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Reactivity and Selectivity in Hydrovinylation of Strained Alkenes

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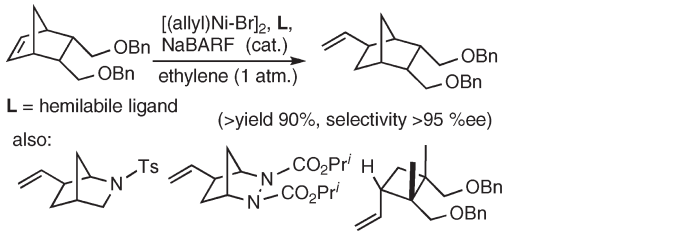

- Strained alkenes are viable substrates for Ni-catalyzed hydrovinylation
- Highest ee recorded for a C-C bond-forming reaction of a norbornene derivative
- Azabicyclo[2.2.1]heptenes do not undergo ring-opening during carbametallation

The scope of Ni(II)-catalyzed hydrovinylation has been extended to strained alkenes such as heterobicyclic [2.2.1]heptanes and cylobutenes. Reactions involving the heterobicyclic compounds are rare examples for this class of compounds where the metal-catalyzed C−C bond-forming reactions proceed *without* a concomitant ring-opening process. While the enantioselectivity in these systems remains modest, hydrovinylation of *endo*-5,6–bis-benzyloxymethylbicyclo[2.2.1]hept-2-ene gives excellent yield (> 90%) of the product with one of the highest enantioselectivities (95−99% ee) reported for a C−C bond-forming reaction of norbornenes.

Introduction

Heterodimerization of alkenes is a reaction with a huge potential for the synthesis of valuable intermediates since the starting materials are often readily available, or can easily be synthesized.[1,2] Advantages of alkenes over other conventional carbon feedstocks such as CO or HCN include their lack of toxicity and ease of handling while possessing sufficient reactivity to permit activation by transition metal complexes. In addition, depending on the substitution pattern, an alkene could be prochiral, and thus can serve as a cheap source for enantiomerically pure intermediates. However, since the two starting materials and the expected product(s) in a dimerization necessarily carry the same functional group, viz., an alkene, finding successful reaction conditions without concomitant side reactions such as homodimerizations, oligomerizations, and isomerizations is more challenging. The success of the reaction depends on the judicious choice of two alkenes, where there are significant differences in their reactivities. Such differences might result from either electronic or steric reasons. Proper choice of a catalyst can augment such differences, and a number of these dimerization reactions have been developed.[3] Hydrovinylation (addition of ethylene) of alkenes (eq 1) is one such reaction where significant progress has been achieved in several areas including the development of enantioselective processes. Codimerization of ethylene with more reactive partners like vinylarenes and 1,3-dienes has been carried out with excellent overall selectivity, and advances in broadening the scope of this

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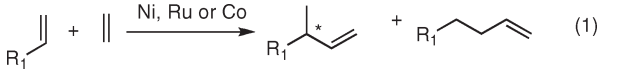
reaction with respect to substrates and catalysts continue unabated.[4]

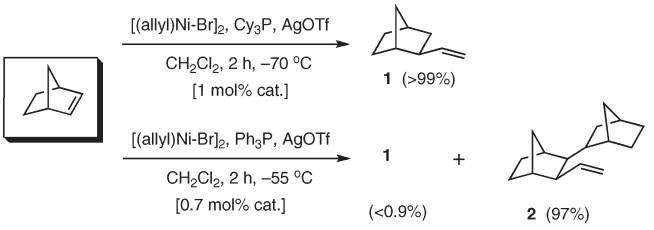


(1)

Results and Discussion

Norbornene represents a class of substrates where the viability of the reaction depends presumably on the enhanced reactivity of the strained bicyclic system as compared to ethylene and the dimerization product (Scheme 1). Indeed hydrovinylation of norbornene was among the first metal-catalyzed asymmetric carbon−carbon bond-forming reactions ever reported,[5] even though the enantioselectivity was unacceptable by current standards. Other reports of codimerization of norbornene with ethylene include the use of $[Ni(2,4,6\text{-}Me_3C_6H_2)(CH_3CN)(phosphane)]^+[BF_4]^-$,[6]

SCHEME 1. Ligand Dependence on the Ni-Catalyzed Hydrovinylation of Norbornene



$(PCy_3)_2(CO)RuHCl/HBF_4 \cdot Et_2O$,[7] and Co(pyridineimine)Cl_2/MAO.[8] In 2003 we reported remarkable ligand effects on the course of the Ni-catalyzed hydrovinylation of norbornene (Scheme 1). It was shown that under our then newly developed reaction conditions a ligand with a smaller cone angle (Ph_3P, 145°) gave a 2:1 adduct (norbornene:ethylene) whereas a larger ligand (Cy_3P, cone angle 180°) gave a 1:1 adduct.[9] Among several chiral ligands examined, a phosphoramidite ligand (**L4**, Figure 1) derived from 1,1′-binaphthol gave quantitative yield, giving the 1:1 adduct (**1**)

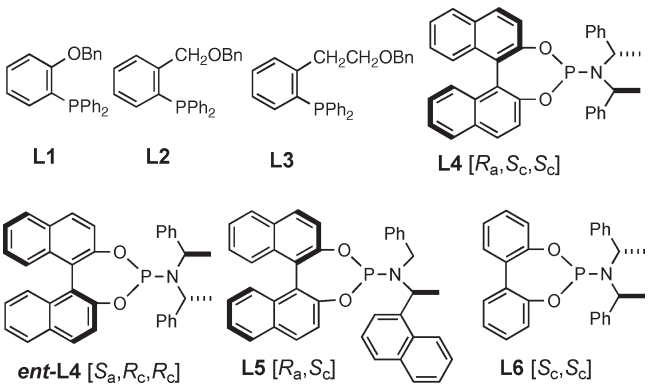


FIGURE 1. Ligands for hydrovinylation of strained alkenes.

in ~80% ee. Even though this represents one of the highest enantioselectivities reported for a carbon−carbon bond-forming reaction of norbornene,[10] the generality of this reaction, or the broader question of whether reactivity differences brought about by strain can be used to effect a selective heterodimerization, has not been addressed. In this paper we disclose the first experiments that deal with this aspect of hydrovinylation.

