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

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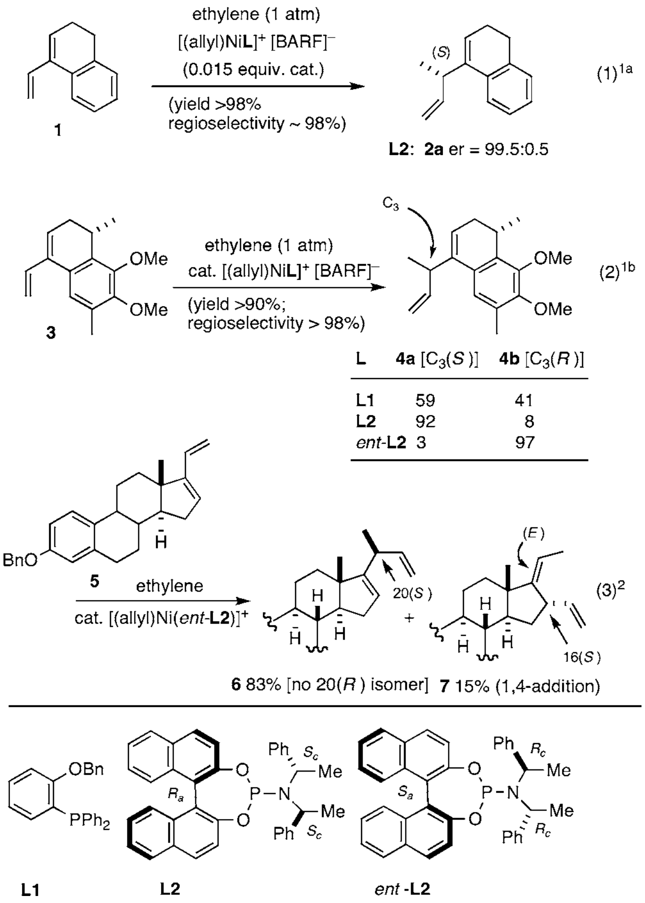
Supporting Information

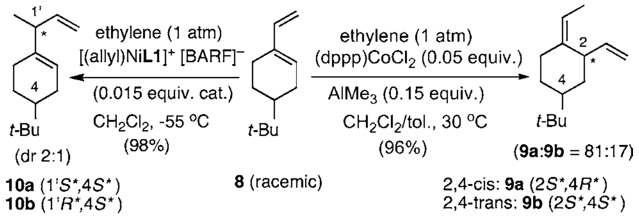
ABSTRACT: 1-Vinylcycloalkenes undergo highly regio- and enantioselective (>98% ee) 1,4-hydrovinylation (HV) when treated with ethylene (1 atm) at room temperature in the presence of [(*S*,*S*)-2,4-*bis*-diphenylphosphinopentane (BDPP)]$CoCl_2$ (0.05 equiv) and methylaluminoxane. The minor 1,2-HV products, 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-*tert*-butyl-1-vinylcyclohexene, when treated with Co[(*S*,*S*)-(BDPP)]Cl_2 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 the starting diene (eqs 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 by 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.



L	**4a** [C_3(*S*)]	**4b** [C_3(*R*)]
L1	59	41
L2	92	8
ent-**L2**	3	97

Scheme 1. 1,2- vs 1,4-Hydrovinylation of 4-*tert*-Butyl-1-vinylcyclohexene



Our studies started with an examination of Co(II)-catalyzed hydrovinylation of 4-*tert*-butyl-1-vinylcyclohex-1-ene (**8**, Scheme 1). After optimization of the reaction conditions using various combinations of $(L)_2CoCl_2/AlMe_3$ (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)$CoCl_2/Me_3Al$-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 place of the hydrocarbon

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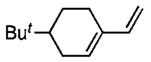
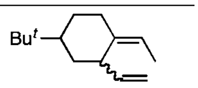
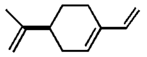
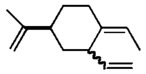
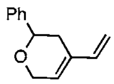
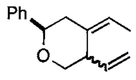
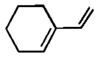
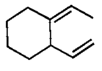
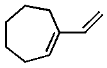
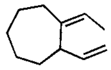
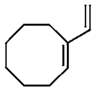
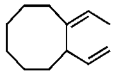
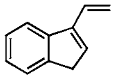
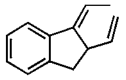
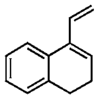
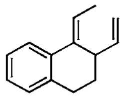
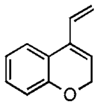
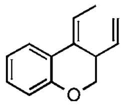
solutions of Me_3Al. Both the Ni(II) and Co(II) reactions are highly regioselective in the formation of the respective 1,2- and 1,4-adducts with less than 4% of the isomeric products (**9** and **10** respectively) formed in each case.

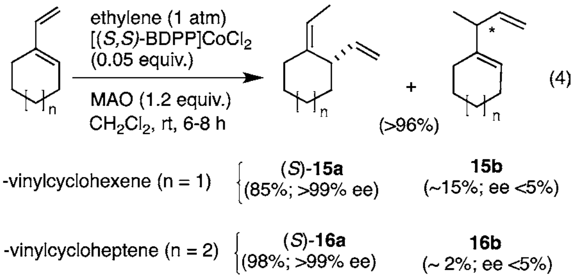
The scope of the reaction is illustrated with the examples shown in Table 1. Under the standard reaction conditions, the hydrovinylation is highly chemoselective for the 1,3-diene moiety, as shown by the reaction of the enantiopure substrate **11**, which was prepared from commercially available (−)-perrilaldehyde (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-hydrovinylations are 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).

