Published in final edited form as:

J Am Chem Soc. 2012 April 18; 134(15): 6556–6559. doi:10.1021/ja301640e.

Asymmetric Hydrovinylation of 1-Vinylcycloalkenes. Reagent Control of Regio- and Stereoselectivity

Jordan P. Page and T. V. RajanBabu*

Department of Chemistry, The Ohio State University, 100 West 18th Avenue, Columbus, Ohio 43210, United States

Abstract

1-Vinylcycloalkenes undergo highly regio- and enantioselective (>98% ee) 1,4-hydrovinylation (HV) when treated with ethylene (1 atmosphere) at room temperature in the presence of [(*S,S*)-2,4-*bis*-diphenylphosphinopentane (BDPP)]CoCl₂ (0.05 equiv.) and methylaluminoxane. The minor 1,2-HV products, seen only in 1-vinylcyclohexene (~15%) and 1-vinylcycloheptene (2%), are formed as racemic mixtures. The corresponding Ni(II)-catalyzed HV reactions of these substrates give mostly the 1,2-adducts. Racemic 4-*t*-butyl-1-vinylcyclohexene, when treated with Co[(*S,S*)-(BDPP)]Cl₂ and ethylene undergoes a rare enantiodivergent reaction giving two diastereomers each in >98% ee.

Nickel(II)-catalyzed asymmetric hydrovinylation (HV) of 1-vinylcycloalkenes is a powerful reaction that has been used to install exocyclic methyl-bearing chiral centers with exceptional enantio- and diastereoselectivity depending on the nature of

* (rajanbabu.1@osu.edu).

Supporting Information Available. Details of the experimental procedures, spectroscopic and chromatographic data for key compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

the starting diene (eq 1-2).¹ While excellent ligand-dependent selectivity has been demonstrated even in a demanding *chiral* precursor such as **3**,^{1b} with a disparate inherent substrate-specific stereochemical preference, an occasional complication in the reaction was noted during the attempted diastereoselective 1,2-hydrovinylation of the steroidal substrate **5** (eq 3).² Even though the formation of the desired 1,2-adduct (**6**) is totally stereoselective (and controllable by the choice of the ligand), a minor product, **7**, arising via a highly selective 1,4-addition of ethylene is also formed. Since configurationally well-defined 2-vinylcycloalkylidenes such as **7** could be potentially important intermediates for further stereoselective transformations, we decided to explore ways of optimizing such 1,4-hydrovinylation reactions of 1-vinylcycloalkenes. We find that using variations of a recently disclosed Co(II)-mediated HV protocol,^{3a} it is possible to effect highly regio- and enantioselective 1,4-hydrovinylation of 1-vinylcycloalkenes.⁴ The results of this study are reported here.

Our studies started with an examination of Co(II)-catalyzed hydrovinylation of 4-*t*-butyl-1-vinylcyclohex-1-ene (**8**, Scheme 1). After optimization of the reaction conditions using various combinations of (L)₂CoCl₂/AlMe₃ (L = DPPM, DPPE, DPPP and DPPB),⁵ temperatures and solvents, it was found that, in sharp contrast to the Ni(II)-catalyzed HV reaction (Scheme 1, **8** → **10**),^{1a} and a related Ru(II)-catalyzed reaction,⁶ the (DPPP)CoCl₂/Me₃Al-mediated reaction gave almost exclusively the 1,4-adducts as a mixture of *cis* (**9a**) and *trans* (**9b**) isomers (81:17).⁷ We also recognized that experimentally it was advantageous to use methylaluminoxane,⁸ which can be easily weighed out, in the place of the hydrocarbon solutions of Me₃Al. Both the Ni(II) and Co(II) reactions are highly regioselective in the formation of the respective 1,2- and 1,4-adducts with less than 4% of the isomeric products (**9** and **10** respectively) formed in each case.

