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Sequential Pd-Catalyzed Asymmetric Allene Diboration/α-Aminoallylation

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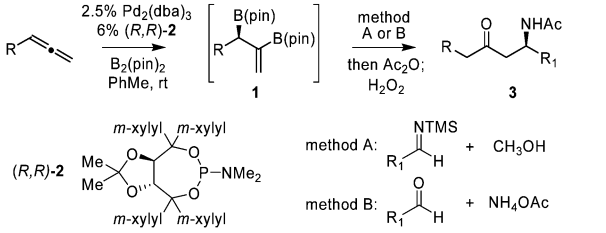
The significance of chiral amines in organic chemistry has stimulated aggressive research into the development of catalytic enantioselective additions to imines. Because of the particular importance of β-amino acids and β-amino ketones, the enantioselective catalytic Mannich[1] and allylation[2] reactions have attracted much attention. While spectacular successes have been recorded in each of these areas, many obstacles persist. For instance, both Lewis acid-catalyzed and organo-catalytic direct Mannich reactions require aryl or sulfonyl imines for effective reaction. Post-reaction removal of the resulting nitrogen appendage requires conditions which may not be compatible with resident substrate functionality. The catalytic allylation of imines is less developed than the Mannich reaction, and recent examples also require specialized substrates. For instance, an outstanding recent example by Kobayashi requires a glyoxal-derived acyl hydrazone.[2e] In this report, we describe a convenient approach to chiral addition products that proceeds directly on ammonia-derived imines.[3] In its most convenient form, this process operates as a multicomponent α-aminoallylation[4] involving an allene, a diboron reagent, an aldehyde, and an ammonia source. Other attractive features of this transformation are that chirality arises from catalytic amounts of palladium and a readily available chiral ligand, it runs at room temperature and employs commercially available inexpensive diboron reagents, and it provides access to both optically enriched (87−97% ee) Mannich products and uncommon allylation products.

Recently, our laboratory has engaged in the development of catalytic asymmetric reactions which produce reactive chiral intermediates that may provide access to diverse arrays of complex organic structures quickly and efficiently. Along these lines, we have focused on developing catalytic asymmetric diboration processes[5] and, most recently, have studied the asymmetric diboration of prochiral allenes.[6] This transformation affords chiral diboron adducts (**1**, Table 1) that contain both allylboronate and vinylboronate functional groups. These reactive intermediates are effective in the asymmetric allylation of aldehydes, and excellent levels of chirality transfer are observed.[7] Considering the above-mentioned significance of chiral amines in organic chemistry, it was important to examine the reactivity of diboron intermediates **1** with imine electrophiles.

Initial experiments directed toward development of a tandem allene diboration/imine allylation were performed using purified **1** and silyl, benzyl, and sulfonyl imines derived from benzaldehyde. When these electrophiles were treated with bisboronate **1**, no reaction was observed by ^{1}H NMR analysis even after heating to 60 °C in $CDCl_3$. Suspecting that steric demands imposed by the pinacol groups might prohibit the reaction of substituted imines, the reaction of unsubstituted imines was examined. Upon mixing **1** with *N*-trimethylsilylbenzaldimine, followed by the addition of 1.1 equiv of H_2O to cleave the N−Si bond,[8] rapid consumption (<15 min) of the starting material occurred. On the basis of this observation, a one-pot tandem allene diboration/imine allylation process was developed. Upon executing allene diboration, the reaction mixture was treated with a silylimine and methanol (method A) or the reaction mixture was treated with a methanolic solution of an aldehyde and solid ammonium acetate (method B).[9] After protection with Ac_2O and oxidation with H_2O_2, the β-amidoketone product was isolated in good yield and excellent enantiomeric excess. Considering the selectivity in the allene diboration reaction, the level of chirality transfer in the subsequent allylation reaction often approaches 99%.

Table 1. Enantioselective Diboration/Allylation of Allenes and Imines



entry	R	R^1	method[a]	% yield[b]	% ee **3**[c,d]	% cee[e]
1	Ph	Ph	A	68	97	99
			B	59	96	98
2	Ph	2-furyl	A	68	97	99
			B	69	96	98
3	Ph	(*E*)-hexenyl	A	70	92	94
4	$PhCH_2CH_2$	Ph	A	64	93	95
			B	59	92	94
5	$PhCH_2CH_2$	2-furyl	A	69	92	94
			B	56	91	93
6	$PhCH_2CH_2$	(*E*)-hexenyl	A	70	89	91
7	Cy	Ph	A	46	91	98
			B	30	91	98
8	Cy	2-furyl	A	66	92	99
			B	39	93	100
9	Cy	(*E*)-hexenyl	A	59	87	94

[a] Method A: Imine generated in situ from *N*-(TMS)aldimine and MeOH. Method B: Imine generated in situ from aldehyde and NH_4OAc in MeOH with 4 Å MS. [b] Yield of β-amidoketone after silica gel chromatography; average of two experiments. [c] Enantiomeric excess determined by chiral HPLC or SFC analysis of β-amidoketone. [d] Optical purity of the diboron intermediate for R = Ph, $PhCH_2CH_2$, and Cy was 98, 98, and 93% ee, respectively. [e] Defined as (% ee **3** ÷ % ee **1**) × 100.

