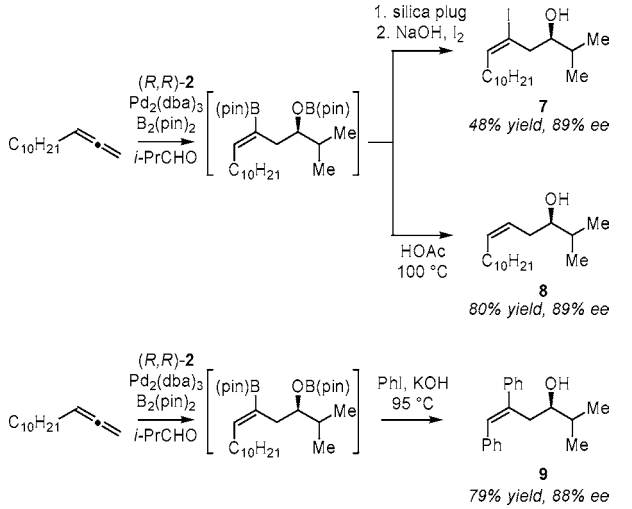
Scheme 2



the ligand enantiomer employed, either the syn or anti product configuration could be obtained almost exclusively. With (*R*,*R*)-**2**, the anti-Felkin product **5** was observed in 21:1 syn:anti selectivity whereas with the (*S*,*S*) enantiomer of **2**, the Felkin product **6** was the only observable product by ^{1}H NMR analysis.

As alluded to above, further transformations might be achieved by alternate transformation of the vinylboronic ester present in the allylation product. As depicted in Scheme 3, *E*-configured vinyl iodide **7** is accessible in 48% yield by filtration of the allylboration reaction mixture through a short

Scheme 3



plug of silica followed by treatment with aqueous NaOH and I_2.[10] Alternatively, simply heating the crude diboration/allylboration reaction mixture with acetic acid provided access to the *Z*-olefin **8** in 80% yield and with no erosion of enantiomeric excess as compared to entry 8 in Table 2.[11] Finally, it was determined that a Suzuki−Miyaura coupling reaction[12] can also terminate a single-pot cascade reaction sequence. In this particular case, simple addition of iodobenzene and KOH to the diboration/allylboration mixture, *without additional palladium catalyst*, afforded the coupling product **9** in 79% yield after heating to 95 °C for 6 h. That is, the palladium catalyst that affects the allene diboration is also competent for the Suzuki−Miyaura coupling and is not destroyed during the allylation reaction.

In summary, a strategy for the tandem allene diboration/allylboration/functionalization reaction has been developed. Future study will be devoted to the applicability of these reactions to the synthesis of structurally and functionally interesting natural products.

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Supporting Information Available: Complete experimental procedures, characterization data (^{1}H, ^{13}C, and ^{31}P NMR, IR, and mass spectrometry), enantiomeric purity data (chiral GC, SFC), and structure proofs (authentic syntheses). This material is available free of charge via the Internet at http://pubs.acs.org.

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