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Scope of Palladium-Catalyzed Alkylative Ring Opening

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Abstract: We have explored the scope of the palladium-catalyzed nucleophilic ring opening methodology. New highly selective and highly active catalysts have been found for the ring opening of oxabenzonorbornadienes. Employing these catalysts, the addition of various alkyl nucleophiles to oxabenzonorbornadiene has been achieved. In addition, reaction of diethylzinc with [3.2.1] oxabicyclic alkenes has been accomplished to yield ring-opened products as well as functionalized alkene addition products.

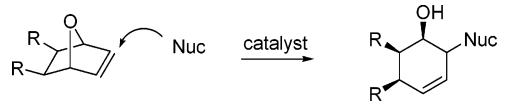
Introduction

The use of oxabicyclic templates to achieve stereoselective functional group introduction in carbocyclic products is a strategy that has been investigated for the synthesis of complex molecular structures.[1] The conformational rigidity of the bicyclic structure allows for predictable, highly selective reactions.

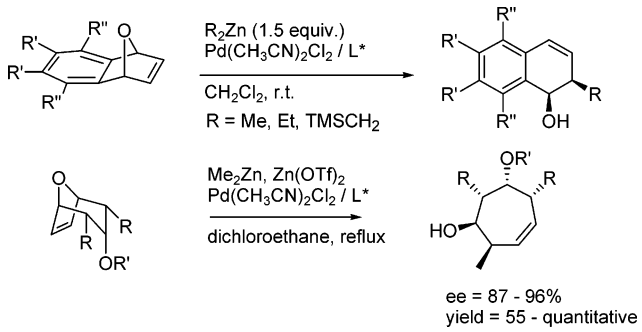
Our group was drawn to the synthetic potential associated with nucleophilic desymmetrization of oxabicyclic alkenes. We envisioned that a suitable enantioselective nucleophilic ring opening reaction would not only reveal the latent stereochemistry embedded within the oxabicyclic framework, but also install specific substituents depending on the nature of the nucleophile (Scheme 1).[2]

We have previously reported the enantioselective addition of alkyl nucleophiles to oxabicyclic alkenes catalyzed by palladium (Scheme 2).[3,4] Using chiral catalysts, we were able to achieve ring opening using dialkylzinc reagents to obtain products in excellent yields and enantioselectivities. Since our initial reports, we have continued to explore the scope and limitations of this methodology in terms of the catalyst, nucleophile, and substrate. We now report our findings, the mechanistic insights we have gained from these studies, and how they have been instrumental in extending the methodology.

Scheme 1



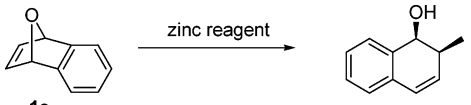
Scheme 2



Results and Discussion

1. Catalysts. a. Uncatalyzed Reactions. Initial studies using organozinc reagents for the alkylative ring opening began with a study of their reactivity in uncatalyzed additions with substrate **1a** (Table 1). Dialkylzinc reagents proved unreactive, with dimethylzinc giving no reaction at room temperature in THF, and diethylzinc giving trace amounts of ring-opened product along with naphthol (obtained by Lewis acid assisted decomposition). The use of lithium trimethylzincate in THF also gave no reaction; however, when lithium tetramethylzincate was employed at room temperature, 15% ring-opened product **2** was obtained. In fact, increasing the temperature to reflux gave a nearly quantitative yield of **2**, supporting the proposal by

Table 1. Uncatalyzed Addition of Zinc Reagents



1a **2**

	zinc reagent	solvent, temp	yield (%)
1	Me_2Zn	THF, rt	NR
2	Me_3ZnLi	THF, rt	NR
3	Me_4ZnLi_2	THF, rt	15
4	Me_4ZnLi_2	THF, reflux	99

(1) For reviews see: (a) Lautens, M. *Synlett* **1993**, 177. (b) Woo, S.; Keay, B. A. *Synthesis* **1996**, 669. (c) Chiu, P.; Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 1.
(2) For a review of the ring opening methodologies developed in our labs see: Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48.
(3) (a) Lautens, M.; Renaud, J.-L.; Hiebert, S. *J. Am. Chem. Soc.* **2000**, *122*, 1804. (b) Lautens, M.; Hiebert, S.; Renaud, J.-L. *Org. Lett.* **2000**, *2*, 1971.
(4) For other examples of enantioselective alkylative ring opening of oxabicycles see: (a) Lautens, M.; Gadja, C.; Chiu, P. *J. Chem. Soc., Chem. Commun.* **1993**, 1193. (b) Moinet, C.; Fiaud, J. C. *Tetrahedron Lett.* **1995**, *36*, 2051. (c) Millward, D. B.; Sammis, G.; Waymouth, R. M. *J. Org. Chem.* **2000**, *65*, 3902. (d) Lautens, M.; Dockendorff, C.; Fagnou, K. Malicki, A *Org. Lett.* **2002**, *4*, 1311. (e) Bertozzi, F.; Pineschi, M.; Macchia, F.; Arnold, L.; Minnaard, A.; Feringa, B. *Org. Lett.* **2002**, *4*, 2703.

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Sakamoto and co-workers that tetramethylzincates display increased reactivity relative to the trimethylzincates.[5]

b. Catalyst Studies. A variety of literature precedents were drawn upon in the attempt to find a suitable catalyst, which would effect an S_N2' addition of dialkylzincs to **1a**. The use of chiral amino alcohols such as those described by Soai,[6] Alexakis' phosphoramidite ligand,[7] and Charette's dioxaborolane[8] gave no reaction with dimethylzinc and only trace amounts of ring-opened product for diethylzinc addition. Similarly, reactions with Ti(O-*i*-Pr)$_4$ and chiral ligands were unsuccessful using Me_2Zn and Et_2Zn in toluene at room temperature.[9]

Inspired by Feringa's work using chiral copper catalysts for conjugate addition of dialkylzincs to enones, we attempted a few reactions using Cu(OTf)$_2$ and a BINOL-derived phosphoramidite ligand.[10] However, attempts to add Me_2Zn using this catalyst in THF at room temperature only resulted in trace amounts of desired ring-opened product. Following our work, Feringa has subsequently reported the use of this catalyst for ring opening of **1a** in excellent yield and enantioselectivity.[4e] The reactions are carried out in toluene using Zn(OTf)$_2$ as an additive—a reagent we showed accelerated ring opening.

We next looked at the use of group IX and X transition metals to catalyze the addition reaction. [Rh(COD)Cl]$_2$/dppe failed to catalyze ring opening with dimethylzinc in THF, and attempts to add diethylzinc resulted in exclusive hydride addition product arising from β-hydride elimination on an ethylrhodium species. The use of nickel catalysts gave results similar to those observed with rhodium; however, more promising results were obtained with palladium. Using 5 mol % Pd(dppf)Cl$_2$ in dichloromethane at room temperature resulted in an 80% isolated yield of methyl addition product **2**.

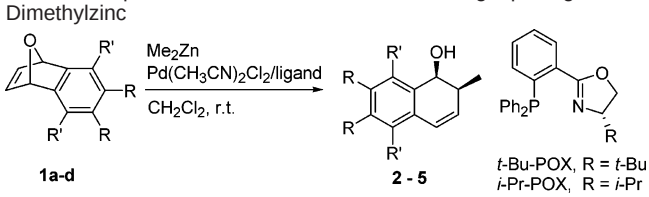
c. Enantioselective Reactions. Having discovered that palladium was a good catalyst for the addition, we went on to develop an enantioselective version of the reaction. Our initial paper described the use of 5 mol % Pd(*i*-Pr-POX)Cl$_2$ as catalyst to give methyl addition products from a variety of oxabenzonorbornadienes in 65−100% yield and 89−91% enantioselectivity.[3a] However, we have found that the analogous Pd(*t*-Bu-POX)Cl$_2$ catalyst gives the dihydronaphthol products in higher enantioselectivities (Table 2). Therefore, products with both electron-rich and electron-deficient substituents on the aromatic ring can be obtained in 96−97% ee.