As depicted in Table 1, high levels of chirality transfer generally result from the one-pot synthesis of β-amidoketones from allenes. In general, the products can be obtained in similar yields and enantiomeric excesses using either method A or method B. However, for cyclohexyl allene, method B proved to be less efficient. This was due, in part, to competitive allylation of the aldehyde present in the reaction pot. Similar to the reaction with benzaldimine, which proceeded with 99% conservation of ee (% cee), the reaction utilizing phenyl allene and furfuraldimine (entry 2) gave essentially complete chirality transfer. However, a slight drop in chirality transfer was observed when an α,β-unsaturated imine was employed in the reaction (entry 3). While 2-phenethyl-

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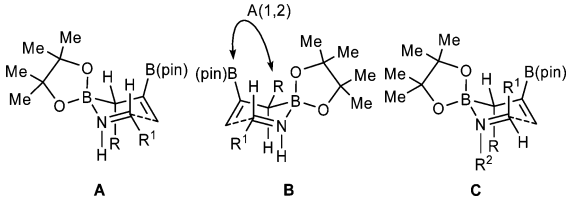


Figure 1. Allylation transition structures.

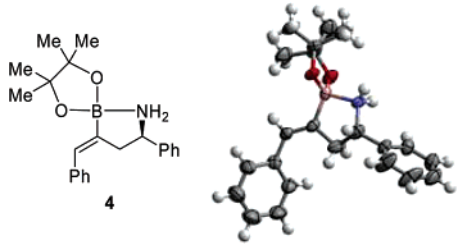


Figure 2. X-ray structure of intermediate **4**.

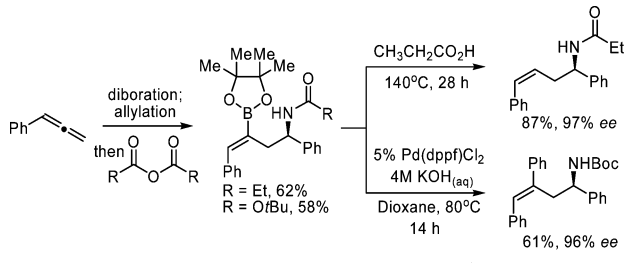
allene afforded compound **1** (R = $PhCH_2CH_2$) in 98% ee, the chirality transfer in reactions utilizing this allene is not as high as with phenyl allene, and therefore, the allylation selectivity is slightly diminished (entries 4 and 5). A similar diminution in chirality transfer occurred in all three allylations involving the α,β-unsaturated imine (entries 3, 6, and 9). The diboration of cyclohexyl allene afforded **1** (R = Cy) in 93% ee. The levels of chirality transfer when utilizing this allene were on par with those observed for phenyl allene (entries 7, 8, and 9).

Due to the fact that the enantiomer of the ligand used in the diboration reaction led to intermediate $\mathbf{1}_{R=Ph}$ with the (*S*) configuration and that the final β-amidoketone product was isolated with the (*R*) configuration, it appears likely that the allylation proceeds through a transition state structure similar to **A** (Figure 1), which would be expected for type I allylmetal compounds.[10,11] In this model, it seems reasonable that the R group of **1** would sit in a pseudoaxial position due to the significant A(1,2) strain present in diastereomeric transition structure **B**. According to these models, *E*-imines would be expected to react through structure **C**, where several penalizing 1,3-diaxial interactions would deter the process, as is observed. Upon reaction through structure **A**, one would expect to observe the *Z*-configured olefin in the allylation intermediate. In fact, it was possible to crystallize the allylation intermediate **4** (Figure 2) directly from the reaction mixture, and the X-ray analysis of this compound is shown in Figure 2. As anticipated, the structure contains the (*Z*) configuration at the olefin, thereby offering structural evidence for the above proposal.

In addition to the preparation of Mannich addition products, the allylation intermediate could be subjected to non-oxidative conditions (Scheme 1). For instance, the vinylboronate could be protonated[12] to afford the homoallylic amide in good yield, without loss of enantiopurity, and as one olefin isomer by NMR spectroscopy. It is notable that these *Z*-configured allylation adducts are not obtainable directly by any other methodology. As an alternative transformation, the allylation adduct was subjected to Boc protection conditions, and the vinyl boronate was then treated with iodobenzene under Suzuki−Miyaura cross-coupling conditions.[13] Here, the trisubstituted allylation product was isolated in good yield without loss of stereochemical purity.

In conclusion, we have developed a one-pot synthesis of β-amidoketones from allenes in good yields and high enantioselectivities. In addition, the sequence provides access to useful vinylboronate intermediates that can be isolated, characterized, and converted to allylation adducts. These compounds may prove to

Scheme 1



be useful in other transformations and allow access to structurally diverse organic compounds. Further applications of this chemistry are currently under investigation.

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Supporting Information Available: Experimental procedures and physical data (^{1}H and ^{13}C NMR, IR, MS, X-ray, chiral HPLC, SFC). This material is available free of charge via the Internet at http://pubs.acs.org.

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