Hydrovinylation of Norbornene Derivatives. Our studies started with a detailed examination of the hydrovinylation of *endo*-5,6-bis-5,6-(benzyloxymethyl)bicyclo[2.2.1]hept-2-ene (**3**), using the ligands **L1**−**L6**. This substrate was chosen as a prototypical bicyclo[2.2.1]alkene since the enantiomers of the product can be detected by UV absorption, and thus directly analyzed on a chiral stationary phase HPLC column. The choice of ligands for this study is based on several previous observations from which we concluded that hemilabile ligands, when used in conjunction with a highly dissociated counterion (e.g., 3,5-[$[(CF_3)_2C_6H_3]_4B]^-$, $BARF^-$), gave the highest selectivity in the reactions of vinylarenes[11,12] and 1,3-dienes.[13,14] It was also known that in ligands **L1**−**L3** the location of the "hemilabile" oxygen in relation to the phosphorus atom is crucial for obtaining high regioselectivity for specific classes of substrates. Thus we have shown that ligand **L1** is the most suitable one for the hydrovinylation of certain classes of 1,3-dienes,[13] ligand **L2** is best for vinylarenes,[15] and ligand **L3** gave low selectivities for all classes

(4) For representative examples, see: (a) Jolly, P. W.; Wilke, G. Hydrovinylation. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; VCH: New York, 1996; Vol. 2, pp 1024−1048. (b) Nomura, N.; Jin, J.; Park, H.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1998**, *120*, 459. (c) Goossen, L. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3775. (d) RajanBabu, T. V.; Nomura, N.; Jin, J.; Radetich, B.; Park, H.; Nandi, M. *Chem.—Eur. J.* **1999**, *5*, 1963. (e) He, Z.; Yi, C. S.; Donaldson, W. A. *Org. Lett.* **2003**, *5*, 1567. (f) Diez-Holz, C. J.; Böing, C.; Franció, G.; Hölscher, M.; Leitner, W. *Eur. J. Org. Chem.* **2007**, 2995. (g) Tsujita, H.; Ura, Y.; Matsuki, S.; Wada, K.; Mitsudo, T.; Kondo, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5160. (h) Ho, C.-Y.; Ohmiya, H.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 1893. (i) Zhang, Q.; Zhu, S. F.; Qiao, X. C.; Wang, L. X.; Zhou, Q. L. *Adv. Synth. Catal.* **2008**, *350*, 1507. (j) 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. (k) RajanBabu, T. V. *Synlett* **2009**, 853. (l) Sharma, R. K.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2010**, *132*, 3295.

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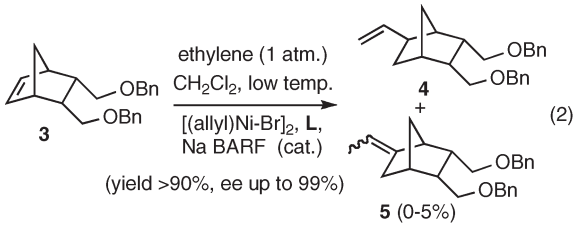
(15) For example, hydrovinylation of styrene with $[(allyl)Ni]Br]_2$/ligand **L2**/NaBARF (0.007 equiv catalyst) at room temperature in an atmosphere of ethylene gave >99% yield of 3-phenyl-1-butene with >99% selectivity for this isomer. Under these conditions most other ligands lead to extensive isomerization of the initial product into (*Z*)- and (*E*)-2-phenyl-2-butenes.

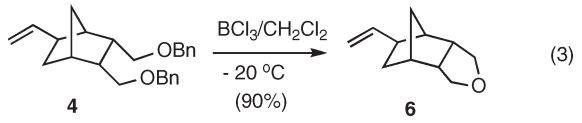
TABLE 1. Hydrovinylation of 3[a]

entry	ligand	conditions (mol % cat./ temp/time h)	yield of **4** (%) selec. (% ee) sign of [α] for major
1	**L1**	3/−22 °C/3	70[b,c]/NA
2	**L1**	4/23 °C/2	< 5/NA
3	**L2**	3/23 °C/2	48[b,c]/NA
4	**L3**	4/23 °C/2	72[b−d]/NA
5	**L4**	3/−78 °C/5	92/93 (−)
6	*ent*-**L4**	3/−78 °C/6	93/95−99 (+)[e]
7	**L5**	3/−78 °C/6	95/66 (−)
8	**L6**	3/−78 °C/6	92/94 (−)

[a]See eq 2 and the Experimental Secion for details of the procedure. [b]Product isolated as a mixture of **3** and **4**. [c]The rest of the starting material. [d]After 10 h, no starting material, only isomerization product, **5** along with other contaminants. [e]Product *ent*-**4**.

of substrates. The phosphoramidites, popularly known as the Feringa ligands, are by far the most successful ligands for this reaction.[16−21] In our work the three ligands shown **L4**−**L6** have been found to be broadly applicable for several of the hydrovinylation reactions.[21]





The Ni(II)-catalyzed hydrovinylation of **3** with the ligands carrying a hemilabile benzyloxy substituent (**L1**−**L3**) parallels our observations in the related reaction with vinylarenes (Table 1). Nickel complex formed from ligand **L1**, allyl nickel bromide dimer, and NaBARF is competent to effect the hydrovinylation of this substrate at low temperature (entry 1), but at higher temperatures, extensive isomerization of the product (to give a mixture of **4** and **5**) is observed (entry 2). Ligands **L2** and **L3**, on the other hand, did not isomerize the initially formed product up to several hours. We had previously found that **L2** was one of the few ligands capable of effecting hydrovinylation of several vinylarenes at room temperature with no isomerization of the initially formed 3-aryl-1-butene.[15] Compound **5** is formed in varying amounts (0−10%) depending on the catalyst and reaction conditions (and its structure is presumed on the basis of ^{1}H NMR, which shows a distinct olefinic H at δ 5.04 (q, J = 6 Hz) and C_{sp^2}-CH_3 signals at δ 1.81 (d, J = 6 Hz). As with the other substrates, finely tuned phosphoramidites are the best ligands for the hydrovinylation of this substrate. Thus ligand **L4** and its enantiomer, *ent*-**L4**, and a simplified analogue containing the biphenyl core (**L6**) gave the best overall yield and selectivity (>90% yield, 93−99% ee) for this reaction (entries 5, 6, and 8). This result represents the highest enantioselectivity ever observed for an asymmetric catalyzed C−C bond-forming reaction of a norbornene derivative. Surprisingly, the ligand **L5**, which gave the highest yields and enantioselectivities (up to 99% yield and >95% ee) for a wide spectrum of vinylarenes,[21] was only moderately selective (66% ee) for hydrovinylation of **3**, even though the yield of the reaction was excellent (entry 7). The enantioselectivities of the products were determined by chiral stationary phase HPLC separation of the primary products on Chiracel-AD-H column, using hexane and isopropanol (99.6:0.4) as the mobile phase. The ratios of enantiomers were further confirmed by conversion of the dibenzyl ether **4** into a THF derivative **6** (eq 3). The enantiomers of the THF derivative show baseline resolution in gas chromatography on a Cyclodex B column. A racemic authentic sample of **6** was prepared via hydrovinylation with ligand **L3**.

