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COMMUNICATIONS

Published on Web 11/24/2004

Palladium-Catalyzed Enantioselective Diboration of Prochiral Allenes

Nicholas F. Pelz, Angela R. Woodward, Heather E. Burks, Joshua D. Sieber, and James P. Morken*

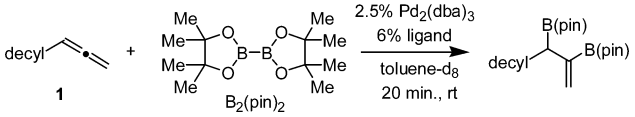
Department of Chemistry, Venable and Kenan Laboratories, The University of North Carolina, Chapel Hill, North Carolina 27599-3290

Received September 25, 2004; E-mail: morken@unc.edu

Enantioselective metalation of prochiral organic substrates is an active area of research in chemical synthesis. In particular, this area of catalysis is attractive because it provides a starting point for the development of cascade reaction sequences which may be useful for the rapid construction of complex chiral structures. Because of the remarkable breadth of stereospecific transformations available to stereogenic carbon−boron bonds,[1] recent research in our laboratory has focused on development of new enantioselective processes that allow for the construction of these chiral organometallics. One method for constructing such chiral reactive reagents is the asymmetric diboration of simple alkenes.[2,3] To expand the scope of this reaction, we have begun to examine the diboration of related prochiral allenes.[4] The product of this process contains both allylboronate and vinylboronate functionality and should prove to be a versatile intermediate in asymmetric synthesis. An analogous asymmetric silylboration has been reported which employs a chiral silylboron reagent in conjunction with a chiral catalyst;[5] however, an asymmetric diboration of allenes has not been described. We envision that introduction of the process and development of ensuing tandem reaction sequences will enable the rapid construction of complex structures.

Initial attempts to execute a catalytic asymmetric diboration of prochiral allenes using previously described chiral rhodium-based diboration catalysts[2a] suffered from a lack of regioselectivity, reactivity, and enantioselectivity. To develop a catalyst with improved performance, we decided to examine new transition metal complexes. Computational studies by Musaev, Morokuma, and Sakaki suggest that for oxidative addition to diboron reagents, palladium complexes face an activation barrier that is smaller than that of their platinum analogues; however, this elementary step with palladium is more endothermic than with platinum.[6] Accordingly, oxidative addition adducts arising from the reaction of Pd(0) complexes with diboron reagents have not been detected, whereas the corresponding platinum complexes have.[7] Likely for these reasons, Pd(0) complexes are heretofore unknown in classical diboration reactions.[8] We reasoned that, similar to the racemic platinum-catalyzed allene diboration described by Miyaura,[4a] addition of external Lewis basic ligands may facilitate the Pd(0)-catalyzed reaction and provide a direction for development of an appropriate chiral catalyst. Initial experiments were conducted with $Pd_2(dba)_3$, bis(pinacolato)diboron,[9] and the simple allene (**1**) depicted in Table 1. Reactions were conducted in toluene-d_8 and followed by NMR analysis. As can be seen in Table 1, addition of Lewis basic ligand structures does indeed provide enhanced reactivity. In contrast to the reported platinum-catalyzed allene diboration reaction which requires 18 h at 50 °C for substituted allenes, with an appropriate ligand, the palladium-catalyzed reaction can proceed to completion in minutes at room temperature. While alkyl phosphines provided the highest levels of reactivity enhancement, phosphites and phosphorus triamides were also effective. As might be expected based on the proposed mechanism for diboration with group 10 complexes (active catalyst = L−Pd),[10] dppe was completely ineffective in the reaction.

Table 1. Effect of Additional Ligand on the Palladium-Catalyzed Diboration of **1**



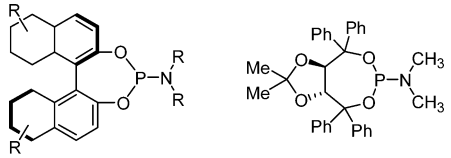
ligand	% conversion[a]
none	<5
PPh_3	<5
dppe	<5
PCy_3	100
PPh_2Cy	86
$PPhMe_2$	83
$P(OEt)_3$	41
$P(OPh)_3$	10
$P(NMe_2)_3$	82
DMAP	<5

[a] Conversion determined by ^{1}H NMR analysis at 20 min. All reactions exhibit <10% side products, as determined by NMR analysis.

