Catalytic Enantioselective Allylation of Dienals Through the Intermediacy of Unsaturated π-Allyl Complexes

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Abstract
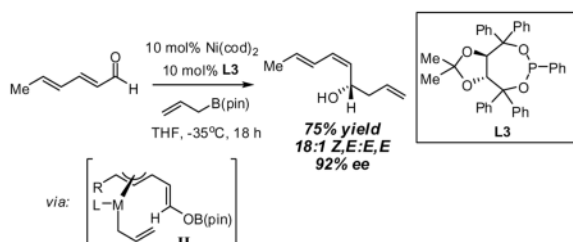
The nickel-catalyzed enantioselective addition of allylboronic acid pinacol ester - allylB(pin) – to α,β,γ,δ-unsaturated aldehydes is described. This reaction results in a remarkable inversion in substrate olefin geometry providing the Z,E configured reaction product in good enantioselectivity and olefin stereoselectivity. The reaction appears to proceed by conversion of the dienal to an unsaturated π-allyl complex, followed by reductive elimination via transition state (II). Enantioselectivities range from 73–94% ee for a range of δ-substituted dienals when chiral ligand **L3** is employed.

3,3′-Reductive elimination of bis(allyl)metal species results in C-C bond-forming allyl coupling at a site remote from the metal center. This mechanistic postulate was recently described computationally by Echavarren[1] and can be used to understand an array of reactions from Yamamoto's allylative dearomatization reaction[2] to the Tsuji allylation.[3] Recently, we reported that Ni and Pd complexes can catalyze the enantioselective conjugate addition of allylboronic acid pinacol ester (allylB(pin), **2**, Scheme 1) to dialkylidene ketones (i.e. **1**, Scheme 1).[4] Mechanistic studies suggest that this conjugate addition also proceeds by 3,3′-reductive elimination, albeit in this case from unsaturated π-allyl complex **I**. Structure **I** is obtained by boron Lewis acid-promoted electron transfer from either Ni(0) or Pd(0) to the enone, followed by transmetalation of the allyl group from boron to the transition metal.[5] Notably, simple enones and their derivatives are inert under the reaction conditions, a feature which is attributed to the reaction mechanism.

Considering the utility of the allyl unit in organic synthesis, we have begun to investigate whether 3,3′-reductive elimination might enable new types of allylation reactions.[6] In light of the structural requirements of transition state **I** in Scheme 1, we considered it plausible that α,β,γ,δ-unsaturated aldehydes (**3**) might access intermediates such as **II** or **III**, thereby gaining access to a path for low-barrier 3,3′-reductive elimination. In this report, we describe the first examples of this allylation, a process that delivers the 1,2 addition product and results in a remarkable inversion of substrate olefin geometry. Significantly, with appropriate chiral

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ligands, reactions of substrate class **3** can occur with high enantioselection and provide products which are not readily accessed by other catalytic allylation reactions.

To investigate the rapidity with which catalysis of the dienal allylation might proceed, the reaction between sorbic aldehyde (**4**) and allylB(pin) was examined (Scheme 2). These reactants undergo non-catalyzed reaction at room temperature in THF solvent achieving >95% conversion to (*E,E*)-**5** after 15 hours (initial [substrates] = 0.5 M). Remarkably, in the presence of $Ni(cod)_2$ and PCy_3, the reaction is complete in 40 minutes and, rather than delivering 1,2 addition product (*E,E*)-**5**, (*E,Z*)-**5** is the predominant reaction product. Consistent with the discussion above, the rate acceleration appears restricted to dienals (crotonaldehyde reacts with comparable rates both in the presence and absence of catalyst) and like reactions through **I** which deliver the *E*-enolate,[4] reaction through **II** furnishes the Z alkene.

Previous investigations of the catalytic enantioselective conjugate allylation reaction employed taddol-derived phosphonite **L1** for optimal selectivity.[7] As depicted in Table 1, this ligand structure is effective for the asymmetric 1,2-allylation of aldehyde **4**, however, enantioselectivity is minimal (entry 1). Analysis of related ligand structures revealed that phosphonites are generally superior to phosphoramidites and that phosphonite **L3** is optimal; in THF at room temperature 65% yield of alcohol (*E,Z*)-**5** was obtained with an enantiomeric purity of 72% ee. *Notably, the reaction with ligand L3 occurs rapidly at room temperature with complete conversion achieved in 25 minutes!* The high rate of this reaction suggested that it might occur efficiently even at lower temperature. Indeed at −35 °C, the catalytic reaction still occurs and, while 18 hours are required to achieve complete conversion, the enantioselectivity and olefin stereoselectivity are enhanced significantly (Table 2).