Determination of the absolute stereochemistry of these products was accomplished by derivatization of **2** (97% ee using (*S*)-*t*-Bu-POX). Treatment with *N*-bromosuccinimide in THF/H_2O gave **6** as a single isomer in 55% yield after recrystallization. The crystals were suitable for X-ray analysis, which showed the absolute stereochemistry of **6** to be as shown in Scheme 3.

d. Cationic Catalyst. Following our disclosure on the development of methodology for the ring opening of various oxabicyclic alkenes, we carried out studies on the mechanism of this reaction. From these studies we obtained evidence to support a pathway that proceeded via an enantioselective carbopalladation of the substrate alkene by a cationic palladium alkyl species such as $[L_2PdR]^+$.[11]

The proposal of a cationic palladium intermediate led us to explore the use of cationic palladium catalyst **7**[12] in the ring opening with diethylzinc (Table 3). For the addition of Et_2Zn we had previously found that Pd(Tol-BINAP)Cl$_2$ gave the best results. Using this catalyst, a variety of dihydronaphthols were obtained in excellent yield and 92−97% ee.[3a] When catalyst **7** was employed with substrate **1a** using 2.5 mol % dimer, the reaction gave product **8** in 95% enantiomeric excess. This compares closely with the Pd(Tol-BINAP)Cl$_2$ catalyst, which gave **8** in 98% yield and 97% ee. However, the reaction using **7** was much faster, taking less than 30 min to reach complete conversion.

Table 2. Improved Enantioselectivities in the Ring Opening with Dimethylzinc



ligand	substrate	product	R	R	yield (%)	ee (%)
t-Bu-POX	**1a**	**2**	H	H	88	97
	1b	**3**	O(CH$_2$)O	H	94	97
	1c	**4**	F	H	93	96
i-Pr-POX	**1a**	**2**	H	H	90	89
	1b	**3**	O(CH$_2$)O	H	100	91
	1c	**4**	F	H	73	90
	1d	**5**	Br	CH$_3$	71	90

Scheme 3

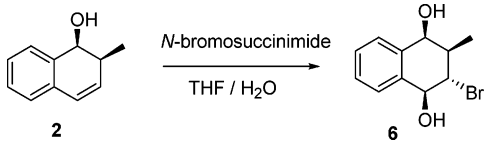
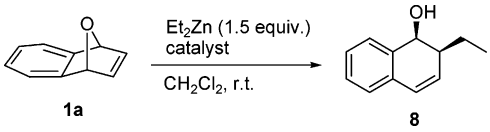
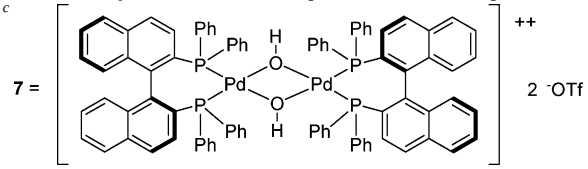


Table 3. Ring Opening with Cationic Catalyst **7**



catalyst	loading (%)	time (h)	yield[a] (%)	ee (%)
Pd(Tol-BINAP)Cl$_2$	5.0	4	98	97
7[c]	2.5	0.5	b	95
7	0.25	4	b	93
7	0.05	16	98	93

[a] Isolated yield. [b] The reaction proceeded with complete conversion. [c]



(5) Uchiyama, M.; Kameda, M.; Osamu, M.; Yokoyama, N.; Koike, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 4934.
(6) Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264.
(7) Alexakis, A.; Frutos, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2427.
(8) Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081.
(9) (a) Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691. (b) Lutjens, H.; Nowotny, S.; Knochel, P. *Tetrahedron: Asymmetry* **1995**, *6*, 2675.
(10) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620.
(11) Lautens, M.; Hiebert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2000**, *2*, 1971.
(12) Synthesized as in: Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450.

Scheme 4

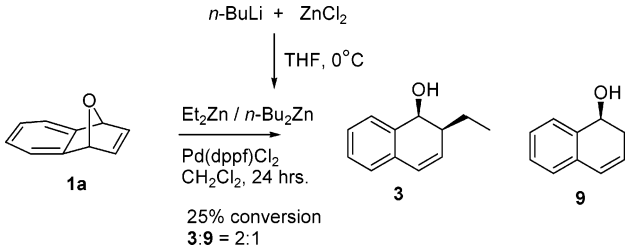
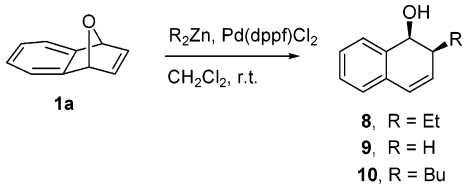


Table 4. Effect of Dialkylzinc Preparation on Ring Opening



	formation of dialkylzinc	product	yield (%)
1	EtMgBr + $ZnCl_2$ in THF	naphthol	–
2[a]	EtMgBr + $ZnCl_2$ in Et_2O	**8**	67
3[a]	*n*-BuMgBr + $ZnCl_2$ in THF/Et_2O	**9**	70
4[b]	EtMgBr + $ZnCl_2$ in Et_2O	**8**	98
5[b]	*n*-BuMgBr + $ZnCl_2$ in Et_2O	**10**	12

[a] 1,4-Dioxane added to precipitate magnesium chloride salts. [b] Pentane added to precipitate salts.

The efficiency of this catalyst made it possible to explore the use of lower catalyst loadings. When 0.25 mol % **7** was used, the reaction took 4 h to go to completion, and gave ring-opened product **8** in 93% ee. In fact, even with 0.05 mol % catalyst (1000:1 substrate/Pd), we were able to isolate **8** in 98% yield and 93% enantiomeric excess after 16 h.

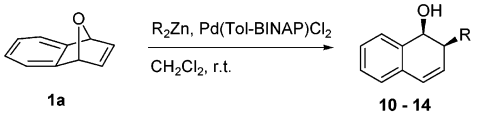
2. Nucleophiles. a. Addition of Other Dialkylzinc Reagents. Having developed successful protocols for the ring opening with Me_2Zn and Et_2Zn, we turned our efforts toward generalizing the ring opening for a variety of alkylzinc nucleophiles. Our initial attention was focused on the use of other, simple alkyl nucleophiles.

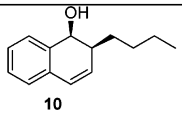
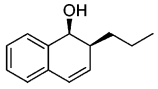
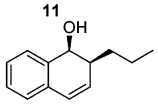
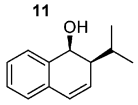
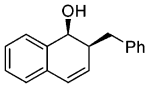
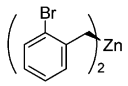
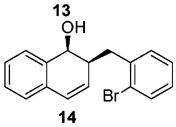
The addition of dibutylzinc proved to be more of a challenge then we had anticipated. Initial attempts to add dibutylzinc, formed from addition of *n*-BuLi to $ZnCl_2$ in THF, to **1a** gave no reaction. We discovered that the method used to generate the *n*-Bu_2Zn was important to the success of the reaction. When a solution of the *n*-Bu_2Zn formed in THF was added to **1a** along with Et_2Zn and catalyst, a slow reaction took place (Scheme 4). After 24 h, 25% conversion to **3** and **9** in a 2:1 ratio along with 75% recovered **1a** was observed. The reaction of Et_2Zn in the absence of *n*-Bu_2Zn was completed in 4 h, indicating that the *n*-Bu_2Zn solution was inhibiting the reaction.

Drawing on our knowledge of the reaction mechanism, we speculated that the presence of the LiCl salts or a coordinating solvent such as THF was likely inhibiting the reaction. The presence of these species might retard the formation of a cationic palladium catalyst, thereby inhibiting binding and reaction of the substrate alkene.

The effect of the salts was confirmed by the reaction of **1a** with Et_2Zn formed from EtMgCl and $ZnCl_2$ (Table 4). When **1a** and the palladium catalyst were transferred to this solution, the ring opening was inhibited, and only formation of naphthol resulted due to the presence of Lewis acidic magnesium salts.

