Ring-Opening Reactions of Oxabicyclic Alkene Compounds: Enantioselective Hydride and Ethyl Additions Catalyzed by Group 4 Metals

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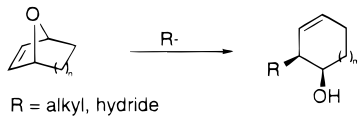
Titanium and zirconium catalysts selectively catalyze either the ethyl or hydride addition to [2.2.1] 4,5-bis(methoxymethyl)-7-oxabicycloheptene (**6**); the ring-opened products formed depend on catalyst, temperature, alkylaluminum reagent, and the concentration of alkylaluminum. Bis(neoisomenthylindenyl)zirconium dichloride catalyzes the ethyl addition ring-opening of **6** to produce (1*R*,-2*S*,3*S*,6*R*)-2,3-bis(methoxymethyl)-6-ethylcyclohex-4-enol (**7**) in 96% ee. Zirconium catalysts catalyze the ring-opening of [3.2.1] 2,4-dimethyl-3-(benzyloxy)-8-oxabicyclo-6-octene (**7**) when ethylmagnesium bromide is used as a reagent. Both hydride and ethyl addition products are obtained at all conditions studied. Bis(neoisomenthylindenyl)zirconium dichloride catalyzes the ethyl addition ring-opening of **7** to produce (1*S*,2*R*,3*S*,4*S*,7*S*)-2,4-dimethyl-3-(benzyloxy)-7-ethyl-5-cyclohexen-1-ol (**8**) in 48% ee.

Desymmetrization can be a powerful method of accessing chiral molecules from achiral precursors.[1] *Meso* oxabicyclic compounds, which can be produced with multiple chiral centers and high stereoselectivity through Diels−Alder and [4 + 3] oxyallyl cation cyclization reactions, are versatile precursors to molecules with high degrees of stereocomplexity[2−4] which can be converted to valuable cyclic and straight chain synthetic intermediates.[3,5]

Lautens and co-workers have demonstrated that both alkyllithiums and cuprates serve as nucleophiles for the S_N2' addition to oxabicycles (eq 1).[3,6−12] This approach provides access to polypropionate natural products. A synthetic route to a fragment of the macrolide rifamycin S containing five contiguous stereocenters was developed using this methodology.[3] Hydride nucleophiles, either directly from metal hydrides or indirectly from metal alkyls are also effective.[3,13−16]



(1)

Transition metals are efficient catalysts in these ring-opening reactions and can effect enantioselective ring-opening reactions. Palladium complexes catalyze the hydrostannylation of oxabicyclic compounds,[15] and nickel complexes have been shown to catalyze hydroalumination as well as the addition of Grignards to oxabicyclo alkenes.[14,17] Nickel compounds with chiral phosphine ligands catalyze the hydride ring-opening reaction with excellent enantioselectivity.[14,16a] A palladium-binap catalyst promotes ring-opening addition of a phenyl group in 96% ee but in 13% yield;[18] more recent results with alkylzinc nucleophiles gave much better yields and ee's from 67% to 96%.[16b]

Zirconium catalysts have proven effective for the enantioselective ring-opening of simple cyclic allyl ethers with >90% enantiomeric excess.[19−22] These results, coupled with the observation that zirconium benzyne complexes mediate the ring-opening of benzooxanorbornene,[23] suggest that early transition metal complexes might also be competent catalysts for the nucleophilic ring-opening of oxabicycles. In light of recent reports that certain early metal catalysts are competent for the stereoselective polymerization and copolymerization of norbornenes,[24−27]

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Table 1. Catalytic Ring-Opening of 6[a] to 7 with Triethylaluminum

entry	cat.		temp, °C	[Et_3Al], M	isomer	% yield[b] 7	% yield[b] 8	$[\alpha]_D$[c]	% ee
1	**1**	toluene	110	1.0		16	32		–
2	**2**	hexanes	70	1.25		94			–
3	**3**	hexanes	70	1.0	1*R*,2*S*,3*S*,6*R*	60[d]			34
4	**4**	toluene	90–95	0.5	1*S*,2*R*,3*R*,6*S*	70		−49[e]	52
5	**5**	toluene	90–95	0.5	1*R*,2*S*,3*S*,6*R*	64		74[f]	96

[a] Conditions: [**6**] = 0.5 M, [TEA] = 1 M, [Zr], [Ti] = 0.025 M. [b] % Yield isolated by chromatography. [c] Polarimetry measured in CH_2Cl_2. [d] 67% conversion by GC. [e] c = 3.3 mg/mL. [f] c = 7.2 mg/mL

Table 2. Catalytic Ring-Opening of 6[a] to 8.

entry	cat.	solvent	temp, °C	AlR_3	[AlR_3], M	yield,[b] %	isomer	% ee
1	**1**	hexanes	70	Et_3Al	2.5	85	–	–
2	**1**	toluene	110	Et_3Al	2.5	99	–	–
3	**1**	hexanes	70	Pr_3Al	1	88		
4	**2**	hexanes	70	Et_3Al	2.5	57	–	–
5	**3**	hexanes	70	Et_3Al	2.5	80	1*S*,2*R*,3*R*	17[c]
6	**4**	toluene	110	$^iBu_3Al$	1.0	30	1*S*,2*R*,3*R*	17[d]
7	**5**	toluene	110	$^iBu_3Al$	0.75	47	–	0

[a] Conditions: [**6**] = 0.5 M, [Ti], [Zr] = 0.025 M, 16–18 h. [b] % Yield isolated by chromatography. [c] % ee determined from methoxymandelate ester. [d] % ee determined by chiral HPLC.

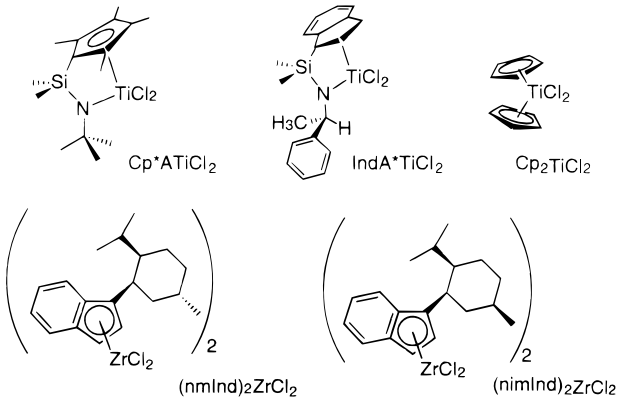


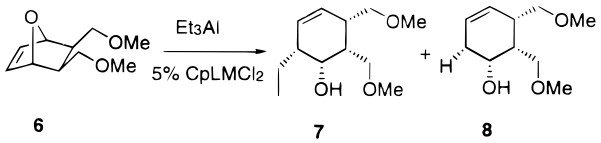
Figure 1. Structures of catalyst precursors.

we initiated investigations on the stereospecific ring-opening of oxabicycles with early transition metal complexes. In this paper, we report our investigations on the enantioselective nucleophilic ring-opening reactions of oxanorbornenes and oxabicyclo[3.2.1]octanes.

