J|A|C|S COMMUNICATIONS

Published on Web 08/13/2009

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

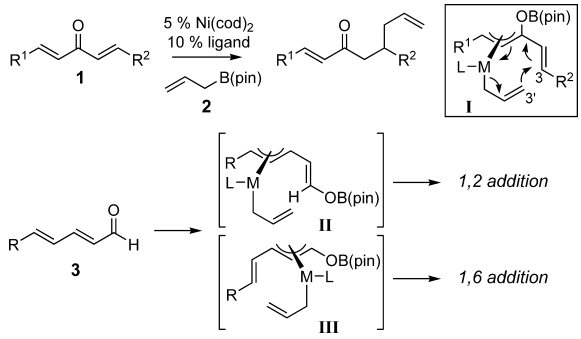
Ping Zhang and James P. Morken*

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467

Received July 14, 2009; E-mail: morken@bc.edu

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** in Scheme 1] to dialkylidene ketones (**1** in 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.

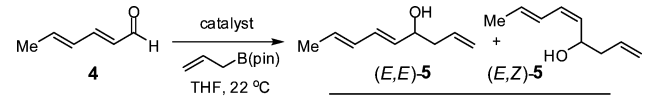
Scheme 1



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 $\alpha,\beta,\gamma,\delta$-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 ligands, reactions of substrate class **3** can occur with high enantioselectivity and provide products that 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 noncatalyzed reaction at room temperature in THF solvent, achieving >95% conversion to (*E,E*)-**5** after 15 h ([substrate]$_0$ = 0.5 M). Remarkably, in the presence of Ni(cod)$_2$ and PCy$_3$, the reaction is complete in 40 min, and (*E,Z*)-**5** rather than the 1,2 addition product (*E,E*)-**5** is the predominant reaction product. Consistent with the discussion above, the rate acceleration appears to be restricted to dienals (crotonaldehyde reacts with comparable rates in both the presence and

Scheme 2



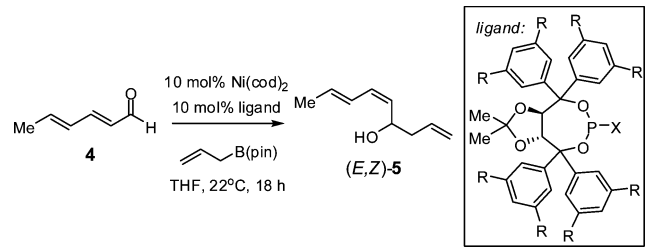
catalyst	(*E,E*)-**5** : (*E,Z*)-**5**
none	>20 : 1
10% Ni(cod)$_2$, 10% PCy$_3$	1 : 4.8

absence of catalyst), and like reactions through **I** that 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**, but the 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, a 71% yield of alcohol (*E,Z*)-**5** was obtained with an enantiomeric purity of 75% ee. *Notably, the reaction with ligand* **L3** *occurs rapidly at room temperature, with complete conversion achieved in 25 min!* The high rate of this reaction suggested that it might occur efficiently even at lower temperature. Indeed, at −35 °C, the catalytic reaction still occurred, and while 18 h was required to achieve complete conversion, the enantioselectivity and olefin stereoselectivity were enhanced significantly (Table 2).

Under optimized conditions, many δ-substituted dienals also participate in the Ni-catalyzed enantioselective allylboration reaction.

Table 1. Ni-Catalyzed Enantioselective Dienal Allylation



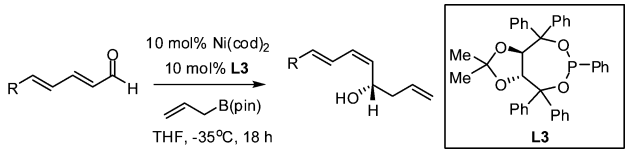
entry	ligand	R	X	%yield[a]	[E,Z]:[E,E][b]	%ee[E,Z][c]
1	**L1**	^{t}Bu	Ph	62	20:1	19
2	**L2**	Me	Ph	65	>20:1	48
3	***L3***	***H***	***Ph***	***71***	***17:1***	***75***
4	**L4**	H		60	>20:1	52
5	**L5**	Me		59	>20:1	25

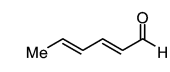
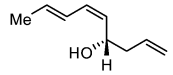
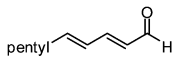
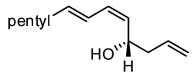
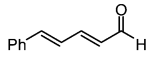
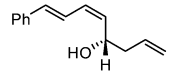
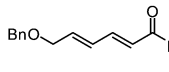
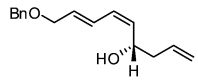
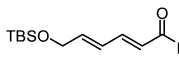
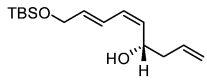
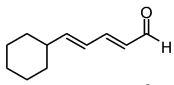
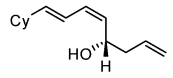
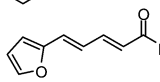
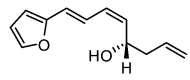
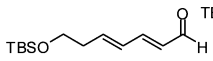
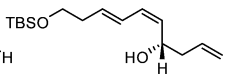
[a] Isolated yield of purified material. [b] Determined by NMR analysis of the unpurified product. [c] Determined by chiral GC analysis.

10.1021/ja9058537 CCC: $40.75

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. Notably, 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 noncatalyzed reaction that occurs during room-temperature workup. Indeed, addition of 30 equiv of acetaldehyde prior to workup served to eliminate much of the *E*,*E* product. In regard to the substrate scope, aromatic and aliphatic substituents are tolerated at the δ carbon and provide products with high enantiomeric purity. In view of 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.

Table 2. Scope of Ni-Catalyzed Enantioselective Dienal Allylation[a]

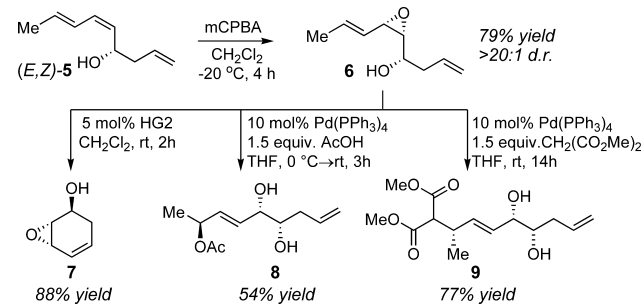


entry	substrate	product	yield (%)[b]	(E,Z):(E:E)	%ee
1			84	>20:1	88
2			75	18:1	92
3			84	>20:1	87
4			76	>20:1	90
5			68	>20:1	91
6			86	15:1	73
7			81	7:1	85
8			92	>20:1	93
9			73	15:1	94
10			83	16:1	90

[a] For entries 1, 3, and 5−10, the reaction was carried out in a glovebox freezer. For entries 2 and 4, the reaction was performed outside the glovebox and then quenched by addition of 30 equiv of acetaldehyde and warmed to ambient temperature. See the Supporting Information for details. [b] Isolated yield of purified material.

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 selectively. For example, as shown in Scheme 3, these effects lead to selective epoxidation through which (*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 alternative 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]

Scheme 3



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 regarding the scope of this transformation and its use in asymmetric synthesis are in progress.

Acknowledgment. Frontier Scientific is thanked for a donation of allylB(pin), as are the NIGMS (R01 GM-64451) and the NSF (DBI-0619576; BC Mass Spectrometry Center).

Supporting Information Available: Characterization and procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA9058537