Hydrovinylation of Azabicyclo[2.2.1]alkenes. Even though carbametalation and related reactions of norbornene and similar [2.2.1]-bicyclic molecules are well documented, reactions of the corresponding heterocyclic analogues where the bicyclic motif is preserved are rare.[22−24] Such metalation reactions involving Ni, Pd, and Rh intermediates most often lead to ring-opening reactions.[24−31] In earlier work we had noticed that substrates carrying heteroatoms, especially nitrogen, are slow to undergo hydrovinylation under moderate conditions.[19] In light of this observation it is surprising that the azabicyclic alkene **7** undergoes hydrovinylation in very good yields, even though, not unexpectedly, the product is obtained as a mixture of two regioisomers (Scheme 2, Table 2). For this reaction, the achiral ligands **L1**−**L3** are much less effective (entries 1−3) compared to the phosphoramidite ligands **L4**−**L6**, the Ni-complexes of the former requiring higher temperatures to get reasonable yields. Yields up to 89% are obtained by using the latter class of ligands at −47 °C (entries 4−6). In these hydrovinylations, ligands **L2** and **L3** are the least reactive. For **L1**, at temperatures where full conversion is observed (−10 °C), the primary products are completely isomerized to the ethylidene derivatives **10**−**13**. The compounds **12** and **13** were not separable by column chromatography, and were identified as the ketone **14**, prepared by Ru-mediated oxidation of the alkenes **12** and **13**.

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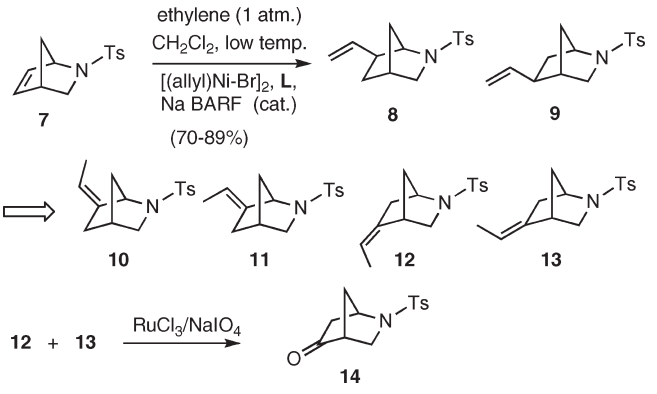
TABLE 2. Ni-Catalyzed Hydrovinylation of 7[a]

entry	ligand	conditions (mol % cat./temp/time, h)	yield of HV (%)	products (%)	enantioselectivity for **8**, **9** (% ee)
1	**L1**	14/−10 °C/4	78[b]	**10** (25), **11** (22) [**12** + **13**] (31)	
2	**L2**	8/20 °C/21	79	**8** (46), **9** (33)	
3	**L3**	8/20 °C/21	70	**8** (40), **9** (30)	
4	**L4**	8/−47 °C/5	80	**8** (38), **9** (42)	**8** (21), **9** (33)
5	**L5**	8/−47 °C/6	89	**8** (53), **9** (36)	**8** (7), **9** (0)
6	**L6**	8/−47 °C/6	89	**8** (37), **9** (52)	**8** (20), **9** (31)

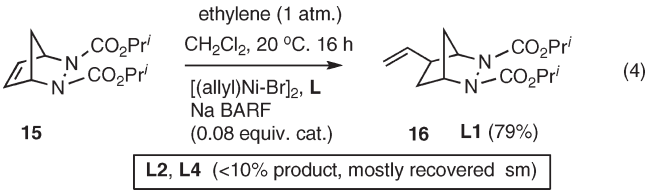
[a]See Scheme 2 and the Experimental Section for procedure. [b]At −10 °C, **8** and **9** fully isomerized to **10**, **11**, **12**, and **13**; at −47 °C, 22% yield of [**8** + **9**] with the rest of the starting material.

SCHEME 2. Hydrovinylation of a [2.2.1]-Heterobicyclic Amide (7)

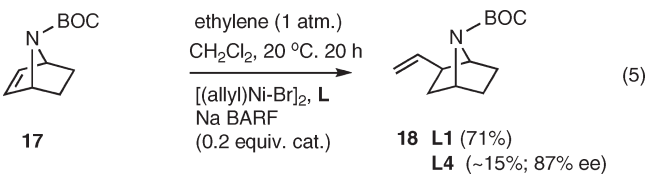


Note that the enantioselectivities of these reactions are among the lowest we have seen even with the highly successful phosphoramidite ligands (entries 4−6, column 6).

Two other [2.2.1]-heterobicyclic molecules that undergo hydrovinylation are shown in eqs 4 and 5. In general, these substrates react only sluggishly with most ligands, and invariably higher temperatures are required to obtain acceptable conversion to the products. Curiously for both these substrates ligand **L1** works best. Attempts to achieve complete conversion lead to extensive isomerization of the initial products and other side reactions. The hydrovinylation reaction of **17** with a Ni(II)-**L4** complex gave a poor yield of the product **18**, yet with an unusually high enantioselectivity (> 87% ee) as determined by chiral stationary phase GC, where baseline separation of the enantiomers was observed. The configuration of the major product has not been confirmed independently, but the proposed structure is based on the previous results from hydrovinylation of norbornene.[9]



(4)



(5)

Finally, the bicyclic heterocycles shown in Figure 2 failed to undergo the Ni-catalyzed hydrovinylation under a variety of conditions. The exact reason why these substrates fail to undergo the reaction is not obvious. One might speculate that the first two substrates are Lewis basic and probably form stable Ni(II) intermediates. The third and the fourth substrates, because of the disposition of the substituents on N (over the lone double bond), are sterically encumbered. Recall that a reactive Ni(II)intermidiate, possibly a hydride, has to initially coordinate with the double bond before the reaction can take place.

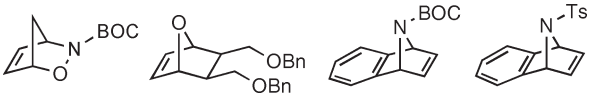


FIGURE 2. Heterocyclic compounds that failed to undergo hydrovinylation.