Results

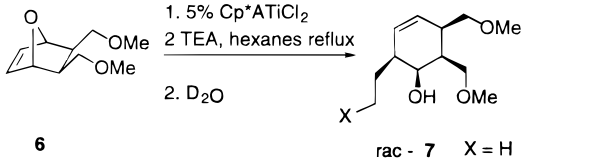
Five metallocenes were investigated for the ring-opening of oxabicycles: Titanocene dichloride (Cp_2TiCl_2) **1**, η-5,η-1-(tetramethylcyclopentadienyl)(dimethylsilyl)-(*tert*-butyl)amidotitanium dichloride (Cp*ATiCl$_2$) **2,** (+)-η-5,η-1-(indenyl)(dimethylsilyl)(α-methylbenzyl)amidotitanium dichloride ((+)-IndA*TiCl$_2$) **3**,[28] bis(neomenthylindenyl)zirconium dichloride ((nmInd)$_2$ZrCl$_2$) **4**, and bis(neoisomenthylindenyl)zirconium dichloride ((nimInd)$_2$ZrCl$_2$) **5** (Figure 1). [29,30]

Treatment of 4,5-bis(methoxymethyl)-7-oxabicyclo-2-heptene (**6**) with 2–5 equiv (1–2.5 M) of trialkylaluminum reagents (R_3Al) at 70–110 °C in the presence of 0.05 equiv of a titanium or zirconium catalyst yields the cyclohexenols **7** and **8** upon hydrolytic workup (eq 2, Table 1). No reaction was observed under these conditions in the absence of a catalyst with up to 1.25 M Et_3Al; however, **6** is slowly converted to **7** in refluxing toluene in the presence of 2 M Et_3Al. The selectivity for alkylation to give **7** versus hydride addition to give **8** depends on the catalyst, conditions and alkylaluminum reagent (Tables 1 and 2).



(2)

Both the ethyl product **7** and the hydride product **8** are formed in refluxing toluene with titanocene dichloride as the catalyst precursor in yields of 16% and 32%, respectively (Table 1, entry 1). Yields obtained in hexanes were from 60% to 94% with titanium catalysts **2** and **3**, although conversion was only 67% for **3** under these conditions (entry 3). No deuterium was incorporated into **7** upon deuteriolytic workup of the reaction of **6** with triethylaluminum and a catalytic amount of Cp*ATiCl$_2$ (eq 3).



(3)

Careful temperature control is critical for the ring-opening of **6** in the presence of the zirconocene catalysts. In toluene at 90–95 °C, yields of 64–70% could be obtained, but reaction temperatures below 90 °C led to no conversion of substrate, while temperatures above 95 °C led to a mixture of products

The enantioselective ring opening of **6** with the chiral titanocene **3** in hexanes at 70 °C gave (1*R*,2*S*,3*S*,6*R*)-**7**

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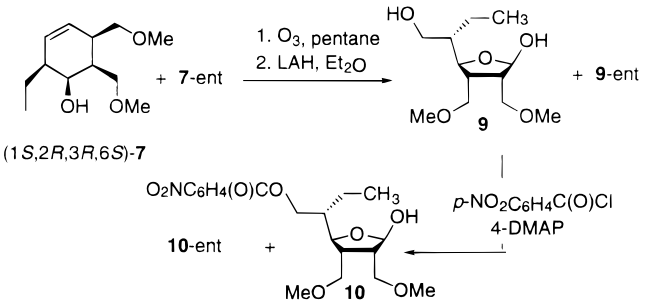
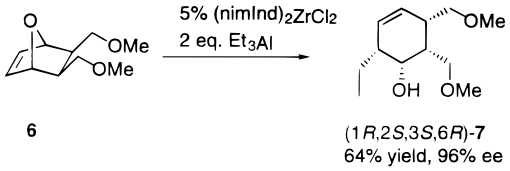
Scheme 1. Derivatization of 7 To Determine Enantiomeric Excess

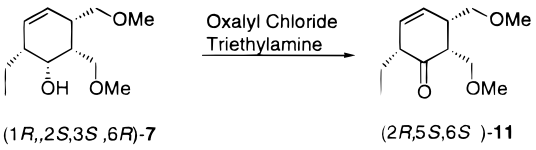


in 60% yield and 34% ee. Higher ee's were obtained with the zirconocene catalysts **4** and **5**. Addition of Et_3Al to **6** in the presence of the neomenthylindenyl zirconocene **4** at 90−95 °C in toluene yields (1*R*,2*S*,3*S*,6*R*)-**7** in 52% ee, whereas the diastereomeric neoisomenthyl zirconocene **5** yields the enantiomer (1*R*,2*S*,3*S*,6*R*)-**7** in 64% yield and 96% ee (eq 4).



(4)

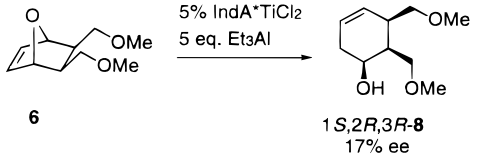
The enantioselectivities were determined from HPLC analysis of the furanose nitrobenzoate ester **10** obtained by ozonolysis of **7** (Scheme 1). The absolute stereochemistry of (1*R*,2*S*,3*S*,6*R*)-**7** from $(nimInd)_2ZrCl_2$ was determined from the circular dichroism spectrum of cyclohexenone (2*S*,3*S*,6*R*)-**11** obtained from the Swern oxidation of **7** (eq 5).[31−33] The absolute stereochemistry of the products from other catalysts were established by comparison of the optical rotations or the HPLC traces of the furanose esters of (1*R*,2*S*,3*S*,6*R*)-**7.**



(5)

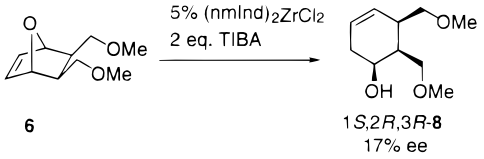
The selectivity of the titanium catalysts for ring-opening to **7** or **8** depends on the concentration of the triethylaluminum. At concentrations $[Et_3Al] = 2.5$ M, the titanium catalysts selectively yield the hydride addition product **8** in yields of 57−99% (Table 2). The enantioselective ring-opening of **6** with the titanocene **3** gives (1*S*,2*R*,3*R*)-**8** in 80% yield but a low ee of 17%; the absolute stereochemistry was determined from the (*R*)-α-methoxymandelate ester (eq 6).[34]

No reaction was observed in the absence of a catalyst under these conditions. Triisobutylaluminum can also be used as a hydride donor with the titanium catalysts, but the reactions proceed more slowly; less than 50% conversion had occurred after 18 h. Tripropylaluminum (1 M) is an efficient hydride donor with titanocene dichloride, 100% conversion and 88% yield of **8** (determined by GC) occurred after 24 h in refluxing hexanes.



(6)

In contrast to the titanium catalysts, the zirconocenes are selective for delivery of an ethyl group to oxanorbornene **6**, even at high Et_3Al concentrations. However, **6** ring-opens with 0.05 equiv of optically active zirconocene and excess triisobutylaluminum ($^iBu_3Al$) to give (**8**) upon hydrolysis (eq 7, Table 2).