Table 5. Addition of Various Dialkylzinc Reagents



	Dialkylzinc[a]	Product	Yield	ee
1	*n*-Bu_2Zn	 **10**	84%	95%
2	*n*-Pr_2Zn	 **11**	95%	95%
3	*i*-Pr_2Zn	 **11**	92%	**11** = 96%
		 **12**	**11**:**12** = 3:1	**12** = 62%
4	Bn_2Zn	 **13**	35%	82%
5		 **14**	25%	89%
6	$[TBSO(CH_2)_3]_2Zn$	no reaction	-	-

[a] Formed by addition of an alkyllithium or Grignard reagent to $ZnCl_2$ in ether at 0 °C, followed by addition of pentane to precipitate halide salts. The clear solution was then added to a solution of **1a** and the catalyst in dichloromethane at room temperature.

When the reaction was carried out following precipitation of the magnesium salts using 1,4-dioxane, as described by Seebach,[13] conversion to **8** was observed. The same reaction with *n*-Bu_2Zn gave ring-opened product; however, only hydride addition was observed to give **9** in 70% yield.

On the basis of the premise that the presence of coordinating solvents was responsible for the presence of hydride addition product over the butyl addition, a new protocol was developed in diethyl ether, which has less coordinating ability than THF and dioxane. Diethylzinc formed by addition of the Grignard reagent to $ZnCl_2$ in ether at 0 °C, followed by addition of pentane to precipitate the salts, gave a quantitative conversion of **1a** to **8**. When the same protocol was employed using *n*-BuMgBr to form the dibutylzinc, a small amount of butyl addition product, **10**, was isolated.

Better results were obtained when *n*-BuLi was used to form dibutylzinc. When this solution was employed in the enantioselective ring opening with 5 mol % Pd(Tol-BINAP)Cl_2 catalyst, an 84% yield of **10** was obtained in 95% ee (Table 5). Similarly, dipropylzinc addition was accomplished to give ring-opened product **11** in good yield and 95% enantiomeric excess.

Interestingly, the addition of a secondary alkyl group from *i*-Pr_2Zn did not give the expected ring-opened product from isopropyl addition. Instead, a 92% yield of an inseparable 3:1 mixture of **11** and **12** was obtained. Evidently, the isopropyl

(13) Bussche-Hunnefeld, J. L.; Seebach, D. *Tetrahedron* **1992**, *48*, 5719.

group is rearranging on the palladium by β-hydride elimination and readdition, resulting in *n*-propyl addition. The enantiomeric excess of **11** was similar to that obtained when *n*-Pr_2Zn was used (Table 5, entry 2); however, the ee of **12** was only 62%.

Using the same protocol, addition of dibenzylzinc was also accomplished; however, the reaction was less efficient, giving **13** in 35% yield and 82% enantiomeric excess after 2 days at room temperature. Similar results were obtained for addition of bis(2-bromobenzyl)zinc, which gave **14** in 25% yield and 89% ee after 2 days. Product **14** is interesting because the aryl bromide could potentially participate in further intramolecular ring forming reactions.

One of the attractive features of the organozinc reagents was their compatibility with various functional groups and the many methods available for the formation of functionalized dialkylzincs.[14] We attempted to employ the same protocol described above to the formation of a functionalized dialkylzinc. A lithium−halogen exchange was used to generate an alkyllithium species from $TBSO(CH_2)_3I$, which was then added to $ZnCl_2$; however, no reaction was observed with substrate **1a** (Table 5, entry 6).

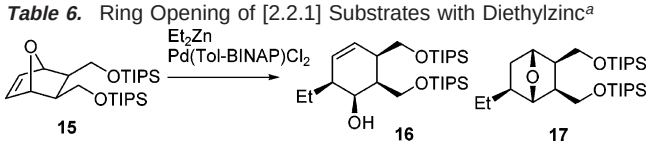
A variety of literature protocols were employed in synthesizing other functionalized organozinc reagents.[15] Unfortunately, none of these dialkylzinc reagents were successful in effecting the ring opening reaction of substrate **1a** with palladium catalyst. In most of the cases, **1a** along with quenched nucleophile was recovered after the reaction. The addition of the larger alkyl groups such as butyl and propyl is noticeably slower than that of Et_2Zn, so steric factors may be important in the lack of reactivity of oxygen-containing nucleophiles. More likely, complexation of the oxygen or some other, as of yet undetermined factor, is also playing a role.

b. Addition of Diethylzinc to Less Reactive Oxabicyclic Alkenes. We have previously described the addition of Me_2Zn to less reactive [2.2.1] and [3.2.1] oxabicyclic alkenes, giving cyclohexenols and cycloheptenols in good yields and enantioselectivities.[3b] Our initial attempts at addition of diethylzinc to these substrates, however, resulted in low yields of ring-opened product. Instead, side products were formed, which during the mechanistic studies we realized were arising from carbometalation of the alkene without ring opening. For example, reaction of [2.2.1] oxabicyclic substrate **15** led to a 1.5:1 mixture of **16** and **17** (Table 6).

Evidently, there is a competition between ring opening of intermediate **i**, to give **ii**, and transmetalation to give **iii**, which upon quenching with water gives **17**. We found that the ring opening is favored at higher temperatures (entry 2), although at too high temperature decomposition is observed (entry 4). The addition of $Zn(OTf)_2$ also led to increased yields of ring-opened product (entry 3) perhaps due to coordination to the bridging oxygen aiding ring opening, or to the formation of a more reactive cationic palladium catalyst, which undergoes ring opening at a faster rate.

We were able to use this knowledge to take advantage of, and improve upon, the ring-opening reactions with diethylzinc. It was discovered that premixing the palladium catalyst with

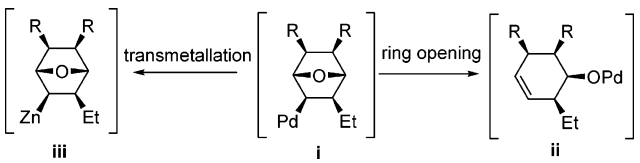
Table 6. Ring Opening of [2.2.1] Substrates with Diethylzinc[a]



15 16 17

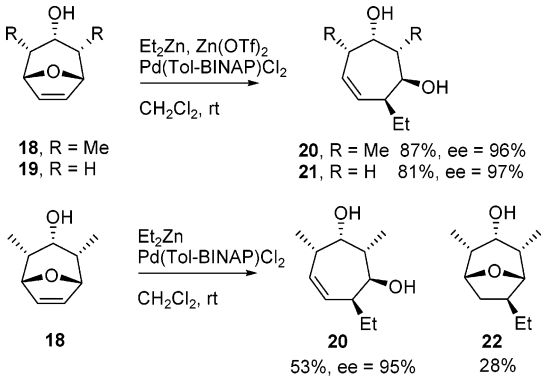
	conditions	16:17 ratio
1	CH_2Cl_2, rt	1.5:1
2	CH_2Cl_2, reflux	3:1
3	CH_2Cl_2, $Zn(OTf)_2$ (1 equiv), reflux	3.5:1
4	dichloroethane, $Zn(OTf)_2$ (1 equiv), reflux	decomposition

[a]



iii i ii

Scheme 5



$Zn(OTf)_2$ for 1 h produced a more reactive catalyst. Using this catalyst, the ring opening of [3.2.1] oxabicyclic alkenes **18** and **19** proceeded at room temperature to afford ethyl addition products **20** and **21** in high yield and enantioselectivity (Scheme 5). The same reaction with **18** carried out in the absence of $Zn(OTf)_2$ led to mixtures of **20** and **22** along with 16% recovered **18**.

Using the same reaction conditions for *O*-protected substrates **23** and **24** did not result in ring opening; however, carbometalated products **25** and **26** were obtained in good yield and 98% and 94% ee, respectively (Scheme 6). The benefit of this divergent reactivity is that the product obtained can be controlled by the substrate used. If ring opening is desired, the free alcohol is used; however, if the products from carbometalation are desired, the use of *O*-protected substrates is preferred.

