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Scope of the Nickel Catalyzed Asymmetric Reductive Ring Opening Reaction. Synthesis of Enantiomerically Enriched Cyclohexenols.

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Abstract: Subjecting a variety of oxabicyclo[2.2.1]heptenes to diisobutylaluminum hydride (DIBAL-H) in the presence of a catalytic amount of $Ni(COD)_2$ and (*R*)-BINAP results in a highly enantioselective ring opening to generate cyclohexenols with ee's typically greater than 90%. The scope of this reaction has been delineated and alternative nickel catalysts have been examined which are less sensitive than $Ni(COD)_2$.
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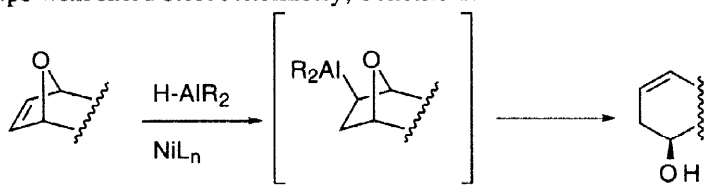
The discovery by Ziegler and Holzkamp in 1954 that traces of nickel salts markedly alter the reaction of ethylene with triethylaluminum, the *aufbau* process, has been termed the "Nickel Effect."[1] It was later conclusively shown by Eisch that nickel accelerates the hydroalumination of alkynes by diisobutylaluminum hydride (DIBAL-H).[2] Eisch examined the regio- and stereoselectivity of the process including solvent effects. Detailed mechanistic investigations into the "Nickel Effect" and extensive structural studies were carried out at the Max-Planck-Institute in Mülheim which indicated that Ni-μ-H-Al bridged compounds may be intermediates in the hydroalumination.[3] Remarkably, very few reports have appeared in the literature since then describing attempts to develop an asymmetric hydroalumination reaction and prior to our initial disclosure, none have been synthetically useful.[4] This is puzzling in view of the fact that organoaluminum compounds have significant synthetic utility in organic synthesis.[5]

We had been interested in the reductive ring opening of oxabicyclic alkenes as part of our efforts to control cyclic and acyclic stereochemistry by using rigid cyclic molecules as templates.[6a] One approach we have investigated was to couple a hydroalumination with an elimination reaction thereby regenerating the alkene and generating hydroxyl groups with fixed stereochemistry, Scheme 1.



Scheme 1

We previously reported that the reaction is highly regioselective when unsymmetrical oxabicyclic compounds are treated with DIBAL-H in the presence of bis(cyclooctadiene)nickel ($Ni(COD)_2$) and phosphines and have optimized this process so that selectivities exceeding 19:1 are routinely obtained.[4a,7] Furthermore we reported the first synthetically useful enantioselective reductive ring opening of meso oxabicyclic compounds.[4a] Optimization of our initial success with the DIBAL-H, $Ni(COD)_2$/BINAP system provided us with a highly

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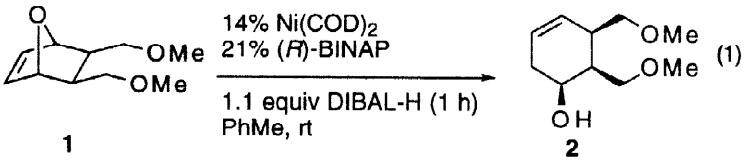
enantioselective ring opening of the oxabicyclic compound **1** to provide cyclohexenol **2** in 97% ee, eq. 1. We now describe additional details associated with the development of this reaction and its scope and limitations.