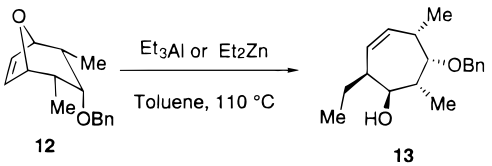


(7)

The yields are modest under these conditions, and the enantioselectivity is low. The (1*S*,2*R*,3*R*) isomer of **8** was formed in 17% enantiomeric excess when $(nmInd)_2ZrCl_2$ catalyst precursor was used; chiral HPLC was used to determine the % ee from the 4-nitrobenzoate ester of **8**. Absolute stereochemistry was determined by comparing the sign of optical rotation to (1*S*,2*R*,3*R*)-**8** produced from $IndA*TiCl_2$.

Efforts to selectively introduce a methyl group by ring-opening of **6** were unsuccessful. These included reacting trimethylaluminum with **6** in the presence of $Cp*ATiCl_2$ or with $(nmInd)_2ZrCl_2$; no product was seen in either case.

To investigate the scope of the oxybicycle ring-opening reactions, the [3.2.1]oxybicycle 2,4-dimethyl-3-(benzyloxy)-8-oxabicyclo-6-octene (**12**) was also investigated. Unlike the oxanorbornene substrate **6**, the [3.2.1] bicycle **12** reacts with 2.2 equiv TEA in toluene at 90 °C in the absence of a catalyst to give 2,4-dimethyl-3-(benzyloxy)-7-ethyl-5-cyclohexen-1-ol (**13**) in 42% isolated yield (eq 8). Diethyl zinc will also ring-open **12** without a catalyst, but more slowly than triethylaluminum. Substrate **12** does not react at all with ethylmagnesium bromide after 6 h in refluxing hexanes and reacts only slightly in refluxing toluene.



(8)

In the presence of $(nmInd)_2ZrCl_2$ and triethylaluminum, **12** also ring-opens to **13** in 17% yield and 20% ee; however, an unidentifiable compound was the major product. A series of experiments with ethylmagnesium bromide and zirconium catalysts were performed to determine optimal conditions for the ring opening addition to **12** (eq 9, Table 3).

In all cases, both the ethyl and hydride addition products **13** and **14** were formed in 50−67% combined total yield; the relative amounts varied slightly with solvent, catalyst, and temperature. Methylmagnesium

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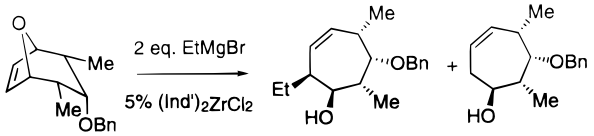
Table 3. Zirconium-Catalyzed Ring-Opening Additions to 12[a]

entry	catalyst	solvent	temp, °C	**13**:**14**[b]	% yield[c]	% ee
1	$(nmInd)_2ZrCl_2$	hexanes	70	2.9:1	**13** - 40	6
					14 - 17	ND[e]
2	$(nmInd)_2ZrCl_2$	THF	67	1:1	15[d]	–
3	$(nmInd)_2ZrCl_2$	toluene	22	1:1	<30[d]	ND[e]
4	$(nmInd)_2ZrCl_2$	toluene	55	2.9:1	**13** - 35	6
					14 - ND[e]	–
5	$(nmInd)_2ZrCl_2$	toluene	110	1:2	**13** - 17	11
					14 - 28	7
6	$(nimInd)_2ZrCl_2$	toluene	60	1:1.8	**13** - 16	46
					14 - 35	0
7	$(nimInd)_2ZrCl_2$	toluene	75	1.4:1	**13** - 26	36
					14 - 20	ND[e]
8	$(nimInd)_2ZrCl_2$	toluene	110	1:1.5	**13** - 27	48
					14 - 40	0

[a] Conditions: [**12**] = 0.5 M, [EtMgBr] = 1.05 M, [Zr] = 0.025 M. [b] Ratio determined by GC. [c] % Yield isolated by chromatography. [d] % Total Yield (**13** + **14**) measured by GC. [e] Not determined.

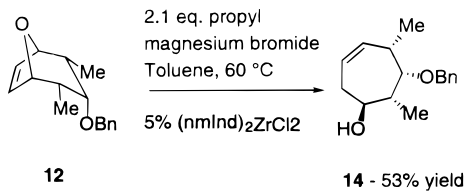


(9)

bromide failed to react with **12** in the presence of $(nmInd)_2ZrCl_2$ after 24 h in toluene at 75 °C (less than 10% conversion, 5% unidentified product). The $(nmInd)_2ZrCl_2$ catalyst precursor is more selective for (1*R*,2*S*,3*R*,4*R*,7*R*)-**13** in toluene at 55 °C or in refluxing hexanes (entries 1 and 4), with approximately 3:1 preference as measured by gas chromatography. However the enantioselectivity is no better than 6% enantiomeric excess under these conditions. In refluxing toluene, the selectivity is reversed with the hydride product favored in a ratio of 2:1. The enantioselectivity for the ethyl product **13** improves slightly to 11% enantiomeric excess, only 6% ee for (1*R*,2*S*,3*R*,4*R*)-**14** is seen at these conditions. The reaction is sluggish in either refluxing tetrahydrofuran or toluene at 22 °C; no more than 30% conversion occurs after 24 h.

The $(nimInd)_2ZrCl_2$ catalyst precursor also reacts with **12** and ethylmagnesium bromide to form both hydride and ethyl addition product. No straightforward correlation with reaction temperature was observed in this case, although the relative ratio changed in each experiment (entries 6−8). Compound (1*S*,2*R*,3*S*,4*S*,7*S*)-**13** in 48% ee can be isolated in approximately 20% yield; compound **14** is formed racemically.

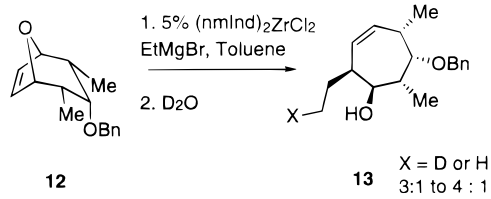
The hydride product **14** was formed more selectively (74% yield by GC, 53% isolated yield) with propylmagnesium bromide and $(nmInd)_2ZrCl_2$; no product corresponding to a propyl addition could be isolated (eq 10). The enantiomeric excess was not determined.



(10)

Monitoring the ring opening of **12** by GC reveals that the $(nmInd)_2ZrCl_2$ catalyst precursor reacts with **12** at room temperature to form a small amount of hydride product **14** within 5 min; no ethyl product **13** is observed initially. Upon heating to 110 °C, the reaction proceeds rapidly (<30 min) to form **13** and **14** in a 1:1 ratio. To compare rates of product formation, the reaction was carried out at 67 °C and monitored at regular intervals. Product **14** was formed in 7% yield after 10 min; this yield remained constant for over 60 min and then began increasing. Product **13** was formed more slowly but at a more steady initial rate which decreased as formation of product **14** began to increase again.