Under optimized conditions, many δ-substituted dienals also participate in the Ni-catalyzed enantioselective allylboration reaction. As shown in Table 2, the stereoselectivity is dependent upon the diene substituents even when these groups are five atoms away from the newly formed stereocenter. This observation is completely consistent with the proposed reaction mechanism. Of note, the reaction delivers the *E,Z* stereoisomer as the predominant product. The *E,E* olefin isomer, when observed, is racemic and assumed to arise from non-catalyzed reaction that occurs during room temperature work-up. Indeed, addition of 30 equivalents of acetaldehyde prior to work-up serves to eliminate much of the *E,E* product. Regarding substrate scope, aromatic and aliphatic substituents are tolerated at the δ carbon and provide products with high enantiomeric purity. Considering the lability of allylic oxygenated substituents in the presence of late transition metal catalysts, it is notable that the substrates in entries 6 and 7 provide good product yields and high levels of stereocontrol.

The functional group pattern present in the allylation products is useful for further manipulation. In particular, transformations that make use of directing effects[8] and A(1,3) strain[9] as stereocontrol elements can render substrate functionalization selective. For example, as shown in Scheme 3 these effects lead to selective epoxidation such that (*E,Z*)-**5** is efficiently converted into epoxide **6** with a high level of stereocontrol.[10] Richly functionalized epoxide **6** itself leads to a variety of building blocks that are not readily accessible by alterative strategies. For instance, ring-closing metathesis of **6** with the second generation Hoveyda-Grubbs catalyst furnishes novel epoxycyclohexadienol **7**.[11] Alternatively, Pd-catalyzed substitution of **6** with oxygen and carbon nucleophiles provides **8** and **9** as single isomers.[10c,12]

In conclusion, we have described a unique catalytic enantioselective allylation of unsaturated carbonyls that appears to occur by 3,3′-reductive elimination. The functional group pattern that is packaged in the reaction products is relatively unique and should be amenable to rapid

complexity generation. Future studies in regards to the scope of this transformation and its use in asymmetric synthesis are in progress.
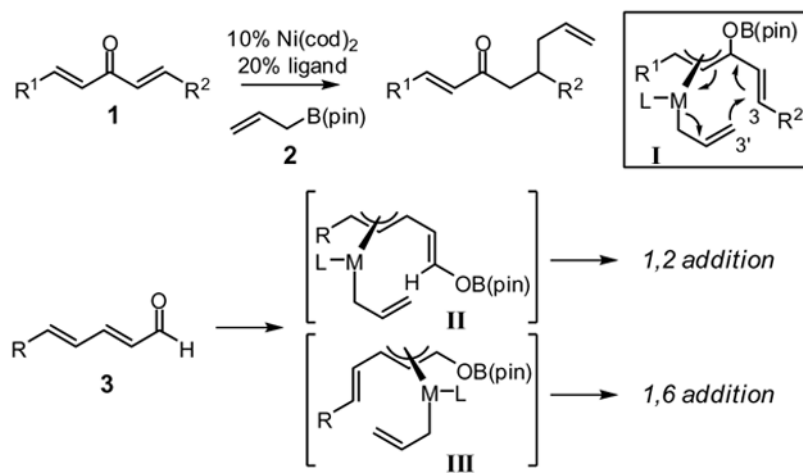
Supplementary Material

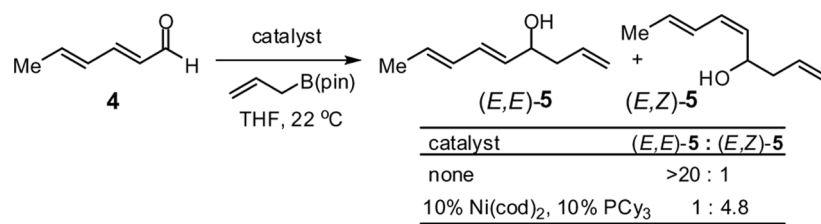Refer to Web version on PubMed Central for supplementary material.
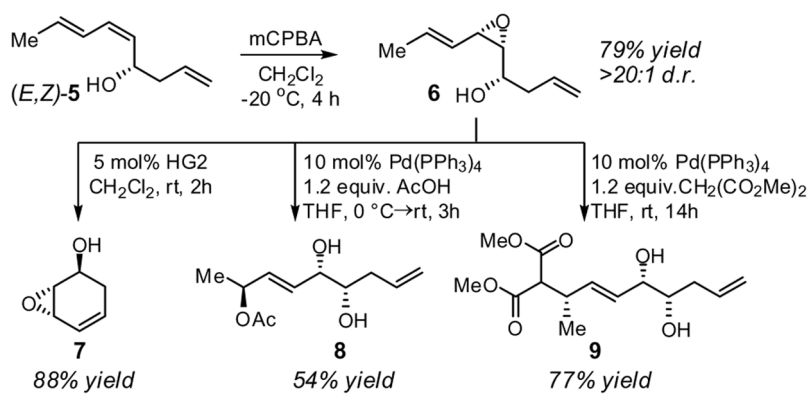
Acknowledgments