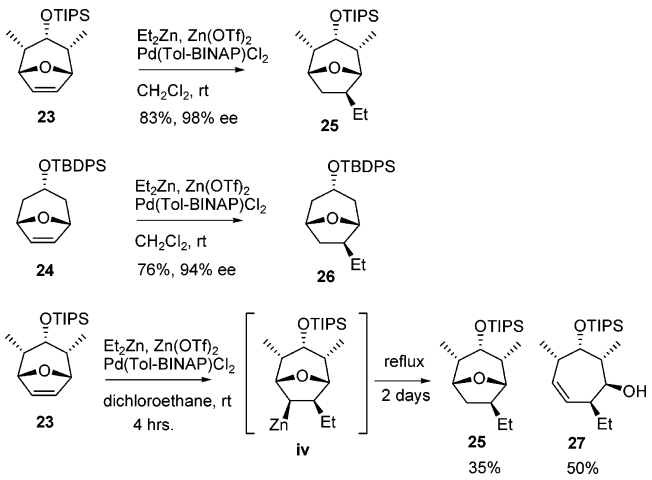
In an attempt to effect ring opening of **23**, the reaction was carried out at room temperature until no starting material remained. The reaction was then heated to reflux (80 °C); however, only slow conversion to **27** was observed. After 2 days at reflux only 50% **27** was isolated along with 35% **25**.

c. Trapping Carbozincated Intermediates. Since a carbozincated intermediate is formed en route to **25** and **26**, we decided to look at trapping reactions with various electrophiles to form more highly substituted products. The reactions were carried out by addition of Et_2Zn to a dichloromethane solution of **23**, $Zn(OTf)_2$, and $Pd(Tol\text{-}BINAP)Cl_2$ (premixed with the zinc triflate for 1 h). The reaction was stirred for 4 h, until no more **23** remained, and then the electrophile was added. In this

(14) (a) Knochel, P.; Jones, P. *Organozinc Reagents*; Oxford University Press Inc.: New York, 1999. (b) Knochel, P.; Almena Perea, J. J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275.

(15) For details on the synthesis and use of these reagents see the Supporting Information.

Scheme 6



way a variety of functionalized products were obtained in good yield and 98% ee (Table 7).[16]

The addition of iodine to intermediate **iv** resulted in slow formation of alkyl iodide **28** (entry 1). After 6 h a 58% yield of **28** was isolated along with 18% **25**. The slow reaction is likely due to the high steric hindrance around the zinc in intermediate **iv**. In an attempt to form a more reactive nucleophile, a transmetalation to copper was carried out as described by Knochel.[17] Addition of CuCN·2LiCl to **iv** at 0 °C gave an intermediate cuprate, which was trapped with allyl bromide to form **29** in 64% yield (entry 2). This protocol could potentially be used to add a wide range of electrophiles such as enones, alkynes, and acyl chlorides to give highly functionalized products in high enantiomeric excess.

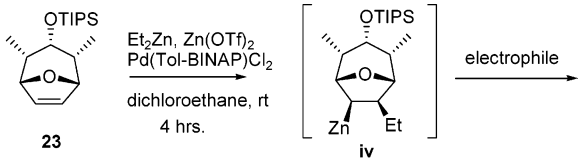
Unexpectedly, upon treatment of **iv** with benzoyl chloride, the ring-opened product **30** was obtained after 30 min in 80% yield (entry 3). Reaction of the electrophile with the bridging oxygen, instead of the zinc-bearing carbon, was occurring to give ring-opened product. The addition of trimethylsilyl chloride or trimethylsilyl triflate also resulted in ring-opened products (entries 4 and 5). When the reaction with TMSCl was carried out at −20 °C, a 65% yield of **31** was obtained. Interestingly, when TMSOTf was used under the same conditions, slow conversion to alcohol **27** was observed instead of silyl ether **31**.

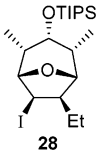
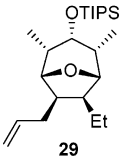
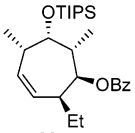
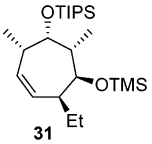
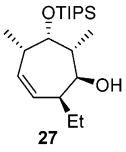
Thus, addition of Lewis acidic, hard electrophiles resulted in attack on the bridging oxygen with ring opening; however, when a soft electrophile such as iodine was used, reaction occurred on the carbon. The use of the Lewis acidic electrophiles to effect ring opening led to the idea that perhaps a more Lewis acidic metal such as magnesium could be added to give the ring-opened alcohol. The addition of solid $MgBr_2 \cdot OEt_2$ to intermediate **iv**, however, gave no ring-opened product after 2 h at room temperature. Even addition of boron trifluoride induced less than 10% conversion to the ring-opened product. On the other hand, the addition of EtMgBr to **iv** resulted in clean, rapid conversion to cycloheptenol **27** in 84% yield (entry 8).

(16) The enantiomeric excess of **30**, **31**, and **27** (entries 5 and 8) were all determined to be 98%. The enantiomeric excess of these products is determined in the carbopalladation step leading to intermediate **iv**.

(17) (a) Knochel, P. *Synlett* **1995**, 393. (b) Knochel, P.; Rozema, M. J.; Tucker, C. E. In *Organocopper Reagents*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994; p 85.

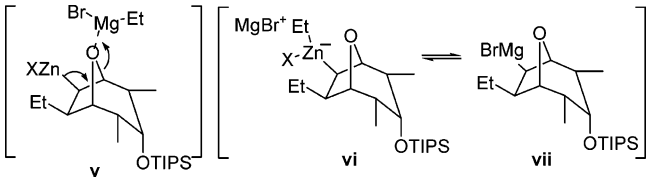
Table 7. Trapping of Carbopalladated Intermediate



	Electrophile	Product	Yield
1	iodine	 **28**	58%
2	(a) CuCN·2LiCl [a] (b) allyl bromide	 **29**	64%
3	PhCOCl	 **30**	80% [c]
4	TMSCl [b]	 **31**	65% [c]
5	TMSOTf [b]	 **27**	39% [c]
6	$MgBr_2 \cdot OEt_2$	no ring opened product	-
7	$BF_3 \cdot OEt_2$	**27**	<10%
8	EtMgBr	**27**	84% [c]

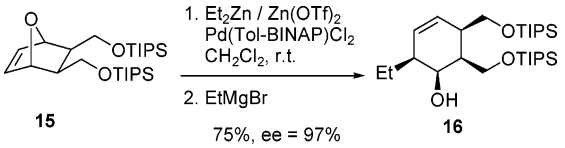
[a] Addition of CuCN at 0 °C. [b] Addition of electrophile at −20 °C. [c] The enantiomeric excess was determined to be 98% by chiral HPLC ananlysis.

Scheme 7

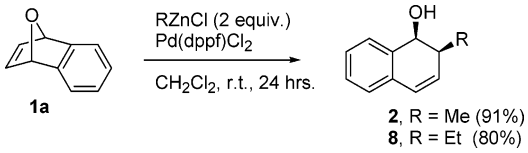


There are a number of conceivable mechanisms for the ring opening using EtMgBr. The magnesium could simply coordinate the bridging oxygen to aid ring opening through a species such as **v** (Scheme 7). However, the failure of magnesium bromide and boron trifluoride to induce ring opening seems to suggest a different mechanism involving a species such as zincate **vi** or alkylmagnesium species **vii**—obtained from transmetalation. In either case, this proves to be a good protocol for achieving the ring-opened products from *O*-protected substrates in good yield and high enantiomeric excess.

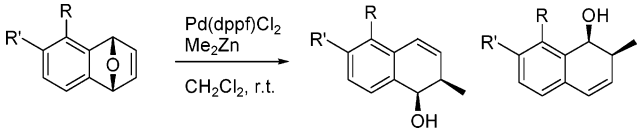
Scheme 8



Scheme 9



Scheme 10



Extension of this protocol to [2.2.1] oxabicyclic substrate **15**, which had given mixtures of ring-opened and alkene addition products, was successful in giving exclusively ring-opened product **16** in 75% yield and 97% enantiomeric excess (Scheme 8).

d. Addition of Alkylzinc Halides. We reacted alkylzinc halides in place of the dialkylzinc reagents, as they could potentially be employed using fewer equivalents of the alkyl group. Indeed, employing 2 equiv of MeZnCl or EtZnCl in the ring opening of **1a** in dichloromethane resulted in clean conversion to ring-opened products in 91% and 80% yields, respectively (Scheme 9). However, when the reactions of [3.2.1] oxabicyclic substrates were attempted, only low conversions to the ring-opened products were observed. In addition, when we attempted to use a simple Grignard reagent such as MeMgBr in the presence of a catalytic amount of $Zn(OTf)_2$ and Pd(dppf)-Cl_2, only slow addition to substrate **1a** was observed.