Deuteriolysis of the reaction of **12** with ethylmagnesium bromide and a catalytic amount of $(nmInd)_2ZrCl_2$ in toluene showed a 3−4:1 ratio of the monodeuterated to undeuterated **13** (eq 11). The ratio varied with temperature. The reaction of **12** with 2,2,2-(trideutero)-ethylmagnesium bromide and a catalytic amount of $(nmInd)_2ZrCl_2$ in toluene afforded primarily dideuterated products **13a**,**b**, as well as trideuterated products **13c**,**d** in a relative ratio of four to one. Integration of the ^2H NMR spectrum of these products showed an equal distribution of deuterium atoms at the methyl and methylene positions (eq 12). In the presence of the same Grignard reagent, deuterium is incorporated into the allylic position adjacent to the alcohol of **14** (eq 13).



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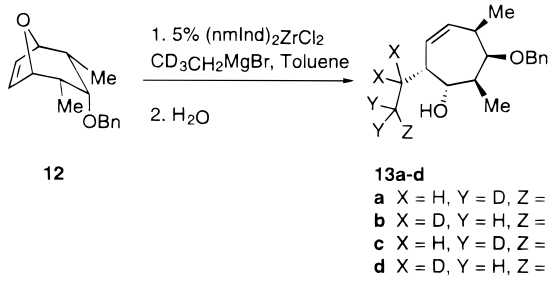
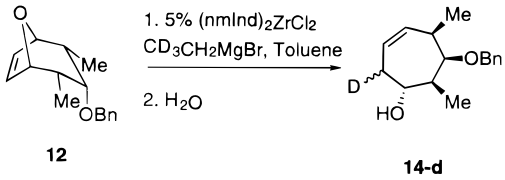


(12)



(13)

Discussion

The catalytic ring-opening of bicycles with hydride reagents has proven a powerful synthetic method; the nickel-catalyzed ring-opening of oxabicycles with diisobutylaluminum hydride proceeds in good yield with high enantioselectivity.[16] The corresponding nickel- and palladium-catalyzed ring-opening with delivery of an alkyl group has also been reported.[16b,17,18] In this paper we report that early transition metal catalysts can be effective for the alkylative ring-opening of oxabicycles in good yields with moderate to excellent enantioselectivity.

The catalytic ring-opening of the oxanorbornene **6** with 1 M TEA in the presence of chiral zirconocenes of the

Erker type[30] yields the substituted cyclohexanol **7** in 64−70% yield and up to 96% ee. Both isomers can be preferentially formed by choice of zirconocene. The titanium catalysts also ring-open **6** in good yields; the chiral catalyst precursor (+)-IndA*$TiCl_2$ produces the (1*R*,2*S*,3*S*,6*R*) isomer in 34% ee. For the ring-opening of **6** to **7**, the zirconium catalysts afford similar yield with improved enantioselectivity.

These results show that catalytic alkyl addition to a [2.2.1] oxabicyclo alkene can afford cyclohexenol products in good yield and excellent enantioselectivity when the $(nimInd)_2ZrCl_2$ catalyst precursor is used. The scope of alkyl nucleophiles is currently limited only to ethyl groups; attempts to ring-open **6** with 1 M tripropylaluminum in the presence of titanocene dichloride yielded the hydride product **8** exclusively.

The titanium catalysts ring-open **6** with the delivery of a hydride to give **8** at high concentrations (2.5 M) of TEA; the yields range from 60 to 99%, but the enantioselectivity with (+)-IndA*$TiCl_2$ is only 17% for the (1*S*,2*R*,3*R*) isomer (Table 2). The hydride product is also exclusively obtained with 1 M tripropylaluminum and titanocene dichloride.

In the presence of TIBA, the $(nmInd)_2ZrCl_2$ catalyst precursor give the (1*S*,2*R*,3*R*) isomer of **8** in yields of 30−47%. In contrast, the $(nimInd)_2ZrCl_2$ produces racemic **8** (Table 2). For the ring-opening of **6** to **8**, the titanium catalysts at high TEA concentrations give better yields and similar stereoselectivity.

Although good yields of **8** can be obtained with the titanium catalysts, the enantioselectivity is uniformly poor and consistently lower than that observed in the ethyl addition reactions; previously developed methods with chiral nickel catalysis are more selective.[16] Use of the group 4 metal catalysts offers some measure of convenience, as the hydride source is added all at once rather than over the course of several hours via a syringe pump.

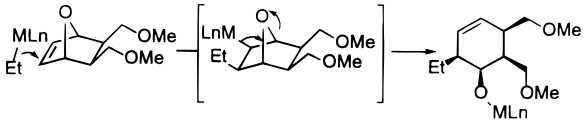
The catalytic ring-opening of [3.2.1] bicycles is also possible with zirconocenes and alkylmagnesium reagents; however, in these reactions we have been unable to find conditions for the selective S_N2' addition of alkyl groups to **12**; in all cases we observe a mixture of the ethyl adduct **13** and the hydride adduct **14**. One of the surprising differences in the [3.2.1] oxabicycle **12** relative to the oxanorbornene **6** is the higher reactivity of **12** for the uncatalyzed ring-opening reactions. Compound **6** is unreactive with 2.5 equiv of triethylaluminum even in refluxing toluene, whereas compound **12** reacts with 2.2 equiv of either triethylaluminum or diethyl zinc to produce ethyl cycloheptenol compound **13**. This was somewhat unexpected, as the opposite trend occurs in nickel-catalyzed ring-opening hydride addition to oxabicyclic alkenes with DiBAl-H; the [2.2.1] oxabicyclo alkene substrates ring-open at room temperature, whereas [3.2.1] oxabicyclo alkene substrates require elevated temperatures to break the carbon−oxygen bond.[14,16] The stability of oxabicycles to Grignard reagents is not well understood but has been utilized in developing nickel-catalyzed alkylative ring-opening methodology.[17]

For the catalytic ring-opening of the [3.2.1] bicycle **12**, we focused on the zirconocenes as the zirconocene compounds were found to be superior in the ring-opening of **6**, and we observed no uncatalyzed ring-opening of **12** ethylmagnesium reagents. The ring-opening of [3.2.1] oxabicyclo alkene **12** with zirconium catalysts and ethylmagnesium bromide lacks the product selectivity seen in ring-openings of [2.2.1] oxabicyclo alkene **6** with aluminum alkyls and zirconocenes; the enantioselectivity is also uniformly lower. The catalytic ring opening of **12** with EtMgBr and zirconocenes **4** and **5** yields mixtures of **13** and **14** in ratios of 1.4:1 to 1:1.8. The ratio of products does not vary consistently with temperature. The ratio of **13** to **14** can be altered from 3:1 to 1:2 by increasing the temperature when $(nmInd)_2ZrCl_2$ **4** is used as catalyst precursor. The combined yields range from 45 to 67%, and the enantioselectivity for both hydride and ethyl addition with this catalyst is poor; a 12% ee of (1*R*,2*S*,3*R*,4*R*,7*R*)-**13** and a 7% ee of (1*R*,2*S*,3*R*,4*R*)-**14** are obtained. It is noteworthy that when TEA is used in place of the Grignard, **13** is formed as a minor product but with a 20% ee of (1*R*,2*S*,3*R*,4*R*,7*R*)-**13**. The alkylative ring opening with $(nimInd)_2ZrCl2$ **5** to give cycloheptenol **13** gave higher ee's of 36−48%, but the selectivity is poor and the yields low at 16−27%. Higher selectivities and yields for hydride addition is possible with higher alkymagnesiums such as PrMgBr, but no enantioselectivity is observed in the formation of the hydride adduct **14**.