1 **2**

During these studies, we discovered a number of interesting parameters which influenced the enantioselectivity. The most unexpected was a correlation between the ee of the product and the rate of addition of DIBAL-H. Highly enantioselective ring opening was only possible when DIBAL-H was added slowly to the reaction mixture, typically by syringe pump. In fact, we found that if DIBAL-H was rapidly added to the reaction, the ee was no higher than 56%, entry 1 in Table 1. Slowing the addition time to 7 min led to an improvement in the ee to 82%, entry 2. The optimized conditions were found to be addition over 1 h which gives the cyclohexenol with 97% ee in nearly quantitative yield, entry 3. The ratio of metal to ligand also influenced the enantioselectivity. Using less than 1.5 equivalents of BINAP to $Ni(COD)_2$ results in a drop in ee, entry 5 *vs* entry 4. Importantly, although most of our studies have been done using 14 mol% catalyst, it is clearly possible to use lower catalyst loadings and still get ee's in the 90's, entry 6. However, we have found that a delicate balance needs to be found between the amount of catalyst and addition time of DIBAL-H. For example, DIBAL-H was added over 8 h when 4 mol % of catalyst was used.

Table 1. Enantioselective Ring Opening of **1** to **2**

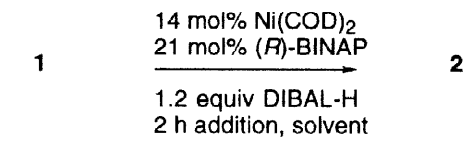
Entry	% $Ni(COD)_2$	% (*R*)-BINAP	time[a]	ee[b]
1	14 mol%	21 mol%	<1 min	56%
2	14 mol%	21 mol%	7 min	82%[c]
3	14 mol%	21 mol%	1 h	97%[d]
4	7 mol%	10.5 mol%	2 h	92%
5	7 mol%	9 mol%	2 h	87%
6	4 mol%	6 mol%	8 h	92%

[a] Addition time to add DIBAL-H to a solution of **1**, $Ni(COD)_2$ and BINAP. Work-up after 1-3 h. [b] Measured by preparing the Mosher ester or by capillary GC (Chiraldex G-TA column). [c] Isolated yield of pure product is 78%. [d] Isolated yield of pure product is 97%.

Encouraged by these results and stimulated by the synthetic utility of enantiomerically pure cyclohexenols,[6b] we have explored the scope of this reaction with a variety of oxabicyclic compounds. In addition, we have investigated solvent effects and searched for alternative catalysts which might be more practical than $Ni(COD)_2$ which is air sensitive. We now report that the reaction is general for oxabicyclic compounds bearing exo or endo substituents and for compounds bearing acid sensitive functionalities.

Aromatic solvents were used in our initial studies (Table 2, entries 1 and 2) but some substrates were not very soluble or tended to decompose under the reaction conditions. Reactions in pentane gave the ring opened product, although the enantioselectivity was much lower, and reactions in dichloromethane were very messy with low ee, entries 3 and 4. However, the most surprising and ultimately important observation was that the reaction worked very well in ethereal solvents, particularly in tetrahydrofuran, entry 5.

Table 2. Effect of Solvent on the Enantioselective Ring Opening



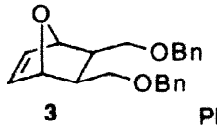
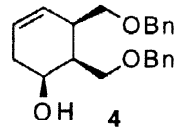
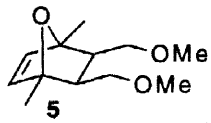
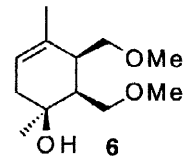
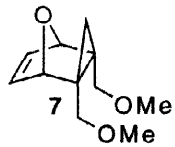
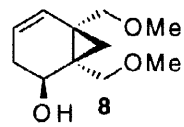
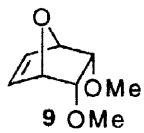
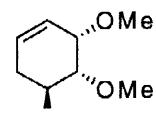
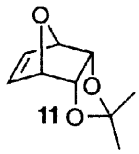
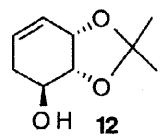
Entry	Solvent	Yield[a]	ee[b]
1	PhMe	96	97
2	PhH	97	97
3	pentane	91	60
4	CH_2Cl_2	58	35
5	THF	91	94

[a] isolated yield. [b] measured by preparing the Mosher ester or by capillary GC (Chiraldex G-TA or B-TA column).