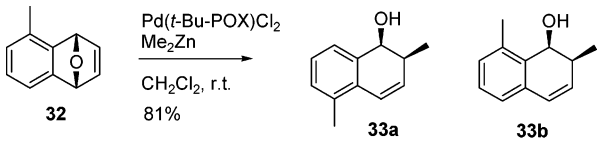
Thus, it appears as though the use of dialkylzinc reagents gives better results for the ring opening reaction, especially for less reactive substrates such as the [3.2.1] oxabicyclic alkenes. The alkylzinc halide reagents could be less reactive in these reactions due to the presence of the halide.

3. Substrates. a. Ring Opening of Unsymmetrical Oxabenzonorbornadienes. Previous studies carried out in our group revealed that remote substituents affect the regioselectivity of the rhodium-catalyzed addition of heteroatom nucleophiles to oxabenzonorbornadienes.[18] It was found that substituents on the benzene ring played a role in influencing the regioselectivity of the reaction. For example, the presence of an alkoxy group on the aromatic ring would stabilize a developing positive charge at one of the benzylic carbons, leading to preferential cleavage of the bridging carbon−oxygen bond at this position.

Thus, an investigation was carried out as to whether substituents on the aromatic ring of the oxabenzonorbornadienes would influence the regioselectivity of the palladium-catalyzed addition of dialkylzincs. Addition to unsymmetrical substrates as shown in Scheme 10 could potentially lead to two regioisomeric products. Reactions on a variety of unsymmetrical substrates were carried out using Pd(dppf)Cl_2 to catalyze the ring opening with Me_2Zn.

(18) Lautens, M.; Schmid, G. A.; Chau, A. *J. Org. Chem.* **2002**, *67*, 8043.

Scheme 11



33a : **33b** = 1 : 1 (95% ee for both isomers)

For R = OMe, R′ = H; R = Me, R′ = H; R = H, R′ = OMe; and R = H, R′ = CF_3 less than 1.2:1 selectivity was observed, while for R = H, R′ = $COCH_3$ a 1.5:1 ratio of regioisomers was obtained. This lack of selectivity is in contrast to that observed for the rhodium-catalyzed addition of heteroatom nucleophiles where very high selectivities were observed in several cases.

Careful examination of the mechanism we proposed for the palladium-catalyzed reaction reveals the origin of the lack of regioselectivity. Unlike the rhodium-catalyzed addition of heteroatom nucleophiles, which likely proceeds by selective ionization of one of the bridging carbon−oxygen bonds, the palladium-catalyzed reaction proceeds via a carbopalladation pathway. Carbopalladation of the alkene is unlikely to be very sensitive to remote electronic effects of the aromatic ring and the stability of a developing charge at the benzylic carbons.

In this sense the palladium-catalyzed reaction should be similar to the rhodium-catalyzed addition of arylboronic acids to oxabicyclic alkenes.[19] A similar mechanism has been proposed for this reaction, involving carborhodation of the substrate alkene by an arylrhodium species.

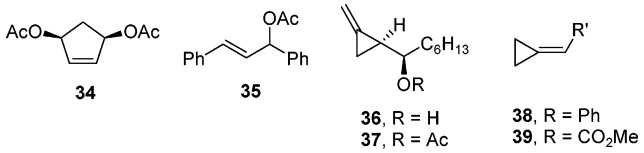
Interestingly though, the use of chiral palladium catalyst Pd[(*S*)-*t*-Bu-POX]Cl_2 with substrate **32**, while also resulting in a 1:1 mixture of regioisomers, gave each isomer in 95% enantiomeric excess (Scheme 11). Thus, it is the chiral catalyst and not the remote methyl group that dictates the sense of ring opening.

b. Reaction of Other Alkene and Alkyne Substrates. We examined the use of other alkene or alkyne substrates, in the hope of developing leads for new reactions involving palladium-catalyzed addition of dialkylzinc reagents. The initial substrate survey carried out during the mechanistic studies seemed to indicate that a strained olefin was necessary for the reaction;[11] however, precedents in the literature prompted us to investigate further.[20−23]

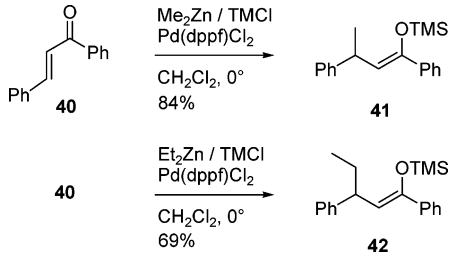
Allylic acetates were investigated with the goal of developing a reaction analogous to that described by Suzuki with vinyl epoxides.[20] Palladium-catalyzed addition of an alkyl group to the alkene, followed by β-acetate elimination, would maintain a Pd(II) oxidation state throughout the reaction, hopefully leading to reactivity complimentary to the Pd(0)-catalyzed reactions of allylic acetates. Unfortunately, substrates such as **34** and **35** (Scheme 12) failed to undergo the desired transformations.

(19) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311.
(20) Miyaura, N.; Tanabe, Y.; Suginome, H.; Suzuki, A. *J. Organomet. Chem.* **1982**, *233*, C13.
(21) (a) Lautens, M.; Meyer, C.; Lorenz, A. *J. Am. Chem. Soc.* **1996**, *118*, 10676. (b) Brase, S.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2545.
(22) (a) Petrier, C.; de Souza Barbosa, J. C.; Dupuy, C.; Luche, J. L. *J. Org. Chem.* **1985**, *50*, 5761. (b) Bolm, C.; Ewald, M.; Felder, M. *Chem. Ber.* **1992**, *125*, 1205. (c) Soai, K.; Okudo, M.; Okamoto, M. *Tetrahedron Lett.* **1991**, *32*, 95. (d) Spieler, J.; Huttenloch, O.; Waldman, H. *Eur. J. Org. Chem.* **2000**, *65*, 391. (e) Studemann, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 93.
(23) Lautens, M.; Yoshida, M. *Org. Lett.* **2002**, *4*, 123.

Scheme 12



Scheme 13



To examine the need for ring strain in the substrate, we explored the use of methylenecyclopropanes as suitable alkene partners. These substrates have been used in palladium-catalyzed hydrostannations and additions of alkenyl halides.[21] Unfortunately, no reaction was observed for any of the attempts to add dialkylzinc reagents to substrates **36**−**39** using palladium catalysis.

Inspired by work published on the use of nickel catalysts for addition of dialkylzinc reagents to alkynes and enones,[22] we investigated the use of palladium in reactions with these substrates. A wide range of substrates were subjected to various reaction conditions and palladium catalysts. The use of aryl alkynes, which proved good substrates for the nickel-catalyzed reaction,[22e] gave no reaction with palladium. Pyridyl alkynes, which have been used in rhodium-catalyzed additions of aryl boronic acids,[23] also gave no reaction, as did a variety of α,β-unsaturated esters and ketones.[24]

The addition of TMSCl to the reaction with chalcone **40** did result in conjugate addition products **41** and **42**, which were obtained in good yields as exclusively the *trans* isomers (Scheme 13). However, although the palladium catalyst was necessary for catalyzing the reaction, only racemic products were obtained with a variety of chiral ligands. Interestingly, Bolm reports that when TMSCl was used in the nickel-catalyzed addition of diethylzinc to chalcones, the silyl enol ethers were also obtained in racemic fashion.[22b]

Thus, at this time it appears that a strained olefin is necessary for the palladium-catalyzed addition of dialkylzinc reagents. Further investigations are under way using other strained alkene systems.

Conclusion

In conclusion, exploration of the scope of the palladium-catalyzed ring opening has led to new developments in terms of the catalyst, nucleophiles, and substrates. New chiral catalysts allowed the isolation of ring-opened products in higher enantiomeric excess using lower catalyst loadings. An understanding of the reaction mechanism was instrumental in extending the scope of alkyl nucleophiles in the ring opening, as well as the trapping of carbometalated products.

(24) For details see the Supporting Information.