The catalytic ring opening of [2.2.1] and [3.2.1] oxabicycloalkenes with Grignard reagents can also be carried out with nickel catalysts;[17] to date, only achiral nickel complexes have been reported with Grignards lacking β-hydrogens. For the nickel catalysts, the selectivity for *exo* versus *endo* attack depends on the solvent.[17] For the zirconocene-catalyzed ring-opening reported here, we observe only *exo* attack.

Three plausible mechanisms can be envisaged for the ring-opening of oxabicycles: Lewis acid-catalyzed S_N2' alkyl addition (eq 14), olefin insertion into a transition metal alkyl (eq 15), and alkene reductive coupling

(14)

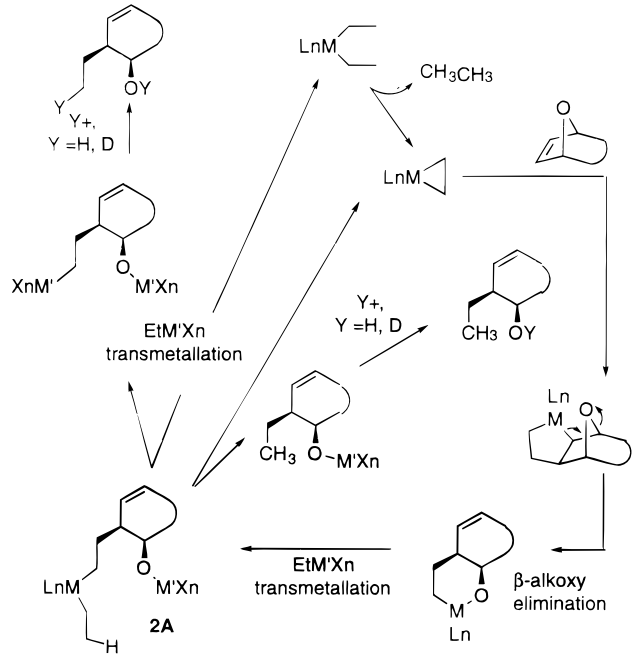


(15)

through a metallacycle intermediate (Scheme 2). The Lewis acid mechanism has been used to rationalize silyl triflate-catalyzed enolate addition to an oxanorbornene.[35] Olefin insertion has been implicated in carbometalation of α-olefins with group 4 metals with trialkyl aluminum compounds.[36,37] Alternatively, reductive coupling of α-olefins with metal alkyls and group 4 metal catalysts has also been postulated for the ethylmagnesation and ethylalumination of olefins.[19,20,38,39] This mechanism has also been proposed for the ring-opening of benzooxanorbornene with a zirconocene benzyne complex.[23]

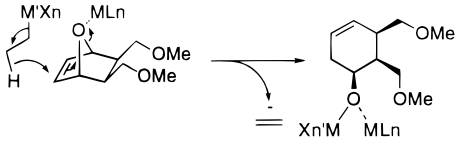
(35) Yamamoto, I.; Narasaka, K. *Chem. Lett.* **1995**, 1129.
(36) Kondakov, D. Y.; Negishi, E.-i. *J. Am. Chem. Soc.* **1996**, *118*, 1577−1578.
(37) Kondakov, D. Y.; Negishi, E.-i. *J. Am. Chem. Soc.* **1995**, *117*, 10771−10772.
(38) Hoveyda, A. H.; Morken, J. P.; Houri, A. F.; Xu, Z. M. *J. Am. Chem. Soc.* **1992**, *114*, 6692−6697.
(39) Dawson, G.; Durrant, C. A.; Kirk, G. G.; Whitby, R. J. *Tetrahedron Lett.* **1997**, *38*, 2335−2338.

Scheme 2. Proposed Reductive Coupling Mechanism for Titanium- and Zirconium-Catalyzed Ring-Opening Ethyl Additions to Oxabicyclo Alkene Compounds

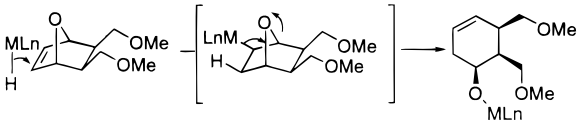


As shown in eqs 14 and 15 and Scheme 2, only the reductive coupling mechanism invokes an alkylmetal species as a key intermediate *after* ring opening by β-alkoxy elimination. Thus, deuteriolytic workup should provide a signature for the reductive coupling mechanism if transmetalation competes with β-hydride elimination from intermediate **2A**.

Two mechanisms can be envisaged for the ring-opening of oxabicycles with delivery of a hydride: a Lewis acid-catalyzed hydride addition via a β-hydride elimination (eq 16) and olefin insertion into a transition metal hydride (eq 17). The transition metal hydride can be generated by prior β-hydride elimination from a transition metal alkyl.



(16)



(17)

Lewis acids can mediate hydride additions by metal alkyls to double bonds; for example, triisobutylaluminum reduces carbonyl groups through a β-hydride elimination process analogous to the Meerwein−Ponndorf−Verley reaction; it also exchanges isobutylene for other olefins in a similar process.[40] The metal alkyl serves as both Lewis acid and reductant in these reactions. The insertion of olefins into zirconocene metal hydrides is also well-known. Discrimination between the two proposed hydride addition mechanisms is more difficult than in the ethyl addition case. The hydrogen source in both mechanisms is the metal alkyl reagent, so isotopic labeling does not distinguish the two possibilities.

For the ring opening of **6** with Et_3Al, a reductive coupling mechanism (Scheme 2) is plausible and consistent with proposals for the ethylalumination of α-olefins in the presence of zirconocenes.[39,41] This mechanism would account for the lack of reactivity of **6** with Me_3Al, but neither an olefin insertion mechanism nor a direct nucleophilic attack via group 4 metal Lewis acid catalysis can be ruled out on the basis of available data.

Isotopic labeling studies on the ring-opening of **12** implicate a metallacycle mechanism for this reaction. The observation of the monodeuterio-**13** upon deuteriolytic workup the reaction of **12** with EtMgBr rules out direct nucleophilic attack and olefin insertion mechanisms. In addition the formation of di- and trideuterated products **13a**−**d** with an equal distribution of deuterium atoms between the methyl and methylene carbons strongly implicates a metal ethylene adduct derived from the magnesium alkyl as postulated in Scheme 2. Production of the four products **13a**−**d** is also consistent with the metallacycle mechanism (Scheme 2), as isotopic effects on the carbon−carbon bond-forming step are expected to be minimal.[38] The label should be found only at the terminal carbon of the ethyl moiety in either Lewis acid or olefin insertion mechanisms; so either mechanism would produce only product **13c**. The catalytic ring opening of **12** with triethylaluminum and $(nmInd)_2ZrCl_2$ yields **13** as a minor product, but the same enantiomer of **13** as that obtained from the ethylmagnesium bromide is observed, implicating a similar mechanism.