The success of the reaction in THF may provide some insight into the reaction pathway. Pioneering work by Eisch showed that alkylalanes retain their stereochemistry in donor solvents.[8] This suggests that the trialkylalane resulting from hydroalumination from the less hindered *exo* face does not invert prior to the subsequent elimination which would occur in a *syn* fashion. Alternatively, it is possible that the organoalane is not an intermediate in the reaction but that ring opening proceeds directly from an organonickel species.

A number of oxabicyclic alkenes were synthesized in order to test the sensitivity of the catalyst to substituent effects. As expected, the size of the protecting group on the distal hydroxyl groups has no effect on the enantioselectivity, entry 1, Table 3 *vs* entry 1, Table 1. Substituents near the reacting olefin have a more pronounced effect on the enantioselectivity, entry 2, Table 3. For example, **5** gave the tertiary alcohol **6** in 84% ee and 81% yield. The reaction also gives good to excellent enantioselectivities with substrates bearing *endo* substituents and/or acid sensitive functional groups including cyclopropylcarbinyl ethers, entries 3 and 4 in Table 3; cyclohexenol **8** is obtained with 91% ee. The presence of heteroatoms in the endo position results in a slight decrease in enantioselectivity, entries 4 and 5 in Table 3. The cyclohexenols **10** and **12** are isolated with 86% and 78% ee respectively. Curiously, the reaction in these cases only proceeds to about 50% conversion. The cyclohexenol **12** has been used in the synthesis of a number of conduritols as well as shikimic acid derivatives.[9]

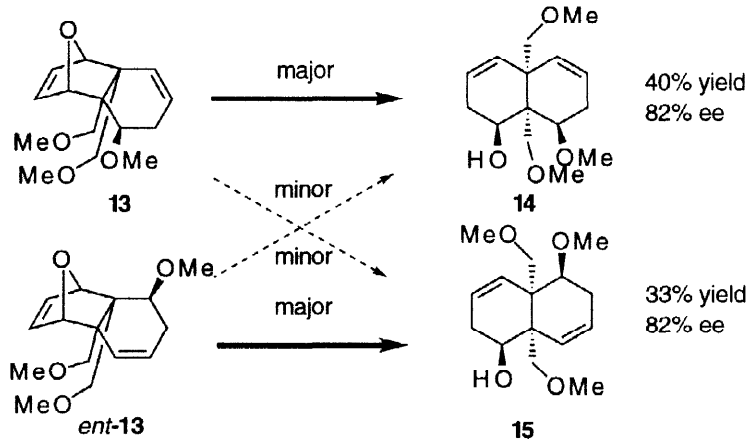
Table 3. Enantioselective Ring Opening of [2.2.1] Oxabicyclics

Entry[a]	Subtrate	Solvent	Time[b]	Product	Yield[c]	ee[d, e]
1	 **3**	PhMe	6	 **4**	96	97
2	 **5**	PhMe	12	 **6**	81	84
3[f]	 **7**	THF	5	 **8**	88	91
4	 **9**	THF	2	 **10**	50	86
5	 **11**	THF	4	 **12**	50[g]	78

[a] All reactions were run in the presence of 14 mol% $Ni(COD)_2$ and 21 mol% (*R*)-BINAP at room temperature unless otherwise noted. [b] Addition of DIBAL-H to a solution of $Ni(COD)_2$, (*R*)-BINAP and the alkene *via* syringe pump. [c] Isolated yield. [d] Measured by preparing the Mosher ester or by capillary GC (Chiraldex G-TA or B-TA column). [e] The absolute configuration of **2** was proven by correlation to a compound of known stereochemistry. Alcohol **12** has the same sense of rotation as that reported in reference 9, and **17** has the opposite sense of rotation as reported in reference 12. All three are consistent with the same absolute sense of hydrometallation. [f] 11 mol% $Ni(COD)_2$ and 18 mol% (*R*)-BINAP used. [g] GC yield.