Motivated by the data in Table 1, we began to explore the utility of chiral phosphoramidites in the allene diboration reaction. These ligand structures are modular, highly tunable, and have proven useful in a variety of catalytic asymmetric transformations.[11] Initial experiments surveyed binaphthol-derived phosphoramidites (**2**, Scheme 1), and while these ligands gave good conversion, enantioselectivity was poor. In contrast, TADDOL-derived phosphoramidite **3**[12] afforded high levels of asymmetric induction and good yields for a number of prochiral monosubstituted allene substrates (Table 2).[13] This reaction appears to be remarkably general and provides similar levels of enantioselectivity whether aromatic, aliphatic, large, or small substituents are appended to the allene. Reaction with most substrates results in moderate yields after 14 h. However, with a large *tert*-butyl substituent (entry 7), the rate diminishes and an extended reaction time (48 h) is required to achieve a useful product yield. Whereas the Pt-catalyzed allene diboration reaction often affords mixtures of regioisomeric addition products, with the Pd−phosphoramidite catalyst, only the internal position of the allene reacts, as determined by ^{1}H NMR analysis of crude reaction mixtures.

While the allene diboration products are bench-stable compounds and may be isolated and purified by silica gel chromatography,

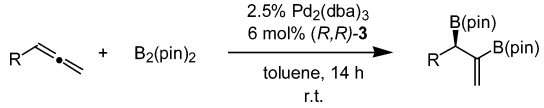
Scheme 1



2 *(R,R)*-**3**

10.1021/ja044167u CCC: $27.50

Table 2. Catalytic Enantioselective Diboration of Prochiral Allenes with $Pd_2(dba)_3$−Phosphoramidite (**3**)



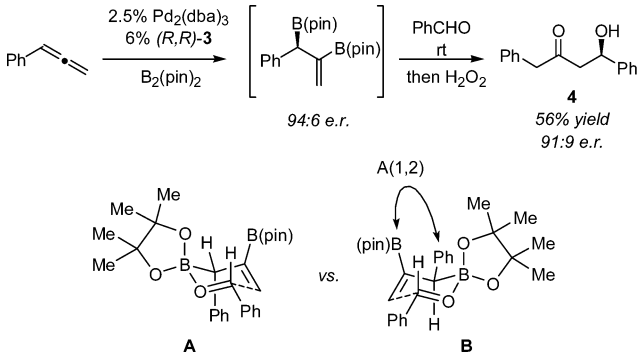
entry	R	% yield[a]	% ee[b]
1	decyl	61	91
2	cyclohexyl	62	89
3	$PhCH_2CH_2$	73	90
4	Bn	65	90
5	CH_3	68	92
6	Ph	75	87
7	*tert*-Bu	42 (58)[c]	89 (88)[c]
8	$BnOCH_2CH_2$	57	91

[a] Isolated yield of diboron adduct after silica gel chromatography. Average of two experiments with a difference in yield of <10% in each case. [b] Enantiomeric excess determined by chiral GLC or SFC analysis of diol obtained from hydrogenation (diimide) of the vinylboronate followed by oxidation (NaOH, H_2O_2) of the resulting saturated 2,3-bis(pinacolboronate) product. The absolute configuration of each product was determined by comparing the derived 2,3-diol to authentic enantiomers. [c] Number in parentheses is that obtained after 48 h of reaction.

they also exhibit reactivity with appropriate electrophiles. As depicted in Scheme 2, addition of benzaldehyde to the reaction vessel at the end of a diboration reaction, followed by addition of basic hydrogen peroxide, results in formation of the β-hydroxyketone **4** in a 91:9 enantiomer ratio (e.r.). Comparison of the optical purity of the diboron intermediate (94:6 e.r.; see Table 2) to that of product **4** suggests that near-perfect levels of chirality transfer may occur in allylboration reactions with allene diboration adducts. Comparison of the β-hydroxyketone (**4**) configuration (*R*) with that of the intermediate diboron adduct (*S*) suggests that the preferred allylation pathway is through transition state **A** (Scheme 2). The selectivity for this transformation is arguably a result of an A(1,2) interaction in transition state **B**, rendering reaction through this pathway energetically less favorable compared to reaction through structure **A**.[14]

Access to chiral allene diboration adducts in an enantioselective fashion provides new opportunities for asymmetric synthesis through tandem reaction sequences. While allylmetalation processes appear promising and will be the subject of a detailed future report, one can imagine a number of other allene diboration-based cascade sequences that may be useful for assembling functional substructures. Current efforts are focused on developing the scope of these transformations.

Scheme 2



Acknowledgment. We thank Andre de Vries and David Ager of DSM for a generous donation of phosphoramidite ligands. This work was supported by the NIH (GM 59417). J.P.M. is a fellow of the Alfred P. Sloan foundation and thanks AstraZeneca, Bristol-Myers Squibb, DuPont, GlaxoSmithKline, and the Packard Foundation for support.

Supporting Information Available: Complete experimental procedures, characterization data (^1H and ^{13}C 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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JA044167U