The nature of the metal alkyl appears to influence the enantioselectivity; in the ring-opening of **12**, reactions with TEA produce **13** with higher % ee than those with ethylmagesium bromide *even though* an uncatalyzed TEA-induced ring-opening competes with the catalyzed reaction. Furthermore, ring-opening of **6** with TEA has much higher enantioselectivity than ring-opening of **12** with ethylmagnesium bromide. To a first approximation, the substrates present the same 2,5-dihydrofuran "face" to the zirconocene catalyst, although the substrates are different. Together, these observations suggest that the metal alkyls play a role in the transition state of the stereochemistry-determining reductive coupling step.

Ring-opening deuteride addition to **12** with 2,2,2-trideuteroethylmagnesium bromide and $(nmInd)_2ZrCl_2$ places a deuterium atom at the allylic position adjacent to the alcohol. This result clearly indicates the β-hydrogen of the metal alkyl as the source of the hydride but does not discriminate between a Lewis acid-catalyzed hydride addition (eq 16) and an insertion mechanism (eq 17). The fact that the ratio of hydride product **14** and ethyl product **13** change with conversion implicates different catalysts for the two reactions.

The hydride and ethyl catalysts formed from $IndA^*TiCl_2$ differ in their absolute stereoselectivity; the ethyl and hydride are delivered to opposite enantiotopic alkene carbon of **6**. In contrast, the catalysts derived from $(nmInd)_2ZrCl_2$ have the same absolute stereoselectivity. This suggests that the nature of the catalytic species

(40) Winterfeldt, E. *Synthesis* **1975**, 617−630.

(41) Dzhemilev, U. M.; Ibragimov, A. G.; Zolotarev, A. P.; Muslukhov, R. R.; Tolstikov, G. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1990**, *12*, 2831−2841.

varies not only by reaction type (ethyl or hydride) but also by metal.

Experimental Section

General. All manipulations involving air-sensitive compounds were carried out under nitrogen in a glovebox or using standard Schlenk line techniques. Hexanes were distilled from lithium aluminum hydride, and tetrahydrofuran was distilled from sodium/ benzophenone prior to use. Toluene was passed through supported copper catalyst and alumina columns to remove moisture and trace oxygen. All solvents were collected and stored in Straus flasks (Kontes glassware). Alkyaluminums (neat) were purchased from Aldrich and used as received. Grignard reagents were either purchased from Aldrich as solutions in tetrahydrofuran or prepared according to literature procedure. Titanocene dichloride was purchased from Aldrich and used as received. η-5-((tetramethyl)cyclopentadienyl)(dimethylsilyl)(*tert*-butyl)amidotitanium dichloride (Cp*ATiCl$_2$), (+)-η-5-(indenyl)(dimethylsilyl)(α-methylbenzyl)amidotitanium dichloride (IndA*TiCl$_2$),[28,42] and zirconocenes[29,30] were prepared according to the literature. All other reagents were obtained commercially and used as received unless otherwise noted.

Preparative chromatography was performed on silica gel 60, 0.02−0.04 mm. GC analyses were obtained with an SE-30 column (30 mm × 0.32 mm i.d. × 0.25 μm coating) with an FID detector. ^{1}H and ^{13}C NMR specta were obtained on Varian Gemini-200 MHz, XL-400 MHz, and Unity Inova-500 MHz spectrometers. FTIR were obtained as thin films on NaCl plates. Chiral HPLC was performed with columns from Chiralcel Technologies as noted.

Substrate Synthesis. Preparation of 4,5-Bis(methoxymethyl)-7-oxabicyclo-2-heptene (6). This substrate was prepared by a modification of a literature procedure.[3] Freshly distilled furan (2.6 mL, 35.7 mmol) and freshly sublimed mandelic anhydride (3.5 g, 35.7 mmol) were dissolved in ether and stirred for several days. The crystalline, insoluble Diels−Alder adduct was recovered by filtration in 64% yield (3.821 g, 22.8 mmol). The product was characterized by NMR spectroscopy. ^{1}H NMR: ($CDCl_3$) δ 6.580 (t, J = 1 Hz, 2H), 5.465 (t, J = 1 Hz, 2H), 3.175 (s, 2H). The Diels−Alder adduct was reduced to 4,5-bis(hydroxymethyl)-7-oxabicyclo-2-heptenediol with 2.2 equiv of lithium aluminum hydride in tetrahydrofuran and used without further purification after aqueous workup. ^{1}H NMR: ($CDCl_3$) δ 6.389 (s, 2H); 4.685 (s, 2H); 3.805 (d, J = 5 Hz, 4H); 1.95 (t, J = 5 Hz, 2H). Methylation was carried out by reacting the diol (2.07 g, 14.31 mmol) with (3.56 mL, 57.24 mol) iodomethane in methyl sulfoxide with potassium hydroxide. The product **6** was purified by fractional vacuum distillation as a pale yellow oil (1.87 g, 10.2 mmol). ^{1}H NMR: ($CDCl_3$) δ 6.329 (s, 2H); 4.815 (s, 2H); 3.462 (dd, J = 9.4, 5 Hz, 2H); 3.345 (s, 6H); 3.305 (d, J = 9.4 Hz, 2H); 1.881 (m, 2H).

Preparation of 2,4-Dimethyl-3-(benzyloxy)-8-oxabicyclo-6-octene (12). This substrate was prepared according to literature procedure.[3] A 5.4 g (35.5 mmol) quantity of 2,4-dimethyl-8-oxabicyclo-6-octene-3-one was prepared by a [4 + 3] oxyallyl cation cyclization.[43] ^{1}H NMR: ($CDCl_3$) δ 6.343 (s, 2H); 4.852 (d, J = 5 Hz, 2H); 2.77−2.84 (m, 2H); 0.968 (d, J = 7.2 Hz, 6H). ^{13}C NMR: ($CDCl_3$) δ 133.578; 82.705; 50.312; 10.014. Reduction of this {3.2.1} oxabicyclic ketone with diisobutylaluminum hydride in tetrahydrofuran at 0 °C selectively produced the *endo* alcohol product upon workup. Flash column chromatography with 1:1 hexane/ethyl acetate as eluent afforded 2.54 g (20.6 mmol, 58% yield) of a white crystalline solid. ^{1}H NMR: ($CDCl_3$) δ 6.526 (s, 2H); 4.48 (d, J = 3.4 Hz, 2H); 3.687 (dt, J = 11.4, 6 Hz, 1H); 2.17−2.23 (m, 2H); 1.535 (d, J = 11.4 Hz, 1H); 0.98 (d, J = 7.6 Hz, 6H). ^{13}C NMR: ($CDCl_3$) δ 136.355; 82.143; 72.797; 38.143; 12.851. The alcohol product reacted with benzyl bromide and sodium hydride to form the desired benzyloxy product. The product was purified by flash column chromatography (4:1 hexane/ethyl acetate eluent) to afford 2.9 g (17.1 mmol, 83% yield) of substrate **12**. ^{1}H NMR: ($CDCl_3$) δ 7.29−7.35 (m, 5H); 6.325 (s, 2H); 4.425 (s, 2H); 4.4 (d, J = 3 Hz, 2H); 3.534 (t, J = 6 Hz, 1H); 2.247−2.324 (m, 2H); 0.93 (d, J = 7.2 Hz, 6H). ^{13}C NMR: ($CDCl_3$) δ 133.957; 128.161; 127.099; 126.902; 82.189; 80.201; 75.293; 38.826; 12.775.