In order to determine if substrate or reagent control was dominant, we subjected a racemic mixture of **13** to the asymmetric hydrometallation catalyst, Scheme 2. If the reaction was insensitive to remote substituents, the recognition by the chiral catalyst would lead to the formation of two products, **14** and **15**, both with high ee. Enantiomer **13** would give **14** as the major product and *ent*-**15** as the minor one, whereas *ent*-**13** would give **15**

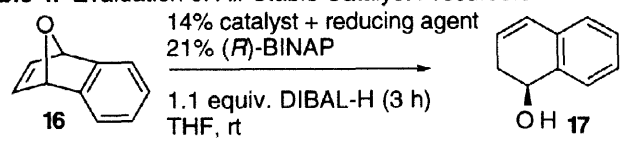
as the major product and *ent*-**14** as the minor one. The net result is a kind of resolution to yield two enantioenriched decalins from a racemic starting material. If the reaction was governed primarily by the substrate, one product of low ee would result. In the event, the reaction proved to be largely reagent controlled. The two products are formed in nearly equal amounts and enantioselectivities. Compounds **14** and **15** are easily separable on silica gel. The structure of each product was apparent following methylation of the alcohols and examination of their ^{13}C NMR spectra.[10]



Scheme 2

In the course of our studies in this area, we have found that $Ni(COD)_2$ must be of high purity to obtain reproducibly high enantioselectivities and we therefore sought a more convenient air stable catalyst. Since $Ni(COD)_2$ is prepared by reduction of $Ni(acac)_2$ in the presence of a trialkylalane[11], we sought to couple the two processes (reduction and hydrometallation) in one pot by treating $Ni(acac)_2$ with an alkylalane in the presence of the chiral phosphine, thereby generating the active Ni(0) catalyst *in situ*. We carried out these studies on a related substrate **16** prepared from benzyne and furan which we have used in a synthesis of sertraline.[12] In this case, the use of THF was essential to avoid decomposition of the substrate under the reaction conditions.

Table 4. Evaluation of Air Stable Catalyst Precursors



Entry	Catalyst	Reducing Agent	Yield[a]	ee[b]
1	$Ni(COD)_2$	none	**88**	**98**
2	$Ni(acac)_2$	DIBAL-H	56	79
3	$NiBr_2$.DME	*n*BuLi	56	88
4	$Ni(acac)_2$	Et_3Al	80	88
5	$Ni[P(OPh)_3]_4$	none	60	**94**

[a] isolated yield. [b] measured by capillary GC (Chiraldex GTA).

Our initial results with **16** were encouraging although the enantioselectivity failed to exceed 88%, Table 4,

entries 2, 4. Similar results were obtained by using *n*-butyllithium as the reducing agent and nickel halides as the catalyst precursors, entry 3. Other sources of nickel(0) were also investigated and tetrakis(triphenylphosphite)nickel, an air stable source of nickel(0), was found to be the best catalyst precursor for the enantioselective reaction. As might be expected, the bidentate triarylphosphine BINAP binds in preference to the monodentate phosphites on the active catalyst but the enantioselectivity is not significantly reduced by the presence of the additional achiral ligands.

In summary, we have developed a highly enantioselective route to a variety of substituted cyclohexenols using the nickel catalyzed hydroalumination reaction. We have also developed air stable catalyst precursors and have shown them to be nearly as selective as the air sensitive $Ni(COD)_2$. Application of this methodology to the synthesis of biologically important targets is under way.

Experimental

The following includes experimental procedures, specific details for representative reactions, isolation and spectroscopic information for the prepared compounds. *All procedures were carried out under strictly anaerobic conditions using freshly distilled solvents. The purity of the solvents and the substrate was of considerable importance for reproducible, highly enantioselective reactions. Solvents were freshly distilled prior to use and the substrates were kept in a desiccator for periods of up to two or three weeks.*

