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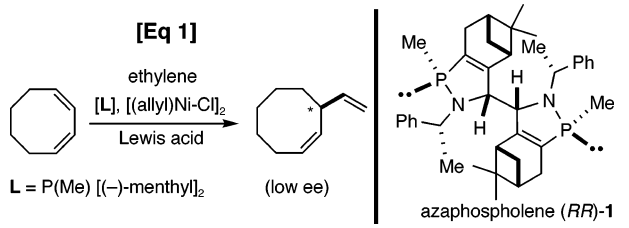
Hydrovinylation of 1,3-Dienes: A New Protocol, an Asymmetric Variation, and a Potential Solution to the Exocyclic Side Chain Stereochemistry Problem

Aibin Zhang and T. V. RajanBabu*

Department of Chemistry, 100 W. 18th Avenue, The Ohio State University, Columbus, Ohio 43210

Received September 6, 2005; E-mail: rajanbabu.1@osu.edu

Although asymmetric hydrovinylation of 1,3-cyclooctadiene (eq 1), is one of the earliest reported metal-catalyzed asymmetric C−C bond-forming reactions,[1] no satisfactory solution to the problem



of hydrovinylation of 1,3-dienes has emerged.[2] Both the Wilke conditions,[3] using an azaphospholene ligand **1**, and the use of a catalyst from aminophosphine−phosphinite/Ni(COD)$_2$/Et$_2$AlCl,[4] reported for 1,3-cyclohexadiene, are limited either by the esoteric nature of the azaphospholene ligand, which permits no structural simplifications,[5] and/or by the constraints imposed by the need for a strong Lewis acid such as Et$_2$AlCl. The isomerization of the product 1,4-diene at higher conversion is one of the serious limitations of a recently reported nonasymmetric Ru-catalyzed reaction.[6]

In previous work we developed highly practical asymmetric hydrovinylation of vinylarenes by employing monodentate phospholane or diarylphosphinite ligands carrying hemilabile groups.[2a,7] Since then Leitner has reported[8] the use of binaphthol-derived phosphoramidite ligands[9] for the same reaction, and we reported their use in asymmetric hydrovinylation of norbornene.[10a,b] An interaction between a hemilabile group on the ligand and the cationic Ni center and a synergistic relation between such a group and a highly dissociated counteranion such as [1,3-(CF$_3$)$_2$ C$_6$H$_3$)$_4$B]$^-$ or SbF$_6^-$ appear to be crucial for the success of these reactions.[7b,c]

We recently discovered that hydrovinylation of 1,3-dienes also benefit from such effects, and with the right choice of ligands, exquisite selectivity for this reaction can be realized. An asymmetric version of this reaction would be especially attractive for 1-vinylcycloalkenes, since the product 1,4-dienes would allow control of absolute and relative configurations of the side chains and of other stereogenic centers on the ring, a common feature in many important natural products,[11] including D-ring-functionalized steroids, serrulatanes, and psuedopterosins[12] (Scheme 1).

Scheme 1. Controlling Exocyclic and Ring Junction Configurations through Hydrovinylation

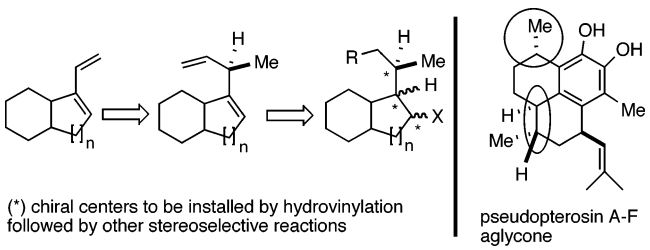


Table 1. Hydrovinylation of 1,3-Dienes (eq 2)[a]

no.	diene	conv. (%)	regiosel. (%)	product(s)
1.	**2**	94	>99	**5**
2.	Bu^t **3**	>99	98	Bu^t **6**[b]
3.	**7**	>99	68[c]	**8a**
4.	BnOCH$_2$ BnOCH$_2$ **9**	>99	72[d]	BnOCH$_2$ BnOCH$_2$ **10a**
5.	**11**	>99	>99	**12**
6.	**13**	>99	98	**14**
7.	**15**	~97	>99	**16**
8.	Ph **17**	>99	95	Ph **18**
9.	MeO$_2$C **19**	99	98	MeO$_2$C **20**

[a] See Supporting Information for details. [b] Mixture of two diastereomers (~2:1). [c] Rest isomerized plus 1,4-adducts. [d] ~20% 1,4-adduct.