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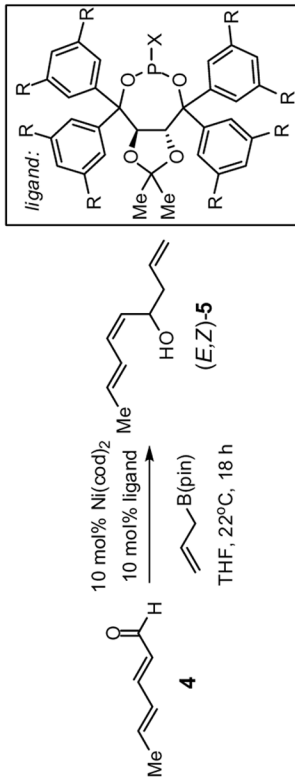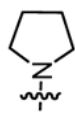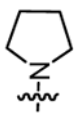
Scheme 1.

Scheme 2.

catalyst	(E,E)-5 : (E,Z)-5
none	>20 : 1
10% Ni(cod)$_2$, 10% PCy$_3$	1 : 4.8

Scheme 3.

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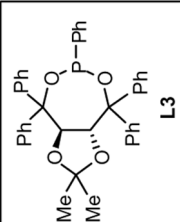
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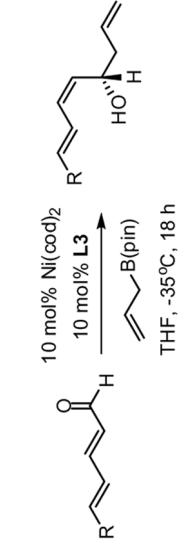
Ni-Catalyzed Enantioselective Dienal Allylation.

entry	ligand	R	X	[E,Z]:[E,E][b]	%ee[E,Z][c]
1	L1	tBu	Ph	20:1	19
2	L2	Me	Ph	>20:1	48
3	*L3*	*H*	*Ph*	*17:1*	*75*
4	L4	H	(pyrrolidine)	>20:1	52
5	L5	Me	(pyrrolidine)	>20:1	25

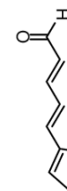Note: There is also a %yield[a] column with values 62, 65, *71*, 60, 59.
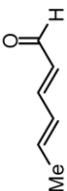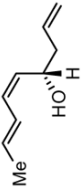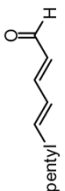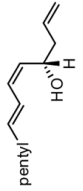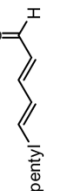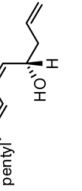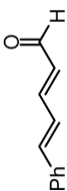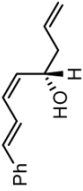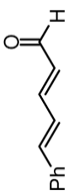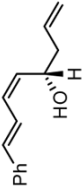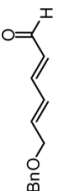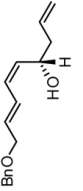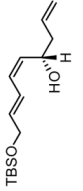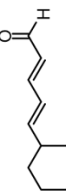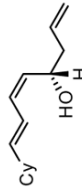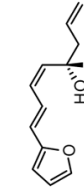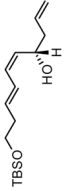
[a] Isolated yield of purified material.

[b] Determined by NMR analysis of unpurified product.

[c] Determined by chiral GC analysis.

Table 2

Scope of Ni-Catalyzed Enantioselective Dienal Allylation[a]

entry	substrate	product	yield (%)[b]	(E,Z):(E,E)	%ee
1			84	>20:1	88
2			75	18:1	92
3			84	>20:1	87
4			76	>20:1	90
5			68	>20:1	91
6			86	15:1	73
7			81	7:1	85
8			92	>20:1	93
9			73	15:1	94
10			83	16:1	90

[a]For entries 1,3, and 5–10: reaction carried out in a glovebox freezer. For entries 2 and 4, reaction carried out outside glovebox and quenched by addition of 30 equiv. of acetaldehyde, followed by warming to ambient. See the SI for details.

*b*Isolated yield of purified material.