Ethyl Ring-Opening Reaction of Oxabicycle 6. Representative Procedure for Titanium Catalysts. In the drybox, a 25 mL Schlenk flask was charged with 50 mg (0.136 mmol) of IndA*TiCl$_2$, 500 mg (2.71 mmol) of **6**, and 10 mL of hexanes. A 0.835 mL (6.78 mmol) portion of neat triethylaluminum was added to the reaction solution, and the flask was fitted with a coldfinger condenser. The reaction flask was attached to a Schlenk line and the solution was heated to reflux with an oil bath. After 12 h, the solution was cooled to 0 °C. A 10 mL amount of a 10% HCl solution was added dropwise (**This quenching is extremely exothermic − exercise great care in adding the HCl solution)**. The products were extracted with 3 × 50 mL of diethyl ether, and the combined organics were dried over magnesium sulfate. After filtration, the solvents were removed on a rotary evaporator. The cyclohexenol product **7** was obtained in 94% yield (550 mg) in 95% purity (starting material was the only impurity).

Representative Procedure for Zirconium Catalysts. In the drybox, a 25 mL Schlenk flask was charged with 34 mg (0.05 mmol) of (nmInd)$_2$Cl$_2$, 184 mg (2.71 mmol) of **6**, and 2 mL of toluene. A 0.28 mL (2 mmol) portion of neat triethylaluminum was added to the reaction solution and the flask was fitted with a coldfinger condenser. The reaction flask was attached to a Schlenk line and the solution was heated to reflux with an oil bath. After 17 h, the solution was cooled to 0 °C. Ten milliliters of a 10% HCl solution was added dropwise (**This quenching is extremely exothermic − exercise great care in adding the HCl solution)**. The products were extracted with 3 × 15 mL of diethyl ether, and the combined organics were dried over magnesium sulfate. After filtration, the solvents were removed on a rotary evaporator. After flash column chromatography with 1:1 hexane/diethyl ether, the cyclohexenol product **7** was obtained in 70% yield (128 mg) in 95% purity (starting material was the only impurity). The product was nonracemic: $[\alpha]_D = -48.8°$, $c = 0.33$ in methylene chloride.

2,3-Bis(methoxymethyl)-7-ethyl-4-cyclohexen-1-ol (7). ^{1}H NMR: ($CDCl_3$) δ 5.55−5.60 (m, 2H), 4.024 (d, J = 10 Hz, 1H), 3.7−3.85 (bm, J = 10 Hz, 1H), 3.573 (d, J = 7.8 Hz, 2H), 3.449 (d, J = 3 Hz, 2H), 3.383 (s, 3H), 3.376 (s, 3H), 2.5−2.5 (m, 1H), 2.331 (qd, J = 7.8, 2 Hz, 1H), 1.92−2.0 (m, 1H), 1.2−1.8 (m, 2H), 0.992 (t, J = 7.3 Hz, 3H). ^{13}C NMR: ($CDCl_3$) δ 130.953, 127.130, 73.177, 73.0737, 64.908, 58.854, 58.808, 41.421, 36.338, 24.291, 11.546; MS 214 (M^+). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.29; H, 10.28. Found: C, 67.10; H, 10.69.

Hydride Ring-Opening Reaction of Oxabicycle 6: Representative Procedure for Titanium Catalysts. In the drybox, a 25 mL Schlenk flask was charged with 21.5 mg (0.05 mmol) of IndA*TiCl$_2$, 184 mg (1 mmol) of **6**, and 2 mL of hexanes. A 0.7 mL (5 mmol) portion of neat triethylaluminum was added to the reaction solution, and the flask was fitted with a coldfinger condenser. The reaction flask was attached to a Schlenk line, and the solution was heated to reflux with an oil bath. After 12 h, the solution was cooled to 0 °C. Ten milliliters of a 10% HCl solution was added dropwise (**This quenching is extremely exothermic − exercise great care in adding the HCl solution)**. The products were extracted with 3 × 15 mL of diethyl ether, and the combined organics were dried over magnesium sulfate. After filtration, the solvents were removed on a rotary evaporator. Flash column chromatography with 3:2 hexanes/ethyl acetate as eluent afforded the cyclohexenol product **7**, 98.5% pure by GC (66% yield, 122 mg). The product was nonracemic: $[\alpha]_D = -14.6°$, $c = 0.5$ in methylene chloride.

Representative Procedure for Zirconium Catalysts. In the drybox, a 25 mL Schlenk flask was charged with 35 mg

(42) Shapiro, P. J.; Bunel, E.; Schaefer, W. P.; Bercaw, J. E. *Organometallics* **1990**, *9*, 867−869.
(43) Hoffmann, H. M. R. *Org. Synth.* **1978**, *58*, 17.

(0.05 mmol) of $(nmInd)_2Cl_2$, 184 mg (1 mmol) of **6**, and 2 mL of toluene. A 0.5 mL (2 mmol) portion of neat triisobutylaluminum was added to the reaction solution, and the flask was fitted with a coldfinger condenser. The reaction flask was attached to a Schlenk line, and the solution was heated to reflux with an oil bath. After 18 h, the solution was cooled to 0 °C. Ten milliliters of a 10% HCl solution was added dropwise. The products were extracted with 3 × 15 mL of diethyl ether, and the combined organics were dried over magnesium sulfate. After filtration, the solvents were removed on a rotary evaporator. Flash column chromatography with 1:1 hexanes/ethyl acetate as eluent afforded the cyclohexenol product **7** in 30% yield (55 mg).

2,3-Bis(methoxymethyl)-4-cyclohexen-1-ol (8).[14] ^{1}H NMR: ($CDCl_3$) δ 5.70 (m, 1H), 5.56 (m, 1H), 4.3 (d, J = 10 Hz, 1H), 3.92 (m, 1H), 3.56 (m, 2H), 3.37 (s, 3H), 3.37 (d, J = 3.2 Hz, 2H), 3.36 (s, 3H), 2.61 (m, 1H), 2.4 (m, 1H), 2.31 (m, H), 2.20 (m, 1H). ^{13}C NMR: ($CDCl_3$) δ 127.26, 126.24, 72.50, 72.36, 66.83, 59.23, 40.16, 37.55, 33.96.

Ring-Opening Reactions of Oxabicycle 12: Representative Procedure. A 25 mL Schlenk flask was charged with 0.7 mL of 3.0 M ethylmagnesium bromide in diethyl ether. The solvent was removed in vacuo for 1 or more hours; in all cases the final pressure was below 100 milliTorr. The reaction flask was taken to the drybox and charged with 34 mg of $(nimInd)_2Cl_2$, 244 mg of **12**, and 2 mL of toluene. The flask was fitted with a coldfinger condenser and adapted to a Schlenk line where it was heated to 60 °C. The reaction was stirred for 12 h and then cooled to room temperature and quenched by careful addition of 10 mL of a 10% HCl solution. The products were extracted with 3 × 15 mL of diethyl ether; the organics were then dried over magnesium sulfate and dried on a rotary evaporator. Flash column chromatography with 4:1 hexane/ethyl acetate as eluent afforded 44 mg (16% yield) of ethyl cycloheptenol **13** and 85 mg (35% yield) of hydride cycloheptenol **14**. Both compounds are white crystalline solids when all traces of solvent are removed.