Hydrovinylation of a Cyclobutene (19). Except for a few notable examples that involve metathesis reactions (Ru)[32−36] and rearrangements (Rh),[37] activation of the strained double bond in cyclobutenes for metal-catalyzed carbon−carbon bond-forming reactions has not been explored.[38] We find that the cyclobutene double bond is sufficiently reactive to take part in a heterodimerization reaction with ethylene even at low temperatures. Thus under the standard reaction conditions described earlier, compound **19** undergoes hydrovinylation reactions giving the expected product in moderate yields (Scheme 3 and Table 3). Attempts to isolate **20** from a mixture of **19** and **20** were unsuccessful, and this mixture was subjected to hydroboration in order to isolate the hydrovinylation product as a primary alcohol derivative **21**. As with other substrates, the phosphoramidites, in particular the ligand **L6**, gave the best selectivities for this substrate. While the absolute configuration of the product has not been determined, the relative configuration of **20** was established by NOE measurements on the hydroboration product **21**. We have not optimized these reactions except for examining the viability of these ligands.

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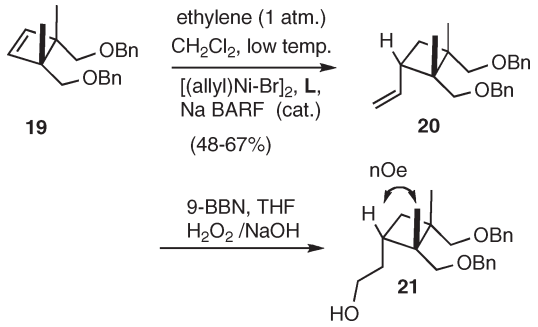
TABLE 3. Ni-Catalyzed Hydrovinylation of Cyclobutene 19

entry	ligand	conditions (mol % cat./temp/time, h)	yield of **20** (%); (**20**:**19**)[a]	% ee (**20**) (sign of [α])
1	**L1**	14/−30 °C/15	32; 20:1	
2[b]	**L2**	14/43 °C/12	67; 5:1	
4	**L3**	14/23 °C/18	0[c]	
5	**L4**	10/−50 °C/8	47; 4.3:1.0	55 (−)
6	**L4**	14/−45 °C/6.5	40; 32:1	
8	**L5**	10/−50 °C/3.5	46; 1.4:1.0	52 (−)
7	**L6**	10/−50 °C/5	48; 4.7:1.0	82 (−)

[a]Ratio and yield of product calculated based on ^{1}H NMR of a mixture of **19** and **20**. [b]In $ClCH_2CH_2Cl$. [c]Complex mixture.

SCHEME 3. Hydrovinylation of a Cyclobutene (19)



Conclusions

An *endo*-5,6-bis(benzyloxymethyl)bicyclo[2.2.1]hept-2-ene derivative undergoes Ni(II)-catalyzed asymmetric hydrovinylation giving the highest enantioselectivities (∼95% ee) reported for a C−C bond-forming reaction of norbornene derivatives. Other results reported in this paper clearly demonstrate that the scope of Ni(II)-catalyzed hydrovinylation extends to strained alkenes such as heterobicyclic-[2.2.1]heptenes and cyclobutenes. Reactions involving the heterobicyclic compounds are rare examples for this class of compounds where the metal-catalyzed C−C bond-forming reactions proceed *without* a concomitant ring-opening process. While the enantioselectivity in these systems remains modest, we hope that these results will stimulate further work in this area, especially since the products of this reaction can potentially be transformed into highly substituted cyclohexane derivatives.

Experimental Section

General Methods. Reactions requiring air-sensitive manipulations were conducted under an inert atmosphere of nitrogen by Schlenk techniques or with the aid of a Vacuum Atmospheres glovebox. Methylene chloride and 1,2-dichloroethane were distilled from calcium hydride under a dry atmosphere and stored over molecular sieves. Tetrahydrofuran was distilled under nitrogen from sodium/benzophenone ketyl. The ligands **L1**−**L3**,[39] **L4**−**L6**,[40] and $Na^+\{[3,5\text{-}(CF_3)_2C_6H_3]_4B\}^-$ (NaBARF)[41] were prepared according to the methods described in the literature. Ethylene (99.5%) was purchased from Matheson and passed through Drierite before use. Flash column chromatography was carried out on silica gel 40. Enantiomeric excesses of volatile chiral compounds were determined by gas chromatographic analysis on chiral stationary phase GC columns (Cyclodex B, 25 m × 0.25 mm ID, 0.12 mm film thickness or Cyclosil 30 m × 0.25 mm ID, 0.25 μm thickness). Enantiomeric excesses of other compounds were determined by HPLC using a Chiralcel OJ-H or a Chiralcel AD-H column with hexane/isopropanol as solvents. Conditions are described under specific compounds. Optical rotations were recorded at the sodium D line in chloroform.

Synthesis of *endo*-5,6-Bis(benzyloxymethyl)bicyclo[2.2.1]hept-2-ene (3). To a solution of 2,3-bis(hydroxymethyl)bicyclo[2.2.1]-hept-2-ene[42] (1.79 g, 11.6 mmol) in THF (30 mL) was added NaH (1.39 g, 60 wt % in mineral oil, 34.8 mmol) in one portion at 0 °C under argon. The resulting suspension was stirred at 0 °C for 60 min and then benzyl bromide (4.4 mL, 37 mmol) was added dropwise at 0 °C. The mixture was allowed to warm to room temperature and stirred for 18 h. Water was added carefully to quench the reaction, and the mixture was extracted with ether and the organic layers were combined, washed with brine, dried, and concentrated. The resulting residue was purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate =30/1) to obtain 3.4 g (88%) of **3** as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (d, J = 8.2 Hz, 1 H), 1.39 (d, J = 8.2 Hz, 1 H), 2.46−2.47 (m, 2 H), 2.89 (s, 2 H), 2.95−2.99 (m, 2 H), 3.21−3.24 (m, 2 H), 4.32 and 4.38 (AB quartet, J = 12.0 Hz, 4 H), 5.96 (s, 2 H), 7.17−7.27 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.6, 45.6, 49.0, 70.5, 73.0, 127.5, 127.6, 128.3, 135.3, 138.7; IR (neat) 2920, 2855, 1496, 1454, 1365, 1095 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{26}O_2Na$ ([M + Na]$^+$) 357.1830, obsd 357.1832.