Table 1. Co(II)-Catalyzed 1,4-Hydrovinylation of 1-Vinylcycloalkenes[a]

no	diene	conv. (%)	regiosel.[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.		>99	80:20	 **15a** + **15b**[d]
5.		>99	98:2	 **16a** + **16b**[d]
6.		>99	>99	 **17a**
7.	 **18**	>99	>99	 **19**
8.	 **20**	>99	>99	 **21**
9.	 **22**	~97	>99	 **23**

[a] See Scheme 1 for typical procedure using $(DPPP)CoCl_2$ as catalyst and 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.

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 [$(Ph_3P)_3RhCl$, CH_2Cl_2, H_2 (35 psi), followed by O_3, Me_2S][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.

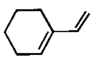
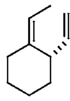
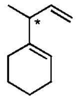
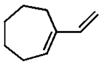
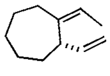
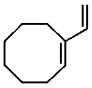
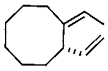
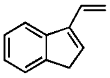
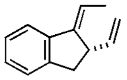
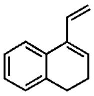
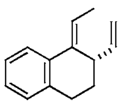
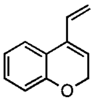
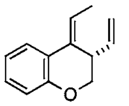
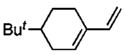
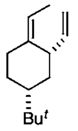
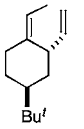


(4)

As illustrated by the examples listed in Table 2, the $(BDPP)CoCl_2$-catalyzed asymmetric 1,4-hydrovinylation is a broadly applicable reaction. Vinylcyclooctene, as compared to the six- and seven-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-*tert*-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- (**9**:**10** = 98:2) and diastereoselectivity (**9a**:**9b** = 81:17) in the formation of the products seen with the achiral

Table 2. Co(II)-Catalyzed Asymmetric 1,4-Hydrovinylation of 1-Vinylcycloalkenes[a]

no	diene	conv. (%)	regiosel.[b]	Product (%ee)[c] (config.)[d]
1.		>99	85:15	  **15a**[c] [>99] **15b** [<5]
2.		>95	98:2	 **16a**[c] [>99]
3.		>99	>99	 **17a** [>99]
4.	 **18**	>99	>99	 **19** [>99]
5.	 **20**	>99	>99	 **21** [>99]
6.	 **22**	~97	>99	 **23** [>98]
7.	 **8** (racemic)	>99	87:13	  **9a**[e] (2*S*,4*R*) **9b**[e] (2*S*,4*S*) [>98] [>98]

[a] See eq 4 and Supporting Information for details. [b] 1,4-HV/1,2-HV. Determined by ^{1}H 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] **9a**:**9b** = 60:40. Assignments (tentative) based on configurations of **16a** and **21**.

(DPPP)-Co(II) complex (Scheme 1, Table 1, entry 1) shows significant erosion when the [(*S*,*S*)-BDPP]Co(II) complex is used (regioselectivity **9**:**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% (entry 7, Table 2). 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 monosubstitued 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.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(2) Saha, B.; Smith, C. R.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2008**, *130*, 9000.

(3) (a) Sharma, R. K.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2010**, *132*, 3295. Other reports of Co-catalyzed asymmetric hydrovinylation: (b) Grutters, M. M. P.; Müller, C.; Vogt, D. *J. Am. Chem. Soc.* **2006**, *128*, 7414. (c) Grutters, M. M. P.; van der Vlugt, J. I.; Pei, Y.; Mills, A. M.; Lutz, M.; Spek, A. L.; 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 to the seminal studies of the Hilt group. For a recent review, see: (a) Hilt, G. *Synlett* **2011**, 1654. For representative examples of hydroalkenylation of dienes, see: (b) Hilt, G.; du Mesnil, F.-X.; Lüers, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 387. (b) Hilt, G.; Lüers, S. *Synthesis* **2002**, 609. (c) Hilt, G.; Danz, M.; Treutwein, J. *Org. Lett.* **2009**, *11*, 3322. (d) Arndt, M.; Reinhold, A.; Hilt, G. *J. Org. Chem.* **2010**, *75*, 5203. (e) Hilt, G.; Roesner, S. *Synthesis* **2011**, 662. (f) Bohn, M. A.; 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, W. A.; Lutz, S.; Wenz, G.; tom Dieck, H. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1556. Moreau, B.; Wu, J. Y.; Ritter, T. *Org. Lett.* **2009**, *11*, 337. 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.

(5) Ligands: BDPP = bis-2,4-diphenylphosphinopentane; DPPM = diphenylphosphinomethane; DPPE = diphenylphosphinoethane; DPPP = diphenylphosphinopropane; DPPB = diphenylphophinobutane; Cy_3P = 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 $(Cy_3P)_2Ru(CO)(H)(Cl)/HBF_4$ also gives mostly the 1,2-hydrovinylaion products, albeit in modest yields. See: He, Z.; Yi, C. S.; Donaldson, W. A. *Org. Lett.* **2003**, *5*, 1567. 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 easiy distinguished by the chemical shifts of the bis-allylic hydrogen. This proton appears as a ddd at δ 2.93 in *cis*-**9** and as broad singlet at δ 3.46 in *trans*-**9**. 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 methyl-silicone column are significantly lower than those of the 1,2-adducts. See Supporting Information for details.

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(10) To a solution of 0.05 equiv of (*S,S*)-(BDPP)$CoCl_2$ and 1.25 equiv of methylaluminoxane in CH_2Cl_2 under an ethylene atmosphere was added a CH_2Cl_2 solution of the diene. The mixture was stirred for 6−8 h at room temperature and was quenched by adding a 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 ^{1}H 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 baseline 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.

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