2,4-Dimethyl-3-(benzyloxy)-7-ethyl-5-cyclohexen-1-ol (13): mp 70−71.5 °C.^{1}H NMR: ($CDCl_3$) δ 7.25−7.35 (m, 5H), 5.41−5.51 (m, 2H) 4.639 (s, 2H), 3.680−3.686 (m, 1H), 3.565 (t, J = 2 Hz, 1H), 2.64−2.67 (m, 2H), 2.10−2.14 (m, 1H), 1.53−1.61 (m, 1H), 1.46−1.51 (m, 1H), 1.179 (d, J = 6.4 Hz, 3H), 1.168 (d, J = 5.6 Hz, 3H), 0.959 (t, J = 7.2 Hz, 3H). ^{13}C NMR: ($CDCl_3$) δ 139.345, 133.888, 130.032, 128.180, 127.169, 126.973, 84.144, 76.024, 74.850, 44.362, 43.264, 39.423, 24.505, 19.221, 17.204, 12.612; MS 274 (M^+). Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 79.020; H, 9.91. Enantiomeric excess was determined by chiral HPLC (chiralcel AD column, 99:1 heptane/2-propanol). For compound **13** formed with $(nmInd)_2Cl_2$ in 6% ee, the optical rotation is $[\alpha]_D$ = +9.7°, c = 1.0 in CH_2Cl_2.

2,4-Dimethyl-3-(benzyloxy)-5-cyclohexen-1-ol (14): mp 40−44 °C. ^{1}H NMR: ($CDCl_3$) δ 7.3−7.4 (M, 5H), 5.72−5.77 (m, 1H), 5.458 (ddd, J = 13, 4.5, 2 Hz, 1H), 4.674 (s, 2H), 3.56−3.59 (m, 1H), 3.47−3.5 (m, 1H), 2.6−2.63 (m, 1H), 2.35−2.4 (m, 2H), 1.81−1.86 (m, 1H), 1.217 (d, J = 6.5 Hz, 3H), 1.201 (d, J = 6.8 Hz, 3H). ^{13}C NMR: ($CDCl_3$) δ 136.268, 128.231, 127.174, 125.456, 86.348, 75.524, 70.255, 49.981, 38.982, 37.420, 20.878, 17.618; MS 246 (M^+). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.74; H, 9.36.

Derivatives of Ring-Opened Products: Ester Derivatives of 8, 13, and 14. The literature procedure using *N*,*N*′-dicyclohexyldiimide was followed in the esterification with (*R*)-α-methoxyphenylacetic acid to determine both enantiomeric excess and absolute stereochemistry of compounds **8**, **13**, and **14**.[34] Compound **7** was unreactive with (*R*)-α-methoxyphenylacetic acid, presumably due to the steric hindrance around the secondary alcohol. The enantiomeric excesses of compound **7** produced by different catalysts was also determined by chiral HPLC of the 4-nitrobenzyl ester derivative (chiralcel OD column, 99.5:0.5 heptane/2-propanol). This ester was prepared according to the literature from 4-nitrobenzoyl chloride, 4-(dimethylamino)pyridine, and pyridine.[44]

Reductive Ozonolysis of 7 to Furanose 9 and Ester Derivative 10. A 215 mg (1 mmol) portion of **7** placed in a 50 mL round-bottom flask was dissolved in 25 mL of diethyl ether. This solution was cooled to −25 °C, and a stream of ozone was bubbled through it for 30 min. Dry oxygen was then bubbled through the solution for 10 min. The solution was warmed to 0 °C, and 161 mg (4 mmol) lithium aluminum hydride was added. The slurry was stirred overnight and then quenched with saturated ammonium sulfate. The product was extracted with 4 × 10 mL of ether. The combined organics were dried over magnesium sulfate, concentrated, and purified by pipet scale chromatography. The product **9** was recovered in 21% yield (53 mg). The peak at 97.9 ppm in the ^{13}C spectrum is consistent only with the furanose structure. ^{1}H NMR: ($CDCl_3$) δ 8.22 (dd, J = 8.5, 1.7 Hz, 2H), (dt, J = 9, 2 Hz, 2H), 5.20 (dd, J = 11.7, 4.8 Hz, 1H), 4.935 (d, J = 11.7 Hz, 1H), 4.406 (d, J = 3 Hz, 1H), 4.395 (d, J = 3 Hz, 1H), 4.147 (dd, J = 6.8,4 Hz, 1H), 3.55−3.48 (m, 2H), 3.37−3.24 (m, 2H), 3.367 (s, 3H), 3.307 (s, 3H), 2.6−2.5 (m, 1H), 2.4−2.3 (m, 1H), 1.8−1.7 (m, 1H), 1.3−1.6 (m, 2H), 0.947 (t, J = 7.5 Hz). ^{13}C NMR: ($CDCl_3$) δ 11.637; 20.361; 42.103; 45.263; 47.095; 59.112; 59.081; 63.739; 68.686; 71.295; 84.419; 97.908. Selective esterification of the primary alcohol to **10** with 4-nitrobenzoic acid was performed with the acid chloride and 4-(dimethylamino)-pyridine.

Oxidation of 7 to Cyclohexenone 11. A two-neck 50 mL round-bottomed flask fitted with a dropping funnel and a nitrogen adapter was purged with N_2 and then charged with 54 μL of oxalyl chloride and 2 mL of CH_2Cl_2. The solution was cooled to −78 °C. Dimethyl sulfoxide, 0.08 mL in 2 mL of CH_2Cl_2, was added dropwise over 2 min. Compound **7**, 120 mg from $(nimInd)_2ZrCl_2$ catalysis, was added in 2 mL of CH_2Cl_2. The reaction was stirred 30 min at −78 °C, and then 1.0 mL of triethylamine was added dropwise. The solution was warmed to 22 °C and stirred 12 h. The reaction was quenched by addition of water. The product was extracted with 3 × 20 mL of CH_2Cl_2; organics were washed with 10% HCl, sodium bicarbonate, and brine and then dried over magnesium sulfate. Flash chromatography on silica with 4:1 hexanes/ethyl acetate afforded 22 mg (18% yield) of cyclohexenone product. ^{1}H NMR: ($CDCl_3$) δ 5.88 (m, 1H), 5.80 (m, 1H), 3.825 (dd, J = 10, 10 Hz, 1H), 3.463 (dd, J = 10, 6 Hz, 1H), 3.356 (s, 3H), 3.2−3.2 (m, 2H), 3.215 (s, 3H), 2.9−3 (m, 2H), 2.8 (m, 1H), 1.8−1.9 (m, 1H), 1.45−1.55 (m, 1H), 0.904 (t, J = 7.5 Hz). ^{13}C NMR: ($CDCl_3$) δ 10.98, 22.44, 40.37, 49.88, 58.79, 58.97, 68.87, 68.90, 128.29, 130.14, 209.11. IR (NaCl plate) 2927 (m), 1719 (w), 1654 (s), 1530 (w), 1458 (w), 1274 (m), 1104 (s).

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