Typical Procedure for Catalytic Hydrovinylation (Table 1, entry 8). The precatalyst was prepared as follows in a glovebox: To di-η-allyl-di-μ-bromonickel(II) (1.0 mg, 0.00278 mmol) in CH_2Cl_2 (1 mL) was added a solution of ligand **L6** (2.5 mg, 0.0057 mmol) in CH_2Cl_2 (1 mL) at ambient temperature. The resulting solution was added to a suspension of NaBARF (5.0 mg, 0.00564 mmol) in dichloromethane (1 mL) and the mixture was stirred at ambient temperature in a septum-sealed 25 mL round-bottomed flask for 10 min affording a dark brown solution containing a small amount of fine particulate (NaBr). The flask was removed from the glovebox and was then cooled to −78 °C (acetone−dry ice bath), creating a small vacuum. Dry ethylene (passed through a 0.5 in. × 4 in. column of Drierite) was introduced via needle through the serum stopper and the vessel atmosphere was slowly evacuated 3 times with a 60 mL syringe. At 78 °C, a solution of **3** (60 mg, 0.18 mmol) in 1 mL of dry CH_2Cl_2 is introduced dropwise into the solution of the precatalyst over a 1 min period via a syringe. The vessel was then maintained at −78 °C for a period of 6 h. At the end of this period the ethylene line is removed and the reaction was quenched by addition of a saturated aqueous NH_4Cl solution. The product was extracted with ether. The organic layers are combined, dried over $MgSO_4$, and concentrated to obtain a yellow oil. The resulting residue was purified by column chromatography

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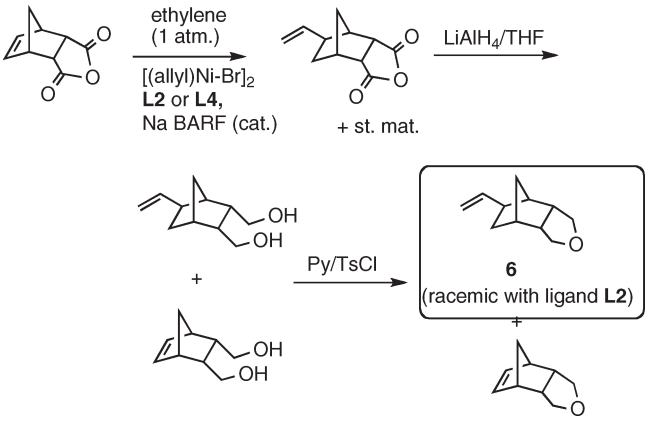
on silica gel (eluting with hexanes/ethyl acetate = 40/1) to obtain 60 mg (92%) of **4** as an oil.

Hydrovinylation of Substrate 3: Product 4. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08−1.12 (m, 1 H), 1.22 (d, J = 9.8 Hz, 1 H), 1.42 (d, J = 9.8 Hz, 1 H), 1.59−1.61 (m, 1 H), 2.14 (s, 1 H), 2.18 (m, 3 H), 2.25 (s, 1 H), 3.30 (t, J = 8.7 Hz, 1 H), 3.37 (t, J = 8.7 Hz, 1 H), 3.43−3.46 (m, 1 H), 3.48−3.51 (m, 1 H), 4.35−4.44 (m, 4 H), 4.80−4.85 (m, 2 H), 5.65−5.72 (m, 1 H), 7.17−7.27 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.1, 36.7, 37.6, 39.5, 40.2, 40.7, 45.6, 67.8, 68.5, 73.1, 112.0, 127.5, 127.6, 127.6, 128.3, 138.6, 138.6, 144.0; IR (neat) 2954, 2871, 1634, 1496, 1454, 1366, 1097 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{30}O_2Na$ ([M + Na]$^+$) 385.2144, obsd 385.2139. $[\alpha]^{22}_D$ −9.1 (*c* 0.33, $CHCl_3$) (**L6** at −35 °C, 82% ee by HPLC); $[\alpha]^{22}_D$ +13.1 (*c* 0.42, $CHCl_3$) (*ent*-**L4** at −78 °C, 95% ee by HPLC; >99% by GC of the corresponding THF derivative **6**, see next experiment). HPLC conditions and retention times (Chiracel AD-H): solvent hexanes:isopropanol 99.6:0.4; flow rate 0.3 mL/min, retention times (min): 25.53 (+)-isomer, 29.54 (−)-isomer. The retention time for starting material: 32.30 min (see the chromatograms in the Supporting Information). Chiral stationary phase GC for **6** (Cyclodex B column, programmed run: 10 min at 80 °C, 1 deg per min to 110 °C, 60 min at 110 °C; retention time: 43.91 min, (−)-isomer: >99% (only one isomer seen in the gas chromatogram). Retention times of authentic mixture (−)-isomer: 43.75 min; (+)-isomer: 44.45 min.

Conversion of 4 into the THF Derivative 6. To a solution of **4** (131 mg, 0.36 mmol, prepared with **L6** at −78 °C) in CH_2Cl_2 (20 mL) was added a hexane solution of BCl_3 (3.6 mL, 1 mol L^{-1}) dropwise at −20 °C under nitrogen. The resulting solution was stirred for 2 h and then quenched with MeOH (10 mL) at the same temperature. The mixture is stirred for 40 min. The solvent was then removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel (eluting with pentane/ethyl ether = 50/1) to obtain 59 mg (90%) of **6** as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05−1.09 (m, 1 H), 1.31 (d, J = 10 Hz, 1 H), 1.52 (d, J = 10 Hz, 1 H), 1.76−1.81 (m, 1 H), 1.99−2.00 (m, 1 H), 2.13−2.15 (m, 1 H), 2.38−2.53 (m, 3 H), 3.31 (dd, J = 9.6, 6.8 Hz, 2 H), 3.80 (d, J = 9.5 Hz, 1 H), 3.80 (d, J = 9.5 Hz, 1 H), 4.78 (d, J = 10.4 Hz, 1 H), 4.85 (d, J = 17.1 Hz, 1 H), 5.65−5.72 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.6, 38.5, 39.7, 40.7, 45.4, 46.1, 46.2, 68.6, 69.0, 111.8, 144.1; IR (neat) 2945, 2848, 1636, 1090, 998, 908 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{16}ONa$ ([M + Na]$^+$) 187.1099, obsd 187.1104. $[\alpha]^{22}_D$ −31.7 (*c* 0.54, $CHCl_3$). GC (methylsilicone) conditions: 110 °C (isothermal), retention time: 29.88 min. GC Cyclodex B column, retention times (min) 43.81 min, confirmed by comparison to authentic product (see next experiment)

Synthesis of Racemic 6 via Hydrovinylation of 4 Followed by THF Formation. A racemic sample was prepared by hydrovinylation of **4** by using the ligand **L3** (4 mol % catalyst, 23 °C, 2 h, 72% yield) followed by the THF formation. GC retention times (min): 43.76 min (~50%), 44.45 min (~50%).