The scope of the reaction is illustrated with the examples shown in Table 1. Under the standard reaction conditions, the hydrovinylation is highly chemoselective for the 1,3-diene moiety, as shown by the reaction of the enantio-pure substrate **11**, which was prepared from commercially available (–)-perrilaldehyde (entry 2). The 1,4-adducts **12a** and **12b** (ratio of 4:1) are obtained in excellent yield. The allyl ether **13**, readily prepared via intramolecular cross-metathesis of an enyne,⁹ is a compatible substrate giving 2,5-*cis* (**14a**) and 2,5-*trans* (**14b**) adducts in a ratio of 1:9 (entry 3). Conformationally flexible 1-vinylcyclohexene (entry 4) also gave predominantly the 1,4-adduct (**15a**), with up to 22% of the 1,2-HV product. The Co(II)-catalyzed 1,4-hydrovinylation is particularly effective for 1-vinylcycloheptene (entry 5) and 1-vinylcyclooctene (entry 6), under the typical reaction conditions using DPPP as the ligand. Substrates **18**, **20** and **22**, which gave exclusive 1,2-

hydrovinylation under the Ni-catalyzed reaction conditions described in Scheme 1,^{1a} gave quantitative yields of the 1,4-adduct (1,4-HV vs 1,2-HV > 99:1) in the Co(II)-mediated reactions (entries 7-9).

Searching for a chiral, chelating bisphosphine ligand that bears a structural similarity to 1,3-*bis*-diphenylphosphinopropane (DPPP), we identified commercially available 2,4-*bis*-diphenylphosphinopentane (BDPP), which serves admirably well in an asymmetric version of the 1,4-HV reaction. Reactions of two prototypical substrates, 1-vinylcyclohexene and 1-vinylcycloheptene showing the optimized conditions, and the possible side reactions, are shown in eq 4.¹⁰ The HV reactions of 1-vinylcyclohexene and 1-vinylcycloheptene with the (BDPP)Co(II)-catalyst closely parallel the results obtained with the corresponding (DPPP)Co(II)-complex, except for the proportion of the 1,4-HV product, which is slightly more in the former case (~85%) than what was formed with the DPPP-complex. The reactions using the (*S,S*)-BDPP ligand gave (*S*)-**15a** and (*S*)-**16a** essentially as single enantiomers with <0.2 % of the (*R*)-isomers.¹¹ Predictably, reaction with the (*R,R*)-BDPP gave the enantiomeric products (*R*)-**15a** and (*R*)-**16a** in comparable yields and selectivities. The configuration of (*S*)-**16a** was confirmed by its conversion [(Ph₃P)₃RhCl, CH₂Cl₂, H₂ (35 psi), followed by O₃, Me₂S]¹¹ to (*R*)-2-ethylcycloheptanone whose chiroptical properties have been described in the literature.¹² In sharp contrast to the high selectivity observed for the 1,4-HV product, the corresponding 1,2-HV adducts (**15b** and **16b**) were formed nearly as racemic mixtures.

As illustrated by the examples listed in Table 2, the (BDPP)CoCl₂-catalyzed asymmetric 1,4-hydrovinylation is a broadly applicable reaction. Vinylcyclooctene, as compared to the 6 and 7-membered analogs, gives exclusively the 1,4-adduct, which is formed in >99% ee (entry 3). 1,4-Hydrovinylations of substrates **18**, **20** and **22** (entries 4-6) also proceed giving nearly quantitative yields of the respective 1,4-adducts with >99% ee.

4-*t*-Butyl-1-vinylcyclohexene (**8**) is a chiral (racemic) substrate capable of producing two sets of diastereomers each from the 1,2- and 1,4-HV reactions, and, the selectivity of the reaction is highly dependent on the ligand. For example, the high regio- (**9a:10** = 98:2) and diastereo- (**9a:9b** = 81:17) selectivity in the formation of the products seen with the achiral (DPPP)-Co(II) complex (Scheme 1, Table 1, entry 1) shows significant erosion when the [(*S,S*)-BDPP]Co(II) complex is used (regioselectivity **9a:10** = 87:13; diastereoselectivity **9a:9b** = 60:40). However, both diastereomers of the 1,4-adducts, **9a** and **9b**, are formed with enantioselectivities exceeding 98%. The exceptionally high enantioselectivity in the formation of the two diastereoisomeric products from a chiral *racemic* substrate **8** is another example of a rare, yet growing list of efficient enantiodivergent parallel kinetic resolutions.¹³

In summary, we have discovered a simple procedure for the preparation of enantiopure 1-alkylidene-2-vinylcycloalkanes from readily available 1-vinylcycloalkenes. The enhanced

reactivity of the trisubstituted double bond in electrophilic reactions and the greater access of the monosubstituted alkene to reagents such as dialkylboranes and catalytically competent metal complexes should make these enantiopure skipped 1,4-dienes valuable intermediates for further synthetic applications. Such studies are in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial assistance for this research provided by US National Institutes of Health (General Medical Sciences, R01 GM075107) is gratefully acknowledged.