Experimental Section

General Procedures. All flasks were flame-dried under a stream of nitrogen or argon and cooled before use. Solvents and solutions were transferred with syringes and cannulas using standard inert atmosphere techniques.

NMR spectra were recorded at 300 MHz using a Varian Gemini NMR spectrometer or at 400 MHz using a Varian XL400 spectrometer with $CDCl_3$ as reference standard (δ 7.26 ppm) or some other suitable solvent. IR spectra were obtained using a Nicolet DX FT-JR spectrometer as a neat film between KBr plates or a solution in $CDCl_3$. High-resolution mass spectra were obtained from a VG 70-250S (double focusing) mass spectrometer at 70 eV. Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. HPLC analysis was performed on a Waters 600E with a Chiracel OD, AD, or OJ column. Analytical TLC was performed using EM Separations precoated silica gel 0.2 mm layer UV 254 fluorescent sheets.

Diethyl ether, THF, and toluene were distilled from sodium benzophenone ketyl immediately prior to use. Dichloromethane and dichloroethane were distilled from calcium hydride. All other reagents were obtained from Aldrich or Strem and used as received unless otherwise stated. For characterization of products **3**−**5** see ref 3b.

(1*S*,2*S*)-2-Methyl-1,2-dihydronaphthalen-1-ol (2). Procedure A. To a solution of **1a** (30 mg, 0.21 mmol) in THF (4 mL) was added a solution of Me_4ZnLi_2 (0.31 mmol, formed by addition of MeLi to $ZnCl_2$·TMEDA in THF). The reaction was heated to reflux for 16 h and cooled to room temperature. Quenching with water was followed by extraction with ether. The combined organics were washed with brine, dried with $MgSO_4$, filtered, and evaporated to give crude product. The product was purified using flash chromatography on silica gel (15% EtOAc in hexanes) to give **2** (33 mg, 99%) as a white solid.

Procedure B. To a solution of **1a** (300 mg, 2.1 mmol) and Pd((*S*)-*t*-Bu-POX)Cl_2 (60 mg, 0.1 mmol) in CH_2Cl_2 (20 mL) was added Me_2-Zn (1.5 mL, 2.0 M in toluene). This was stirred at room temperature for 40 h. The flask was then opened to air, and several drops of water were added. This solution was stirred for 20 min, allowing for precipitation of zinc salts. $MgSO_4$ was added as a drying agent followed by filtration and concentration to give the crude product. The crude product was purified by flash chromatography on silica gel (15% EtOAc in hexanes) to give the product (291 mg, 88%) as a white solid. The ee was determined to be 97% using HPLC analysis on a CHIRACEL OD column, $\lambda = 254$ nm. Retention times in 1.25% *i*-PrOH in hexanes were 33.6 and 35.3 (major) min. Mp 64−65 °C; IR ($CHCl_3$) 3456, 3030, 2966, 1588, 1485, 1454, 1364, 1280, 831, 788, 760, 679 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, $J = 7.2$ Hz, 1H), 7.30−7.22 (m, 2H), 7.12 (d, $J = 7.2$ Hz, 1H), 6.52 (dd, $J = 9.5$, 2.3 Hz, 1H), 5.80 (dd, $J = 9.5$, 2.5 Hz, 1H), 4.57 (dd, $J = 7.8$, 4.8 Hz, 1H), 2.67−2.63 (m, 1H), 1.57 (d, $J = 7.8$ Hz, 1H), 1.25 (d, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 132.6, 132.4, 128.6, 127.7, 127.4, 126.7, 126.6, 71.8, 35.4, 14.2; HRMS *m*/*z* calcd for $C_{11}H_{12}O$ $(M)^+$ 160.0888, found 160.0888.

(1*S*,2*S*,3*R*,4*S*)-2-Bromo-3-methyl-1,2,3,4-tetrahydronaphthalene-1,4-diol (6). To a solution of **2** (100 mg, 0.62 mmol, obtained from ring opening with Me_2Zn catalyzed by Pd((*S*)-*t*-Bu-POX)Cl_2) in THF (4 mL) and H_2O (0.5 mL) was added *N*-bromosuccinimide (153 mg, 0.86 mmol). This was stirred for 1 h at room temperature, and then water and ethyl acetate were added. The aqueous layer was extracted with ethyl acetate two times. The combined organics were washed with brine, dried with $MgSO_4$, filtered, and evaporated to give crude product. The crude product was purified by flash chromatography on silica gel (40% EtOAc in hexanes) to give product **6** (87 mg, 55% after recrystallization). Mp 153−155 °C; IR (neat) 3601, 3156, 2984, 2901, 2256, 1795, 1641, 1469, 1382, 908 cm^{-1}; ^1H NMR (400 MHz, CD_3-CN) δ 7.55 (d, $J = 7.3$ Hz, 1H), 7.37−7.29 (m, 3H), 4.79 (dd, $J =$ 8.6, 6.8 Hz, 1H), 4.64 (dd, $J = 5.1$, 3.3 Hz, 1H), 4.32 (dd, $J = 11.8$, 8.9 Hz, 1H), 4.00 (d, $J = 6.6$ Hz, 1H), 3.32 (d, $J = 5.3$ Hz, 1H), 2.23

(m, 1H), 1.30 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 139.2, 130.4, 129.6, 129.1, 128.6, 118.7, 76.6, 72.8, 64.3, 42.1, 18.9; HRMS m/z calcd for $C_{11}H_{12}O_2Br$ $(M - H)^+$ 255.0021, found 255.0033.

(1*S*,2*S*)-2-Ethyl-1,2-dihydronaphthalen-1-ol (8). To a solution of **1a** (290 mg, 2.0 mmol) and $[Pd((S)\text{-Tol-BINAP})OH]_2(OTf)_2$ (1.9 mg, 0.001 mmol) in CH_2Cl_2 (10 mL) was added Et_2Zn (3.0 mL, 1.0 M in toluene). This was stirred at room temperature for 16 h. The flask was then opened to air, and several drops of water were added. This solution was stirred for 20 min, allowing for precipitation of zinc salts. $MgSO_4$ was added as a drying agent followed by filtration and concentration to give the crude product. The crude product was purified by flash chromatography on silica gel (15% EtOAc in hexanes) to give the product (343 mg, 98%) as an oil. The ee was determined to be 93% using HPLC analysis on a CHIRACEL OD column, λ = 254 nm. Retention times in 1.25% *i*-PrOH in hexanes were 14.5 and 16.3 (major) min. IR (neat) 3422, 3030, 2960, 1601, 1486, 1454, 1379, 1201, 813, 785, 768, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 6.9 Hz, 1H), 7.28−7.19 (m, 2H), 7.10 (d, J = 7.1 Hz, 1H), 6.52 (dd, J = 9.7, 2.5 Hz, 1H), 5.81 (dd, J = 9.6, 1.8 Hz, 1H), 4.62 (dd, J = 7.3, 4.5 Hz, 1H), 2.39−2.32 (m, 1H), 1.84 (dquin, J = 13.6, 7.5 Hz, 1H), 1.63 (dquin, J = 13.6, 7.5 Hz, 1H), 1.52 (d, J = 7.3 Hz, 1H), 1.11 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 132.7, 131.1, 128.5, 127.6, 127.5, 126.7, 126.5, 69.9, 42.2, 22.2, 11.8; HRMS m/z calcd for $C_{12}H_{14}O$ $(M)^+$ 174.1045, found 174.1044.

General Procedure for the Formation of Dialkylzinc Reagents. To a solution of $ZnCl_2$ (1 mmol, 1.0 M in ether) in ether[25] at 0 °C was added slowly a solution of alkyllithium or alkylmagnesium halide (2 mmol). This was stirred at 0 °C for 30 min, and then pentane added and stirring stopped to allow precipitated salts to settle. The clear solution was transferred via a gastight syringe to the reaction.