General Procedure for the Nickel Catalyzed Hydroalumination: To a flame dried round bottomed flask containing $Ni(COD)_2$ was added THF directly from the still *via* a cannula. The resulting solution was then transferred *via* a cannula to a flask containing (*R*)-BINAP, and the resulting mixture was stirred vigorously for 45 minutes. The dark burgundy solution was then transferred *via* a cannula to a flask containing the oxabicyclic alkene. The mixture was stirred at room temperature for 10 minutes, then DIBAL-H (1.0 M solution in hexanes) was added to this solution *via* a syringe pump over a period of time. After the addition of DIBAL-H was complete, the reaction was quenched at 0 °C with Rochelle's salt solution (1.1 M) or saturated K_2CO_3 (for acid sensitive substrates). The mixture was allowed to stir at room temperature for 30 minutes and was then extracted 3-5 times with Et_2O or EtOAc. The organic layers were combined, washed with brine, dried over $MgSO_4$ or Na_2SO_4 and concentrated *in vacuo*. The crude mixture was analyzed by CGC on a Chiraldex G-TA or B-TA column (Advanced Separation Technologies). Alternately, the ee could be measured by esterification of the alcohols with Mosher's acid chloride and examination of their ^1H NMR and ^{19}F NMR spectra.

(1S, 2S, 3R)-2,3-Bis(methoxymethyl)-cyclohex-4-en-1-ol (2): $Ni(COD)_2$ (9.1 mg, 0.033 mmol) was transferred to a dry round bottomed flask in the glove box. Compound **1** (43.6 mg, 0.237 mmol) and (*R*)-BINAP (30.8 mg, 0.049 mmol) were combined in a round bottomed flask equipped with a stir bar, and the flask was flushed with nitrogen. Toluene (1 mL, freshly distilled over sodium metal) was added to the $Ni(COD)_2$ and the solution was transferred to a flask containing **1** and (*R*)-BINAP *via* cannula. The dark burgundy red solution was stirred at room temperature for 30 minutes under positive nitrogen pressure. DIBAL-H (0.26 mL, 1.0 M in hexanes, 0.190 mmol) was added *via* syringe pump (addition time about 1 h). After the addition was

complete, TLC indicated complete consumption of the starting material and conversion to product. Aqueous Rochelle's salt solution (1.1 M, 1.5 mL) was added at 0 °C to quench the reaction which was then stirred for 3 h. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The turbid aqueous layer was acidified with 10% H_2SO_4 until the solution cleared, and was then extracted twice more with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography on silica gel (20% ethyl acetate in hexanes) yielded **2** (43.0 mg, 98 %), a colourless oil: R_f (20% ethyl acetate in hexanes) 0.30; bp 100-110 °C/1-2 mm; $[\alpha]_D$=-76.7° (c=0.5, $CHCl_3$); IR (neat, cm^{-1}) 3416 (br), 2904 (s), 1649 (w), 1457 (m), 1193 (m), 1105 (s), 1041 (m), 961 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 5.69 (1H, m), 5.52 (1H, m), 4.27 (1H, s, disappears with D_2O), 3.89 (1H, s), 3.57 (1H, dd, *J* = 9.3, 7.9 Hz), 3.51 (1H, dd, *J* = 9.4, 7.5 Hz), 3.35 (2H, m), 3.35 (3H, s), 3.34 (3H, s), 2.59 (1H, m), 2.39 (1H, ddd, *J* = 14.8, 7.4, 2.6 Hz), 2.31 (1H, dm, *J* = 18.0 Hz), 2.16 (1H, dm, *J* = 17.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.9, 125.9, 72.2, 72.1, 66.6, 59.0, 58.9, 39.9, 37.3 33.7. The ee of this alcohol was determined to be 97% by GC analysis on a Chiraldex GTA column (Advanced Separation Technologies). HRMS calcd for $C_{22}H_{26}O_3$ $(M+H)^+$ 187.1334. Found: 187.1339.