Our studies started with an examination of hydrovinylation of cyclohexa-1,3-diene (**2**) and 4-*tert*-butyl-1-vinylcyclohexene (**3**) using the procedure[7a,b] we had successfully employed for the hydrovinylation of vinylarenes [Ph$_3$P/[(allyl)NiBr]$_2$/AgOTf, 0.07 equiv Ni, low temp, CH$_2$Cl$_2$, 1 atm ethylene]. It soon became apparent that, under these conditions, 1,3-dienes were much less reactive compared to the vinylarenes, and higher temperatures (~25 °C) were needed for the reaction. We decided to explore new protocols for this potentially useful reaction by systematically examining the use of the hemilabile ligand effects[7a−c] using **3** as a substrate. These studies revealed that the best ligand for this reaction was 2-benzyloxyphenyldiphenylphosphine (**4a**).[13] Thus, 0.14 mol % of a catalyst generated from **4a**, allyl-nickel bromide dimer, and Na$^+$\{[1,3-(CF$_3$)$_2$C$_6$H$_3$]$_4$B\}$^-$ effects the reaction of **3** with ethylene (1 atm) to give a quantitative yield of the product **6**, as a mixture of two diastereomers (eq 2 and Table 1, entry 2). This product is

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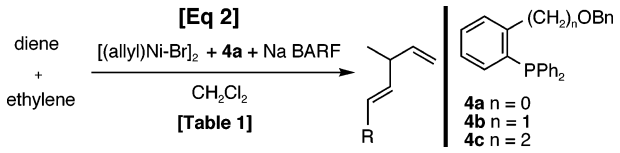
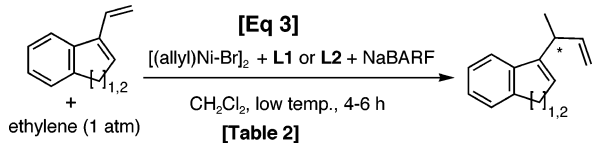


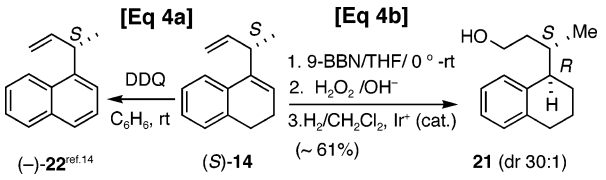
formed with exquisite regioselectivity (1,2-addtion at the less hindered olefin). The racemic chiral olefin **3** gave a nearly ~2:1 mixture of diastereomers. The results of hydrovinylation of other typical dienes are shown in Table 1.[13] In general, excellent yields (>97%) and selectivities (>95%) are observed for the hydrovinylation of both cyclic and acyclic dienes (entries 1, 2, 5−9) under 1 atm of ethylene. Lack of selectivity is seen only for 1-vinylcyclohexene (**7**, entry 3) and the 1-vinylcyclopentene **9** (entry 4, prepared by enyne metathesis), which gave a mixture of 1,2- and 1,4- addition products.

The most promising results with model compounds, suitable for a study of the exocyclic stereochemistry problem, are shown in eq 3 and Table 2. Hydrovinylation of **11**, **13**, and **15**, under our



standard conditions (eq 3) using the phospholane (**L1**)[7e] or the phosphoramidite ligand (**L2**) gave exceptionally high yields and regio- and enantioselectivities for these cyclic dienes.[13] Acyclic diene **17** under these conditions gave nearly racemic product.

The absolute configuration of the **14** was established by its conversion to the fully aromatic product of known[14] configuration (eq 4a). The configurations of **12** and **16** were assigned by analogy.

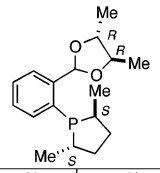
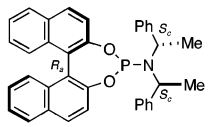


The sense of asymmetric induction is consistent with the model we proposed for asymmetric hydrovinylation of vinylarenes.[7e] The ee's were unambiguously established by GC, HPLC, and/or Mosher ester[13] methods.

A number of different strategies including hydroboration and directed hydrogenation can be envisioned for controlling the configuration of the ring carbon to which the side chain is attached. One example is shown in eq 4b. The hydroboration (9-BBN, H_2O_2) of **14** followed by directed hydrogenation using Crabtree's catalyst, ($[(COD)(Cy_3P)Ir(py)]^+PF_6^-$), gives a reduced product (**21**, dr 30:1) with very high stereoselectivity.[13]

Further expansion of the scope of the asymmetric reaction and its applications for the synthesis of natural products will be reported in due course.

Table 2. Asymmetric Hydrovinylation of 1,3-dienes (eq 3)[a]

Ligand:	L1: 		L2: 	
diene	conv. % (sel. %)	%ee (config.)	conv. % (sel. %)	%ee (config.)
11	>99 (>99)	85 (*R*)	>99 (>99)	96 (*S*)
13	>99 (97)	93 (*R*)	>99 (>99)	>99 (*S*)
15	>99 (99)	38 (*R*)	>99 (>99)	95 (*S*)
17	88 (>99)	<5%	--	--

[a] See eq 3 for typical procedure and Supporting Information for experimental details.

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Supporting Information Available: Full experimental details of various hydrovinylation reactions, spectroscopic and chromatographic data for characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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