(1*S*,2*S*)-2-Butyl-1,2-dihydronaphthalen-1-ol (10). A solution of dibutylzinc (0.41 mmol, prepared from *n*-BuLi and $ZnCl_2$ as in the general procedure) was added to a solution of the substrate **1a** (40 mg, 0.27 mmol) and Pd((*R*)-Tol-BINAP)Cl_2 (11.8 mg, 0.014 mmol) in CH_2Cl_2 (4 mL) at room temperature. The resulting mixture was stirred for 4 h at room temperature. To the reaction were added several drops of water to quench the reaction. This was stirred vigorously for 10 min to allow the precipitation of zinc salts. $MgSO_4$ was added to dry the solution, and then it was filtered and evaporated to give crude product. The crude product was purified by flash chromatography on silica gel (20% Et_2O in hexanes) to give the product **10** (47 mg, 84%) as an oil. The ee was determined to be 95% by HPLC analysis on a CHIRACEL OD column, λ = 254 nm, flow rate 1 mL/min. Retention times in 1.2% *i*-PrOH in hexanes were 12.5 and 15.6 (major) min. IR (neat) 3417, 3029, 2928, 2857, 1453, 1378, 1049 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.10 (m, 4H), 6.52 (dd, J = 9.5, 2.6 Hz, 1H), 5.82 (dd, J = 9.5, 2.6 Hz, 1H), 4.58 (dd, J = 7.6, 4.7 Hz, 1H), 2.45 (m, 1H), 1.79 (m, 1H), 1.64−1.35 (m, 6H), 0.94 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 132.7, 131.3, 128.4, 127.5, 126.6, 126.4, 70.3, 40.4, 29.4, 28.7, 22.9, 14.1; HRMS m/z calcd for $C_{14}H_{18}O$ $(M)^+$ 202.1358, found 202.1360.

(1*S*,2*S*)-2-Propyl-1,2-dihydronaphthalen-1-ol (11). A solution of dipropylzinc (0.3 mmol, prepared from *n*-PrMgCl and $ZnCl_2$ as in the general procedure) was added to a solution of the substrate **1a** (30 mg, 0.2 mmol) and Pd((*R*)-Tol-BINAP)Cl_2 (9.7 mg, 0.01 mmol) in CH_2Cl_2 (4 mL) at room temperature. The resulting mixture was stirred for 12 h at room temperature. To the reaction were added several drops of water to quench the reaction. This was stirred vigorously for 10 min to allow the precipitation of zinc salts. $MgSO_4$ was added to dry the solution, and then it was filtered and evaporated to give crude product. The crude product was purified by flash chromatography on silica gel (20% Et_2O in hexanes) to give the product **11** (37 mg, 95%) as an oil. The ee was determined to be 95% by HPLC analysis on a CHIRACEL OD column, λ = 254 nm, flow rate 1 mL/min. Retention times in 5% *i*-PrOH in hexanes were 6.7 and 7.7 (major) min. IR (neat) 3413, 2955, 1453, 1378, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.10 (m, 4H), 6.53 (dd, J = 9.6, 2.7 Hz, 1H), 5.83 (dd, J = 9.6, 1.9 Hz, 1H), 4.59 (dd, J = 7.6, 4.7 Hz, 1H), 2.49 (m, 1H), 1.60−1.48 (m, 5H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 132.7, 131.3, 128.5, 127.6, 126.7, 126.5, 70.3, 40.2, 31.3, 20.3, 14.2; HRMS m/z calcd for $C_{13}H_{16}O$ $(M)^+$ 188.1201, found 188.1198.

(1*S*,2*S*)-2-Isopropyl-1,2-dihydronaphthalen-1-ol (12). A solution of diisopropylzinc (0.6 mmol, prepared from *i*-PrMgCl and $ZnCl_2$ as in the general procedure) was added to a solution of the substrate **1a** (45 mg, 0.3 mmol) and Pd((*R*)-Tol-BINAP)Cl_2 (14.0 mg, 0.015 mmol) in CH_2Cl_2 (5 mL) at room temperature. The resulting mixture was stirred for 18 h at room temperature. To the reaction were added several drops of water to quench the reaction. This was stirred vigorously for 10 min to allow the precipitation of zinc salts. $MgSO_4$ was added to dry the solution, and then it was filtered and evaporated to give crude product. The crude product was purified by flash chromatography on silica gel (15% EtOAc in hexanes) to give a mixture of products **11** and **12** (54 mg, 92%) in a 3:1 ratio. The ee of **11** was determined to be 96% by HPLC analysis on a CHIRACEL OD column, λ = 254 nm, flow rate 1 mL/min. Retention times in 5% *i*-PrOH in hexanes were 6.7 and 7.7 (major) min, while the ee of **12** determined in the same run was 62%. Retention times were 6.6 and 7.2 (major) min. ^{1}H NMR of **12** (400 MHz, $CDCl_3$) δ 7.33−7.10 (m, 4H), 6.58 (dd, J = 9.7, 2.8 Hz, 1H), 5.95 (d, J = 9.6 Hz, 1H), 4.67 (dd, J = 7.4, 3.7 Hz, 1H), 2.06 (m, 2H), 1.15 (d, J = 6.4 Hz, 3H), 1.07 (d, J = 6.4 Hz, 3H).

(1*S*,2*S*)-2-Benzyl-1,2-dihydronaphthalen-1-ol (13). A solution of dibenzylzinc (0.45 mmol, prepared from BnMgBr and $ZnCl_2$ as in the general procedure) was added to a solution of the substrate **1a** (45 mg, 0.3 mmol) and Pd((*R*)-Tol-BINAP)Cl_2 (14.5 mg, 0.015 mmol) in CH_2Cl_2 (4 mL) at room temperature. The resulting mixture was stirred for 48 h at room temperature. To the reaction were added several drops of water to quench the reaction. This was stirred vigorously for 10 min to allow the precipitation of zinc salts. $MgSO_4$ was added to dry the solution, and then it was filtered and evaporated to give crude product. The crude product was purified by flash chromatography on silica gel (15% EtOAc in hexanes) to give the product **13** (26 mg, 35%) as an oil. The ee was determined to be 82% by HPLC analysis on a CHIRACEL OD column, λ = 254 nm, flow rate 1 mL/min. Retention times in 5% *i*-PrOH in hexanes were 12.8 (major) and 15.2 min. IR (neat) 3347, 3028, 2917, 1699, 1601, 1495, 1205 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.12 (m, 9H), 6.55 (dd, J = 9.7, 2.6 Hz, 1H), 5.79 (d, J = 9.7 Hz, 1H), 4.46 (dd, J = 7.3, 4.2 Hz, 1H), 3.14 (dd, J = 13.1, 8.3 Hz, 1H) 2.87 (dd, J = 13.2, 8.1 Hz, 1H), 2.80 (m, 1H), 1.58 (d, J = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 130.3, 129.3, 129.0, 128.7, 128.6, 128.4, 127.7, 127.1, 126.6, 126.1, 69.7, 42.5, 35.4; HRMS m/z calcd for $C_{17}H_{16}O$ $(M)^+$ 234.1045, found 234.1058.

(1*S*,2*S*)-2-(2-Bromobenzyl)-1,2-dihydronaphthalen-1-ol (14). A solution of bis(2-bromobenzyl)zinc (0.45 mmol, prepared from 2-BrBnMgBr and $ZnCl_2$ as in the general procedure) was added to a solution of the substrate **1a** (45 mg, 0.3 mmol) and Pd((*R*)-Tol-BINAP)Cl_2 (14.5 mg, 0.015 mmol) in CH_2Cl_2 (5 mL) at room temperature. The resulting mixture was stirred for 48 h at room temperature. To the reaction were added several drops of water to quench the reaction. This was stirred vigorously for 10 min to allow the precipitation of zinc salts. $MgSO_4$ was added to dry the solution, and then it was filtered and evaporated to give crude product. The crude product was purified by flash chromatography on silica gel (15% EtOAc in hexanes) to give the product **14** (24 mg, 25%) as an oil. The ee was determined to be 89% by HPLC analysis on a CHIRACEL OD column, λ = 254 nm, flow rate 1 mL/min. Retention times in 5% *i*-PrOH in hexanes were 11.9 (major) and 13.3 min. IR (neat) 3401, 3051, 2914, 1469, 1443, 1023, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59−7.10 (m, 8H), 6.57 (dd, J = 9.6, 2.7 Hz, 1H), 5.80 (d, J = 9.7 Hz, 1H), 4.46 (dd, J = 7.3,

(25) A suitable amount of solvent was used to give a final concentration of R_2Zn of 0.25 M.