(1S, 2R, 3R)-2,3-Bis(benzyloxymethyl)cyclohex-4-en-1-ol (4): Following the general procedure, $Ni(COD)_2$ (8.3 mg, 0.030 mmol) and (*R*)-BINAP (28.2 mg, 0.045 mmol) in 2 mL toluene were added to **3** (72.5 mg, 0.215 mmol). DIBAL-H (0.24 mL, 1.0 M in hexanes, 0.240 mmol) was added via syringe pump (addition time about 1 h). Standard workup and flash chromatography on silica gel (10% ethyl acetate in hexanes to 20% ethyl acetate in hexanes) yielded **4** (68.0 mg, 93 %, 97% ee), a colourless oil. The ee of this alcohol was determined by esterification with Mosher's acid chloride and examination of the ^1H NMR spectrum. R_f= 0.30 on silica (20% ethyl acetate:hexanes). $[a]_D$=+60.5° (c=2.0, $CHCl_3$); IR (neat, cm^{-1}) 3419, 3026, 2908, 2875, 2865, 1496, 1454, 1363, 1214, 1095, 1075, 1028, 736, 697; ^1H NMR (200 MHz, $CDCl_3$) δ 7.30 (10H, m), 5.68 (1H, ddd, *J*=9.9, 6.2, 3.4 Hz), 5.52 (1H, dm, *J*= 9.9 Hz), 4.49 (1H, d, *J*= 12.1 Hz), 4.44 (1H, d, *J*= 11.8 Hz), 4.42 (1H, d, *J*= 12.1 Hz), 4.36 (1H, d, *J*= 11.8 Hz), 4.27 (1H, exchanges with D_2O, d, *J*= 10.0 Hz), 3.91 (1H, dtd, *J*= 10.0, 5.2, 2.7 Hz), 3.63 (1H, dd, *J*= 9.3, 7.8 Hz), 3.53 (1H, dd, *J*= 9.3, 7.5 Hz), 3.42 (1H, dd, *J*= 9.5, 4.6), 3.35 (1H, dd, *J*= 9.4, 4.9 Hz), 2.65 (1H, m), 2.46 (1H, dddd, *J*= 7.8, 7.5, 7.1, 2.7 Hz), 2.31 (1H, dm, *J*= 17.9 Hz), 2.14 (1H, dm, *J*= 18.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.0, 137.5, 128.4, 128.4, 128.0, 127.8, 127.8, 127.7, 127.6, 127.0, 125.8, 73.5, 73.3, 69.7, 69.5, 66.8, 39.9, 37.4, 33.6. HRMS calcd for $C_{22}H_{26}O_3$ (M^+): 338.1882 Found: 338.1867.

(1S, 2S, 3R)-2,3-Bis(methoxymethyl)-1,4-dimethylcyclohex-4-en-1-ol (6): Following the general procedure, $Ni(COD)_2$ (6.1 mg, 0.022 mmol) and (*R*)-BINAP (21.2 mg, 0.034 mmol) in 2 mL toluene were added to **5** (33.6 mg, 0.158 mmol). DIBAL-H (0.18 mL, 1.0 M in hexanes, 0.180 mmol) was added via syringe pump (addition time about 12 h). Standard workup and bulb to bulb distillation yielded **6** (27.0 mg, 81%, 84% ee), a colourless oil. The ee of this alcohol was determined by GC analysis on a Chiraldex GTA column (Advanced Separation Technologies). R_f (30% ethyl acetate in hexanes) 0.33; bp 70-90 °C/1 mm; $[\alpha]_D$=-60.1° (c=1.8, $CHCl_3$); IR (neat, cm^{-1}) 3417 (br), 2963 (m), 2899 (s), 2818 (m), 1446 (m), 1382 (m), 1202 (m), 1103 (s), 966 (m), 908 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 5.24 (1H, m), 4.98 (1H, s, disappears with D_2O), 3.73 (1H,

dd, J = 9.8, 6.0 Hz), 3.61 (1H, dd, J = 9.8, 4.8 Hz), 3.58 (1H, t, J = 9.5 Hz), 3.47 (1H, dd, J = 9.8, 2.4 Hz), 3.37 (3H, s), 3.35 (3H, s), 2.42 (1H, s), 2.15 (1H, dd, J = 3.7, 1.8 Hz), 2.14 (2H, m), 1.73 (3H, s), 1.21 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.1, 122.1, 70.7, 69.2, 67.5, 58.9, 58.8, 44.9, 41.5, 40.5, 27.6, 21.6. HRMS calcd for $C_{12}H_{22}O_3$ $(M)^+$: 214.1569. Found: 214.1562.