An Alternate Synthesis of THF Derivative 6 via Hydrovinylation of Cyclopentadiene/Maleic Anhydride Adduct. The general hydrovinylation procedure was employed for the anhydride adduct (50 mg, 0.30 mmol) with ligand **L4** (13.2 mg, 0.024 mmol, 8 mol % catalyst) at 23 °C over 13 h. The crude product was passed through a short pad of silica gel and redissolved in THF (10 mL) at 0 °C, and $LiAlH_4$ (40 mg, 1.05 mmol) was added to this solution. The reaction mixture was warmed to room temperature and stirred for 14 h and then quenched with saturated NH_4Cl. The aqueous layer was extracted with ether four times. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (eluting with hexanes/ethyl acetate = 1.0/1.2) to obtain 24 mg of a 1.0:2.8 mixture of two diols, one corresponding to the unreacted starting material and one to the hydrovinylation product, in 13% and 36% yields, respectively. To an ice-cooled solution of the mixture of diols (27 mg) and pyridine (27.6 mg, 0.35 mmol) in CH_2Cl_2 (2 mL) was added *p*-TsCl (33.3 mg, 0.17 mmol). The reaction solution was stirred at room temperature for 21 h before addition of H_2O. The organic solution was separated, washed with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). After concentration, the residue was purified by silica gel column chromatography (pentane/ether, 50:1) to obtain 14 mg of a mixture of **6** and THF derivative from the starting material. The mixture analyzed by chiral stationary phase GC on the Cyclodex B column revealed that the product was nearly racemic (< 3% ee).



Synthesis of *N*-(4-Toluensulfonyl)-2-aza-bicyclo[2.2.1]hept-5-ene (7). This compound was prepared according to a literature procedure.[43] Cyclopentadiene (4 mL, 49.0 mmol) was added to a solution of NH_4C1 (1.325 g, 24.8 mmol), 36% aqueous formaldehyde (2.6 mL, 34.0 mmol), and MeOH (5 mL). The reaction mixture was vigorously stirred for 12 h at room temperature before diluting with an equal volume of water and was subsequently washed with diethyl ether (2 × 10 mL). The aqueous phase was made basic with saturated NaOH. The 2-azabicyclo[2.2.1]hept-5-ene was isolated by extraction with ether (3 × 10 mL). To a mixture of this extract and 10% NaOH (10 mL) was added a solution of TsCl (4 g, 21.0 mmol) in a mixed solvent (ether: 6 mL; CH_2Cl_2: 3 mL) over a period of 5 min at room temperature. The mixture was stirred for 12 h. The organic layer was separated, dried with Na_2SO_4, filtered, and concentrated in vacuo. The resulting oil was purified by chromatography (EtOAc: hexanes = 1:7) to obtain the product (2.77 g, 53%) as a white solid: mp 67−70 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40−1.46 (m, 2 H), 2.39 (s, 3 H), 2.52 (dd, J = 8.5, 1.3 Hz, 1 H), 3.11 (broad s, 1 H), 3.31 (dd, J = 8.5, 2.8 Hz, 1 H), 4.62 (broad s, 1 H), 5.97−5.99 (m, 1 H), 6.07−6.09 (m, 1 H), 7.25 (d, J = 8 Hz, 2 H), 7.65 (d, J = 8 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 43.8, 47.1, 64.2, 127.7, 129.5, 133.5, 136.3, 136.7, 143.1; IR 1654, 1458, 1330, 1155, 1092, 662 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}NO_2SNa$ ([M + Na]$^+$) 272.0716, obsd 272.0715.

Typical Procedure for Catalytic Hydrovinylation of Heterobicyclic Alkenes (Table 2, Entry 4). The precatalyst was prepared as follows in a glovebox: To di-η-allyl-di-μ-bromonickel(II) (2.9 mg, 0.0080 mmol) in CH_2Cl_2 (1 mL) was added a solution of ligand **L4** (8.7 mg, 0.016 mmol) in CH_2Cl_2 (1 mL) at ambient temperature. The resulting solution was added to a suspension of NaBARF (14.3 mg, 0.016 mmol) suspended in dichloromethane (1 mL) and the mixture was stirred at ambient

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temperature in a septum-sealed 25 mL round-bottomed flask for 10 min affording a dark brown solution containing a small amount of fine particulate (NaBr). The flask was removed from the glovebox. The flask was then cooled to −47 °C in an acetonitrile−dry ice bath, creating a small vacuum. Dry ethylene (passed through a 0.5 in. × 4 in. column of Drierite) was introduced via needle through the serum stopper and the vessel atmosphere was slowly evacuated 3 times with a 60 mL syringe. After the solution was cooled to −47 °C, a solution of **7** (50 mg, 0.20 mmol) in 1 mL of dry CH_2Cl_2 is introduced dropwise into the solution of the precatalyst over a 1 min period via syringe. The vessel was then maintained at −47 °C for a period of 5 h. At the end of this period the ethylene line was removed and the reaction was quenched by addition of a saturated aqueous NH_4Cl solution. The product was extracted with ether. The organic layers are combined, dried over $MgSO_4$, and concentrated to give a yellow oil. The resulting residue was purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate = 9/1) to obtain 45 mg (80%) of an inseparable mixture of **8** and **9** as an oil.