References

- (1). (a) Zhang A, RajanBabu TV. *J. Am. Chem. Soc.* 2006; 128:54. [PubMed: 16390118] (b) Mans DJ, Cox GA, RajanBabu TV. *J. Am. Chem. Soc.* 2011; 133:5776. [PubMed: 21449569] RajanBabu TV. *Synlett.* 2009; 853
- (2). Saha B, Smith CR, RajanBabu TV. *J. Am. Chem. Soc.* 2008; 130:9000. [PubMed: 18570419]
- (3). Sharma RK, RajanBabu TV. *J. Am. Chem. Soc.* 2010; 132:3295. [PubMed: 20163120] Other reports of Co-catalyzed asymmetric hydrovinylation: Grutters MMP, Müller C, Vogt D. *J. Am. Chem. Soc.* 2006; 128:7414. [PubMed: 16756275] Grutters MMP, van der Vlugt JJ, Pei Y, Mills AM, Lutz M, Spek AL, Müller C, Moberg C, Vogt D. *Adv. Synth. Catal.* 2009; 351:2199.
- (4). Co(I)-catalyzed hydroalkenylation of dienes has attracted significant attention in the past decade, primarily due the seminal studies of the Hilt group. For a recent review, see: Hilt G. *Synlett.* 2011; 1654 For representative examples of hydroalkenylation of dienes, see: Hilt G, du Mesnil F-X, Lüers S. *Angew. Chem. Int. Ed.* 2001; 40:387. Hilt G, Lüers S. *Synthesis.* 2002; 609 Hilt G, Danz M, Treutwein J. *Org. Lett.* 2009; 11:3322. [PubMed: 19583205] Arndt M, Reinhold A, Hilt G. *J. Org. Chem.* 2010; 75:5203. [PubMed: 20597480] Hilt G, Roesner S. *Synthesis.* 2011; 662 Bohn MA, Schmidt A, Hilt G, Dindaroglu M, Schmalz H-G. *Angew. Chem. Int. Ed.* 2011; 50:9689. For related Fe-catalyzed reactions, see: Ehlers J, König WA, Lutz S, Wenz G, tom Dieck H. *Angew. Chem. Int. Ed. Engl.* 1988; 27:1556. Moreau B, Wu JY, Ritter T. *Org. Lett.* 2009; 11:337. [PubMed: 19093845] Control of regioselectivity is a particularly important aspect of coupling reactions of 1,3-dienes. For a noteworthy application of ligand control of regioselectivity in the context of the Co(I)-chemistry, see: Arndt M, Dindaroglu M, Schmalz H-G, Hilt G. *Org. Lett.* 2011; 13:6236. and references cited therein. [PubMed: 22040103]
- (5). Ligands: BDPP = 2,4-diphenylphosphinopentane; DPPM = diphenylphosphinomethane; DPPE = diphenylphosphinoethane; DPPP = diphenylphosphinopropane; DPPB = diphenylphosphinobutane; Cy₃P = tricyclohexylphosphine; DIOP = (2,2-dimethyl-1,3-dioxalane-4,5-diylbismethylene) bis-diphenylphosphine.
- (6). A high pressure Ru(II)-catalyzed hydrovinylation of 1,3-dienes at 75 °C using (Cy₃P)₂Ru(CO)(H)(Cl)/HBF₄ also gives mostly the 1,2-hydrovinylaion products, albeit in modest yields. See: He Z, Yi CS, Donaldson WA. *Org. Lett.* 2003; 5:1567. [PubMed: 12713325] Additionally, we noticed that even the Co(II)-catalyzed reaction is highly dependent on the ligand. For example, (+)-DIOP gave >90% yield of a mixture of diastereomers of the 1,2-hydrovinylation (exocyclic) products (10a and 10b), both of which were formed in low ee's. 1-Vinylcyclohexene also behaves similarly. See Supporting Information for details.
- (7). The 1,2- and 1,4-adducts are easily distinguished by the chemical shifts of the bis-allylic hydrogen. In cis-9, this proton appears as a ddd at δ 2.93, and in trans-9 as broad singlet at δ 3.46. In both diastereomers of 10 this signal appears as a multiplet at δ 2.70. Gas chromatographic retention times for the 1,4-adducts on a methylsilicone column are significantly lower than those of the 1,2-adducts. See Supporting Information for details.
- (8). Reddy SS, Radhakrishnan K, Sivaram S. *Polymer Bulletin.* 1996; 36:165.
- (9). Mori M, Sakakibara N, Kinoshita A. *J. Org. Chem.* 1998; 63:6082. [PubMed: 11672225]