(1R, 2S, 6S)-1,6-di(methoxymethyl)tricyclo[4.1.0]hept-4-en-1-ol (8): Following the general procedure, a solution of $Ni(COD)_2$ (6.6 mg, 0.024 mmol) and (*R*)-BINAP (23.4 mg, 0.037 mmol) in 1 mL of THF was added to **7** (44.0 mg, 0.224 mmol). DIBAL-H (0.24 mL, 0.240 mmol) was added over 5 h. Chromatography yielded 39 mg of **8** (88%, 91% ee). The ee was determined by esterification with Mosher's acid chloride and examination of the ^{1}H NMR spectrum. R_f = 0.21 on silica gel (hexanes : EtOAc 7 : 3); bp 60°C/0.25 mmHg; $[\alpha]^{25}_D$ = 117° (c= 1.2, $CHCl_3$); IR (neat) 3433, 2926, 2893, 1647, 1451, 1193, 1136, 1102, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (1H, dd, J = 9.8, 3.3 Hz), 5.40 (1H, ddd, J = 9.8, 7.1, 2.2 Hz), 4.21 (1H, t, J = 8.2 Hz), 3.91 (1H, dd, J = 10.1, 1.3 Hz), 3.75 (1H, s), 3.63 (1H, d, J = 10.2 Hz), 3.48 (1H, d, J = 9.9 Hz), 3.38 (3H, s), 3.31 (3H, s), 3.24 (1H, d, J = 10.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.3, 121.4, 77.6, 76.2, 69.2, 59.1, 58.8, 32.5, 30.5, 27.9, 20.0; HRMS calcd for $C_{11}H_{18}O_3$ $(M)^+$: 198.1256. Found: 198.1260.

(1S, 2R, 3S)-2,3-dimethoxycyclohex-4-en-1-ol (10): Following the general procedure, a solution of $Ni(COD)_2$ (5.0 mg, 0.018 mmol) and (*R*)-BINAP (17.0 mg, 0.029 mmol) in 1 mL of THF was added to **9** (14.3 mg, 0.092 mmol). DIBAL-H (0.11 mL, 0.110 mmol) was added over 2 h. Chromatography yielded 6 mg of **10** (40%, 86% ee). The ee was determined by CGC on a Chiraldex G-TA column at 120°C, retention time of 10.4 min (major) and 10.8 min. R_f = 0.11 on silica gel (hexanes : EtOAc 1 : 1); bp 60°C/0.25 mmHg; $[\alpha]^{25}_D$ = 33.7° (c= 0.3, $CHCl_3$); IR (neat) 3416, 2924, 1656, 1463, 1264, 1191, 1072, 1005, 912, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (1H, dddd, J = 9.9, 4.8, 2.6, 1.1 Hz), 5.81 (1H, ddd, J = 9.8, 4.8, 2.2 Hz), 4.06 (1H, dddd, J = 9.5, 9.5, 6.2, 1.5 Hz), 3.98 (1H, dd, J = 4.4, 4.4 Hz), 3.49 (3H, s), 3.44 (3H, s), 3.18 (1H, dd, J = 9.8, 3.6 Hz), 2.64 (1H, s, disappears with D_2O), 2.61 (1H, dddd, J = 18.0, 5.8, 4.7, 1.1 Hz), 2.05 (1H, ddddd, J = 18.0, 9.1, 2.6, 2.6, 0.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.9, 124.1, 83.7, 71.7, 65.6, 57.4, 57.1, 33.6; HRMS calcd for $C_7H_9O_2$ $(M\text{-}CH_3, H_2O)^+$: 125.0603. Found: 125.0607.