Products of Hydrovinylation of 7 with Ligand L4. ^{1}H NMR (500 MHz, $CDCl_3$) (**8**) δ 0.84−0.86 (m, 1 H), 1.27−1.29 (m, 1 H), 1.35−1.44 (m, 1 H), 1.62−1.77 (m, 1 H), 2.40 (s, 3H), 2.44 (broad s, 1 H), 2.66−2.70 (m, 1 H), 2.98−3.07 (m, 2 H), 3.96 (broad s, 1 H), 4.89−4.98 (m, 2 H), 5.53−5.60 (m, 1 H), 7.28 (d, J = 8.2 Hz, 2 H), 7.68 (d, J = 8.2 Hz, 2 H); (**9**) δ 0.89−0.91 (m, 1 H), 1.29−1.31 (m, 1 H), 1.35−1.44 (m, 1 H), 2.01−2.06 (m, 1 H), 2.29 (broad s, 1 H), 2.30−2.36 (m, 1 H), 2.40 (s, 3 H), 2.98−3.07 (m, 2 H), 4.15 (broad s, 1 H), 4.89−4.98 (m, 2 H), 5.63−5.69 (m, 1 H), 7.28 (d, J = 8.2 Hz, 2 H), 7.68 (d, J = 8.2 Hz, 2 H); (**8** + **9**) ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 33.8, 34.0, 34.2, 37.4, 38.4, 43.0, 43.7, 47.0, 53.7, 54.0, 60.2, 64.0, 113.4, 114.8, 127.4, 127.4, 129.6, 135.8, 135.9, 139.8, 141.5, 143.2, 143.2; IR (neat) 3430, 2977, 2880, 1638, 1597, 1457, 1341, 1161, 1093, 818 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{19}NO_2SNa$ ([M+Na]$^+$) 300.1029, obsd 300.1041. HPLC conditions and retention times (Chiracel AD-H): solvent (hexanes:isopropanol) 98.5:1.5; flow rate 0.4 mL/min, retention times (min): for **8**, 43.06, 57.81; for **9**, 53.11, 60.77. (see the chromatograms in the Supporting Information)

Hydrovinylation of 7 with Ligand L1. The products of the reaction were separated into **10**, **11**, and a mixture of **12** and **13** by column chromatography on silica gel (eluting with hexanes/ethyl acetate = 9/1). The mixture of **12** and **13** was identified after conversion to a ketone **14** (see later).

10: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (d, J = 10.1 Hz, 1 H), 1.38 (d, J = 10.1 Hz, 1 H), 1.69 (d, J = 6.9 Hz, 3 H), 1.75 (d, J = 16 Hz, 1 H), 2.14−2.18 (m, 1 H), 2.39 (s, 3H), 2.51 (broad s, 1 H), 2.94 (d, J = 8.8 Hz, 1 H), 3.23−3.26 (m, 1 H), 4.71 (broad s, 1 H), 5.04 (q, J = 6.9 Hz, 1 H), 7.24 (d, J = 8.2 Hz, 2 H), 7.67 (d, J = 8.2 H, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.8, 21.5, 35.2, 37.0, 38.0, 53.1, 59.5, 116.8, 127.6, 129.2, 136.1, 138.6, 143.0; white solid, mp 98−102 °C ; IR (neat) 3448, 2980, 1597, 1452, 1338, 1159, 1094, 667 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{19}NO_2$-SNa ([M + Na]$^+$) 300.1029, obsd 300.1037.

11: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (d, J = 6.9 Hz, 3 H), 1.33 (d, J = 10.4 Hz, 1 H), 1.44−1.46 (m, 1 H), 1.51 (d, J = 16.1 Hz, 1 H), 2.07−2.11 (m, 1H), 2.39 (s, 3 H), 2.55 (broad s, 1 H), 2.88 (d, J = 8.8 Hz, 1 H), 3.27−3.30 (m, 1 H), 4.33 (broad s, 1 H), 5.34−5.38 (m, 1 H), 7.22 (d, J = 8 Hz, 2 H), 7.64 (d, J = 8 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.4, 21.5, 32.5, 37.1, 38.4, 53.2, 64.9, 116.8, 127.9, 129.1, 129.2, 135.7, 138.6, 142.8; white solid, mp 95−98 °C; IR (neat) 3427, 2921, 1593, 1449, 1323, 1154, 1090, 1052, 668 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{19}NO_2$-SNa ([M + Na]$^+$) 300.1029, obsd 300.1044.

Oxidation of 12 and 13. The inseparable mixture of the two isomers **12** and **13** was oxidized to ketone **14**. A flask is charged with a magnetic stirrer, 1 mL of carbon tetrachloride, 1.5 mL of water, and 8.7 mg (0.031 mmol) of a mixture of **12** and **13**. To this mixture was added sodium metaperiodate (33.6 mg, 0.157 mmol). To this biphasic solution was added an acetonitrile solution (1 mL) of ruthenium trichloride hydrate (0.65 mg, 0.0031 mmol). The entire mixture was stirred vigorously for 16 h at room temperature. The phases were separated and the aqueous phase was extracted 3 times with CH_2C1_2. The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by chromatography (EtOAc:hexanes = 1.0:1.5) to give the product (4.9 mg, 59%) as an oil. The structure was confirmed by comparison of ^{1}H NMR with the data reported in the literature.[43] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46−1.49 (m, 1 H), 1.75 (d, J = 10.7 Hz, 1 H), 2.09−2.35 (ABX system, υ_a = 2.11, υ_b = 2.32, J_{AB} = 18 Hz, J_{AX} = 4.4 Hz, J_{BX} = 3 Hz, 2 H), 2.42 (s, 3 H), 2.82 (broad s, 1 H), 3.32−3.33 (m, 2 H), 4.54 (broad s, 1 H), 7.32 (d, J = 8.2 Hz, 2 H), 7.72 (d, J = 8.2 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 36.4, 46.0, 48.4, 50.8, 59.1, 127.4, 130.0, 135.0, 144.0, 211.8; IR (neat) 3352, 2918, 2852, 1708, 1679, 1366, 1161 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}NO_3SNa$ ([M + Na]$^+$) 288.0665, obsd 288.0674.

Synthesis of Diisopropyl 2,3-Diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (15). The substrate was prepared following a procedure reported in the literature.[44] To a freshly distilled cyclopentadiene (0.62 mL, 7.60 mmol) solution in CH_2Cl_2 kept at 0 °C was added the diisopropyl azodicarboxylate (1 mL, 5.08 mmol). The reaction was allowed to warm to room temperature and stirred until full consumption of the starting material, as estimated by TLC. The solvent was evaporated under reduced pressure. The crude clear oil was purified by silica gel chromatography with 1:3 EtOAc/hexanes as eluent. The diazabicycle was obtained quantitatively as a white solid: mp 95−98 °C ; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (d, J = 6.3 Hz, 12 H), 1.65−1.70 (m, 2 H), 4.90−4.95 (m, 2 H), 5.10 (broad s, 2 H), 6.46 (broad s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 47.9, 65.2, 70.1, 134.2, 138.4, 158.5; IR (neat) 3411, 2981, 1743, 1700, 1373, 1307, 1174, 1100 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{20}N_2O_4Na$ ([M + Na]$^+$) 291.1315, obsd 291.1311.