- (10). To a solution of 0.05 equivalents of (S,S)-(BDPP)CoCl₂ and 1.25 equivalents of methylaluminoxane in CH₂Cl₂ under an ethylene atmosphere, was added a CH₂Cl₂ solution of the diene. The mixture was stirred for 6-8 h at room temperature, and was quenched by adding stoichiometric amount of methanol. Dilution with pentane and filtration through silica afforded the product in excellent yields and isomeric purity, as judged by both gas chromatography (GC) and ¹H NMR spectroscopy. The enantiomeric ratios of the products were determined by chiral stationary phase GC on a cyclosil-B or a cyclodex-B column, where base-line separations of the enantiomers were observed. For exact conditions of analysis and the chromatograms of racemic and enriched samples, see Supporting Information.
- (11). See Supporting Information for experimental details and analytical data, including gas chromatograms recorded on regular and chiral stationary phase columns.
- (12). Burton JW, Clark JS, Derrer S, Stork TC, Bendall JG, Holmes AB. *J. Am. Chem. Soc.* 1997; 119:7483.
- (13). For recent reviews, see: Miller LC, Sarpong R. *Chem. Soc. Rev.* 2011; 40:4550. [PubMed: 21629881] Kumar RR, Kagan HB. *Adv. Synth. Catal.* 2010; 352:231. Notable examples, Gansauer A, Shi L, Otte M. *J. Am. Chem. Soc.* 2010; 132:11858. [PubMed: 20687604] Wu B, Parquette JR, RajanBabu TV. *Science*. 2009; 326:1662. [PubMed: 20019280] Webster R, Böing C, Lautens M. *J. Am. Chem. Soc.* 2009; 131:444. [PubMed: 19140785] Bertozzi F, Crotti P, Macchia F, Pineschi M, Feringa BL. *Angew. Chem. Int. Ed.* 2001; 40:930.

Scheme 1.1,2- vs 1,4-Hydrovinylation of 4-*t*-Butyl-1-vinylcyclohexene

Table 1

Co(II)-Catalyzed 1,4-Hydrovinylation of 1-Vinylcycloalkenes^a

no	diene	conv. (%)	regioselect. ^b	major product(s)
1.	8 (racemic)	>99	98:2	[9a (cis):9b (trans) = 81:17]
2.	11	>99	>99 (by NMR)	[12a (cis):12b (trans) = 4.0:1.0]
3.	13 (racemic)	93 ^c	96:4	[14a (cis):14b (trans) = 1:9]
4.	15a + 15b^d	>99	80:20	15a + 15b^d
5.	16a + 16b^d	>99	98:2	16a + 16b^d
6.	17a	>99	>99	17a
7.	18	>99	>99	19
8.	20	>99	>99	21

no	diene	conv. (%)	regiosel. ^b	major product(s)
9.		~97	>99	23

^a See Scheme 1 for typical procedure using (DPPP)CoCl₂ as catalyst. Supporting Information for further details.

^b 1,4-HV:1,2-HV, determined by GC and/or NMR.

^c rest starting material.

^d **15b** and **16b** are 1,2-HV products.

Table 2

Co(II)-Catalyzed Asymmetric 1,4-Hydrovinylation of 1-Vinylcycloalkenes^a

no	diene	conv. (%)	regioselect. ^b	Product (config.) ^d	(%ee) ^c
1.		>99	85:15	15a [>99] 15b [<5]	
2.		>95	98:2	16a [>99]	
3.		>99	>99	17a [>99]	
4.		>99	>99	19 [>99]	
5.		>99	>99	21 [>99]	

no	diene	conv. (%)	regioselect. ^b	Product (config.) ^d	(%ee) ^e
6.		~97	>99		23 [>98]
7.		>99	87:13		9a^f (2 <i>S</i> ,4 <i>R</i>) 9b^f (2 <i>S</i> ,4 <i>S</i>) [>98] [>98]

^a See eq 4 and Supporting Information for details.

^b 1,4-HV: 1,2-HV. Determined by ¹H NMR and/or GC.

^c Major product. Determined by chiral stationary phase GC. See Supporting Information for chromatograms.

^d Assigned by analogy to products **16a** and **21**, whose configurations were confirmed by comparison to known derivatives, see text and Supporting Information for details.

^e ee for the 1,2-HV product: <5%.

^e ee of 1,2-HV product <5%.

^f **9a:9b** = 60:40. Assignments (tentative) based on configurations of **16a** and **21**.