(1S, 2R, 3S)-2,3-dimethoxycyclohex-4-en-1-ol (12): Following the general procedure, a solution of $Ni(COD)_2$ (4.7 mg, 0.017 mmol) and (*R*)-BINAP (16.0 mg, 0.026 mmol) in 1 mL of THF was added to **11** (20.8 mg, 0.124 mmol). DIBAL-H (0.15 mL, 0.150 mmol) was added over 4 h. The crude mixture was subjected to GC analysis which showed there to be roughly 50% conversion to product (78% ee). The ee was determined by CGC on a Chiraldex G-TA column at 120°C, retention time of 10.4 min (major) and 10.8 min. The material was found to be identical in all respects by comparison with reported data.[9]

(1S,2R,6S,10S)-10-methoxy-1,6-di(methoxymethyl)bicyclo[4.4.0]deca-4,7-dien-2-ol (14) and (1R,2R,6R,7S)-7-methoxy-1,6-di(methoxymethyl)bicyclo[4.4.0]deca-4,9-dien-2-ol (15): Following the general procedure, a solution of $Ni(COD)_2$ (5.9 mg, 0.021 mmol) and (*R*)-BINAP (20.0 mg, 0.032 mmol) in 1 mL of

THF was added to **13** (39.7 mg, 0.149 mmol). DIBAL-H (0.18 mL, 0.180 mmol) was added over 16 h. Chromatography yielded 16 mg of **14** (40%, 82% ee) and 13 mg of **15** (33%, 82% ee). The ee was determined by esterification with Mosher's acid chloride and examination of the ^{1}H NMR spectrum.

(**14**) R_f= 0.20 on silica gel (hexanes : EtOAc 4 : 1); bp 70°C/0.25 mmHg; $[\alpha]^{25}_D$= 155° (c= 0.3, $CHCl_3$); IR (neat) 3515, 2924, 2360, 1457, 1191, 1105, 1045, 965, 766 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (1H, dddd, *J* = 10.2, 4.7, 2.2, 1.1 Hz), 5.68 (1H, ddd, *J* = 10.2, 4.4, 2.9 Hz), 5.40 (1H, ddd, *J* = 10.2, 2.6, 1.5 Hz), 5.30 (1H, ddd, *J* = 10.2, 4.4, 2.2 Hz), 4.42 (1H, ddd, *J* = 8.5, 6.9, 2.2 Hz), 4.08 (1H, dd, *J* = 3.4, 3.3 Hz), 3.63 (1H, d, *J* = 2.2 Hz), 3.51 (2H, s), 3.33 (3H, s), 3.30 (3H, s), 3.26 (3H, s), 3.09 (2H, s), 2.30 (3H, m), 2.13 (1H, dddd, *J* = 18.3, 3.7, 2.6, 2.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.6, 128.8, 124.7, 124.1, 78.4, 77.8, 74.3, 72.1, 59.4, 59.0, 57.7, 44.8, 44.0, 32.5, 26.6; HRMS calcd for $C_{15}H_{24}O_4$: $(M+H)^+$: 269.1753. Found: 269.1754.

(**15**) R_f= 0.25 on silica gel (hexanes : EtOAc 4 : 1); bp 70°C/0.25 mmHg; $[\alpha]^{25}_D$= -34.3° (c= 0.5, $CHCl_3$); IR (neat) 3476, 2918, 1443, 1198, 1105, 1052, 965, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (1H, s), 5.70 (1H, dd, *J* = 6.2, 1.5 Hz), 5.66 (1H, ddd, *J* = 10.2, 5.5, 2.2 Hz), 5.37 (1H, ddd, *J* = 10.2, 2.7, 1.5 Hz), 4.31 (1H, ddd, *J* = 9.9, 5.5, 1.8 Hz), 3.78 (1H, d, *J* = 9.2 Hz), 3.62 (1H, dd, *J* = 10.2, 5.5 Hz), 3.57 (1H, s), 3.57 (1H, d, *J* = 9.6 Hz), 3.46 (1H, d, *J* = 9.9 Hz), 3.35 (3H, s), 3.34 (3H, s), 3.28 (3H, s), 2.37 (1H, ddd, *J* = 16.8, 5.5, 4.0 Hz), 2.16 (1H, dddd, *J* = 17.2, 5.5, 5.5, 1.1 Hz), 1.91-2.04 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.9, 126.7, 126.5, 125.7, 78.2, 75.6, 73.4, 70.1, 59.1, 58.6, 57.3, 48.1, 47.3, 31.0, 28.0; HRMS calcd for $C_{15}H_{24}O_4$ $(M)^+$: 268.1674. Found: 268.1674.

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