Hydrovinylation of 15. 16: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (d, J = 6.3 Hz, 12 H), 1.58 (broad s, 1 H), 1.61−1.64 (m, 2 H), 2.05 (broad s, 1 H), 2.68 (broad s, 1 H), 4.33 (broad s, 1 H), 4.51 (broad s, 1 H), 4.93−4.97 (m, 2 H), 5.02−5.05 (m, 2 H), 5.63−5.70 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.0, 35.0, 43.3, 60,3, 64.4, 69.9, 115.3, 139.0, 157.3; IR (neat) 2980, 2937, 2878, 1697, 1468, 1374, 1105, 918, 770 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{24}N_2O_4Na$ ([M + Na]$^+$) 319.1628, obsd 319.1627.

Hydrovinylation of 7-*tert*-Butoxycarbonyl-7-azabicyclo[2.2.1]-hept-2-ene (17). The starting material was prepared according to a procedure reported in the literature.[45] **18**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35−1.56 (m, 3 H), 1.42 (s, 9 H), 1.64−1.73 (m, 3 H), 2.29−2.33 (m, 1 H), 4.00 (broad s, 1H), 4.22 (broad s, 1 H), 4.88 (d, J = 10.1 Hz, 1 H), 4.94 (d, J = 17.0 Hz, 1 H), 5.70−5.77 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.3, 29.7, 47.4, 79.3, 113.0, 142.0; IR (neat) 3365, 2920, 2852, 1704, 1454, 1366, 801 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{21}NO_2Na$ ([M + Na]$^+$) 246.1465, obsd 246.1462; GC (Cyclodex B, programmed run, 5 min at 110 °C, 0.5 deg/min, and finally 5 min at 130 °C). Retention times (min): 39.6, 40.3. Retention time for starting material **17** (min): 28.7.

***cis*-3,4-Bis(benzyloxymethyl)-3,4-dimethylcyclobutene (19).** To a solution of *cis*-1,2-dimethylcyclobut-3-ene-1,2-dimethanol[46] (1.06 g, 7.4 mmol) in THF (30 mL) was added NaH (888 mg, 60 wt % in mineral oil, 22.2 mmol) in one portion at 0 °C under argon. The resulting suspension was

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stirred at 0 °C for 60 min and then benzyl bromide (2.83 mL, 23.8 mmol) was added dropwise at 0 °C. The mixture was allowed to warm to room temperature and stirred for another 18 h. Water was carefully added to quench the reaction and the mixture was extracted with ether and the organic layers were combined, washed with brine, dried, and concentrated. The resulting residue was purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate = 40/1) to obtain 2.16 g (90%) of *cis*-3,4-bis(benzyloxymethyl)-3,4-dimethylcyclobutene (**19**) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 6 H), 3.41 (d, J = 9.3 Hz, 2 H), 3.54 (d, J = 9.3 Hz, 2 H), 4.40 (d, J = 12.4 Hz, 2 H), 4.44 (d, J = 12.4 Hz, 2H), 6.08 (s, 2 H), 7.21−7.31 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 51.8, 73.2, 75.4, 127.3, 127.5, 128.2, 138.8, 141.1. IR (neat) 3029, 2852, 1496, 1453, 1362, 1094, 1075 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{26}O_2Na$ ([M + Na]$^+$) 345.1830, obsd 345.1833.

Hydrovinylation of 19. 20: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 3 H), 1.20 (s, 3 H), 1.64 (dd, J = 8.3, 11.1 Hz, 1 H), 1.92 (t, J = 10.4 Hz, 1 H), 2.62−2.68 (s, 1H), 3.25 (d, J = 9.0 Hz, 1 H), 3.35 (d, J = 9.0 Hz, 1 H), 3.42 (d, J = 9.0 Hz, 1 H), 3.51 (d, J = 9.0 Hz, 1 H), 4.37−4.45 (m, 4 H), 4.90−4.94 (m, 2 H), 5.87−5.96 (m, 1 H), 7.24 −7.32 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 21.1, 32.8, 40.2, 43.7, 46.5, 73.1, 73.6, 76.4, 114.0, 127.2, 127.3, 127.3, 127.4, 128.2, 128.2, 138.7, 138.9, 139.1; IR (neat) 2959, 2926, 2854, 1454, 1360, 1095 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{30}O_2Na$ ([M + Na]$^+$) 373.2144, obsd 373.2142.

Determination of Configuration and Enantiomeric Excess of the Hydrovinylation Product 20. To a solution of **20** (48 mg, 0.14 mmol) in THF (4 mL) was added 9-BBN (0.51 mL, 0.5 M, 0.6 mmol) at 0 °C under nitrogen. The mixture was allowed to warm to room temperature and stirred for 3 h. To the solution were added 1 mL of 2 M NaOH and 0.4 mL of 30% aqueous H_2O_2 successively at 0 °C and the resulting mixture was stirred at room temperature for 30 min. Water was added and the mixture was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (eluting with hexanes/ethyl acetate = 10/1) to afford 35 mg (70%) of **21**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.11 (s, 3 H), 1.34−1.42 (m, 1 H), 1.45−1.56 (m, 2 H), 1.63−1.72 (m, 1 H), 1.96−2.06 (m, 1 H), 2.11 (broad s, 1 H), 3.07 (d, J = 9.0 Hz, 1 H), 3.26 (d, J = 9.0 Hz, 1 H), 3.40 (d, J = 9.0 Hz, 1 H), 3.37−3.43 (m, 1 H), 3.50−3.54 (m, 1 H), 3.59 (d, J = 9.0 Hz, 1 H), 4.29−4.37 (m, 4 H), 7.17−7.27 (m, 10 H). The configuration of the product is assigned by the strong NOE observed between the methyl hydrogens and the ring hydrogen shown. ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.3, 21.1, 33.8, 34.2, 37.7, 40.2, 44.7, 62.4, 72.7, 73.1, 73.4, 76.1, 127.3, 127.4, 127.5, 127.6, 128.2, 128.3, 138.3, 138.9; IR (neat) 3364, 2930, 2866, 1717, 1454, 1361, 1072, 736 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{32}O_3Na$ ([M+Na]$^+$) 391.2249, obsd 391.2252; $[\alpha]^{22}_D$ −16.9 (c 0.51, $CHCl_3$) (**L6**); HPLC (chiracel AD-H) conditions: hexanes:isopropanol 99:1, 0.3 mL/min, retention time (min): 73.43 (−)-isomer, 77.38 (+)-isomer. The retention times were confirmed by comparison to an authentic racemic **21** prepared using nickel complex of **L2** (see the chromatograms in the Supporting Information).

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Supporting Information Available: Spectroscopic and chromatographic data for characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.