4.2 Hz, 1H), 3.26 (dd, J = 13.1, 7.9 Hz, 1H) 3.03 (dd, J = 13.0, 7.7 Hz, 1H), 2.96 (m, 1H), 1.64 (d, J = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 136.4, 133.0, 132.6, 132.5, 131.9, 129.9, 128.7, 128.0, 127.7, 127.3, 127.2, 126.6, 124.9, 69.7, 40.4, 35.7; HRMS *m*/*z* calcd for $C_{17}H_{15}OBr$ $(M)^+$ 314.0306, found 314.0304.

(1*S*,2*S*,5*R*,6*S*)-2-Ethyl-5,6-bis(triisopropylsilanyloxymethyl)cyclohex-3-enol (16). A solution of substrate **15** (60 mg, 0.13 mmol), Pd((*R*)-Tol-BINAP)Cl_2 (6.0 mg, 0.006 mmol), and Zn$(OTf)_2$ (4.6 mg, 0.013 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 1 h. To this solution was then added Et_2Zn (190 μL, 1.0 M in toluene, 0.19 mmol). The resulting mixture was stirred for 4 h at room temperature, then EtMgBr (130 mL, 3.0M in ether, 0.4 mmol) was added, and the mixture was stirred for an additional 15 min at room temperature. The reaction was quenched by addition of several drops of water. This was stirred vigorously for 10 min to allow the precipitation of salts. $MgSO_4$ was added to dry the solution, and then it was filtered and evaporated to give crude product. The crude product was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to give the product **16** (48 mg, 75%) as an oil. The ee was determined to be 97% by conversion to the benzoate ester and HPLC analysis on a CHIRACEL OD column, λ = 254 nm, flow rate 1 mL/min. Retention times in 0.5% *i*-PrOH in hexanes were 8.8 (major) and 10.2 min. IR (neat) 3404, 2932, 2857, 1459, 1059 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60−5.52 (m, 2H), 4.20 (d, J = 10.8 Hz, 1H), 4.04−3.92 (m, 2H), 3.76−3.70 (m, 2H), 2.58 (m, 1H), 2.24 (m, 1H), 1.95 (m, 1H), 1.64 (m, 1H), 1.38 (m, 1H), 1.01−1.18 (m, 42H), 0.99 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.2, 127.6, 65.0, 64.1, 61.9, 44.7, 43.7, 38.0, 24.4, 18.0, 17.9, 17.8, 12.0, 11.9; HRMS *m*/*z* calcd for $C_{25}H_{51}O_3Si_2$ $(M - C_3H_7)^+$ 455.3377, found 455.3378.

(1*S*,2*S*,3*S*,4*S*,7*S*)-4-Ethyl-2,7-dimethylcyclohept-5-ene-1,3-diol (20). A solution of substrate **18** (50 mg, 0.32 mmol), Pd((*R*)-Tol-BINAP)Cl_2 (13.9 mg, 0.016 mmol), and Zn$(OTf)_2$ (11.8 mg, 0.032 mmol) in CH_2Cl_2 (6 mL) was stirred at room temperature for 1 h. To this solution was added Et_2Zn (810 μL, 1.0 M in toluene, 0.81 mmol). The resulting mixture was stirred for 4 h at room temperature. The reaction was quenched by addition of several drops of water. This was stirred vigorously for 10 min to allow the precipitation of zinc salts. $MgSO_4$ was added to dry the solution, and then it was filtered and evaporated to give crude product. The crude product was purified by flash chromatography on silica gel (40% EtOAc in hexanes) to give the product **20** (52 mg, 87%) as a white solid. The ee was determined to be 97% by conversion to the bisbenzoate ester and HPLC analysis on a CHIRACEL OD column, λ = 254 nm, flow rate 1 mL/min. Retention times in 1% *i*-PrOH in hexanes were 5.6 and 6.4 (major) min. Mp 56−59 °C; IR (neat) 3425, 2961, 1457, 958 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (m, 1H), 5.32 (dd, J = 11.5, 3.1 Hz, 1H), 3.63 (td, J = 6.4, 2.4 Hz, 1H), 3.57 (m, 2H), 2.76 (m, 1H), 2.48 (m, 1H), 2.00 (quin d, J = 6.9, 3.1 Hz, 1H), 1.66 (d, J = 6.4 Hz, 1H), 1.66−1.50 (m, 2H), 1.45 (d, J = 8.4 Hz, 1H), 1.18 (d, J = 7.3 Hz, 3H), 1.13 (d, J = 7.2 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.2, 131.9, 78.4, 74.1, 44.9, 43.9, 38.2, 23.0, 20.7, 17.1, 12.8; HRMS *m*/*z* calcd for $C_{11}H_{20}O_2$ $(M)^+$ 184.1463, found 184.1460.

(1*S*,3*S*,4*S*)-4-Ethylcyclohept-5-ene-1,3-diol (21). A solution of substrate **19** (40 mg, 0.32 mmol), Pd((*R*)-Tol-BINAP)Cl_2 (13.9 mg, 0.016 mmol), and Zn$(OTf)_2$ (11.8 mg, 0.032 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 1 h. To this solution was added Et_2Zn (810 μL, 1.0 M in toluene, 0.81 mmol). The resulting mixture was stirred for 6 h at room temperature. The reaction was quenched by addition of several drops of water. This was stirred vigorously for 10 min to allow the precipitation of zinc salts. $MgSO_4$ was added to dry the solution, and then it was filtered and evaporated to give crude product. The crude product was purified by flash chromatography on silica gel (EtOAc) to give the product **21** (40 mg, 81%) as an oil. The ee was determined to be 97% by conversion to the bisbenzoate ester and HPLC analysis on a CHIRACEL OD column, λ = 254 nm, flow rate 1 mL/min. Retention times in 1% *i*-PrOH in hexanes were 4.7 (major) and 5.0 min. IR (neat) 3379, 2929, 1452, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (m, 1H), 5.43 (m, 1H), 3.91 (m, 1H), 3.83 (m, 1H), 2.44−2.29 (m, 4H), 1.74 (ddd, J = 13.6, 11.2, 2.4 Hz, 1H), 1.63−1.47 (m, 4H), 0.95 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4, 128.5, 70.6, 64.2, 48.0, 45.4, 37.8, 26.6, 12.2; HRMS *m*/*z* calcd for $C_9H_{16}O_2$ $(M)^+$ 156.1150, found 156.1150.

(1*R*,2*S*,3*S*,4*R*,5*S*,6*S*)-6-Ethyl-2,4-dimethyl-3-(triisopropylsilyl)oxy-8-oxabicyclo[3.2.1]octane (25). A solution of substrate **23** (60 mg, 0.2 mmol), Pd((*R*)-Tol-BINAP)Cl_2 (8.6 mg, 0.01 mmol), and Zn$(OTf)_2$ (7.2 mg, 0.02 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 1 h. To this solution was added Et_2Zn (300 μL, 1.0M in toluene, 0.3 mmol). The resulting mixture was stirred for 16 h at room temperature. The reaction was quenched by addition of several drops of water. This was stirred vigorously for 10 min to allow the precipitation of zinc salts. $MgSO_4$ was added to dry the solution, and then it was filtered and evaporated to give crude product. The crude product was purified by flash chromatography on silica gel (15% Et_2O in hexanes) to give the product **25** (55 mg, 83%) as an oil. $[\alpha]_D = -5.4°$ (c = 1.2, $CHCl_3$); IR (neat) 2955, 1461, 1374, 1077, 1025 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (t, J = 3.9 Hz, 1H), 3.96 (dd, J = 7.4, 3.2 Hz, 1H), 3.58 (d, J = 3.1 Hz, 1H), 2.49−2.37 (m, 2H), 1.98 (m, 2H), 1.35−1.24 (m, 3H), 1.13 (m, 21H), 0.95 (d, J = 7.3 Hz, 3H), 0.93 (d, J = 7.3 Hz, 3H), 0.86 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.6, 79.3, 74.2, 40.1, 40.0, 39.6, 32.7, 29.9, 18.6, 13.9, 13.8, 12.8; HRMS *m*/*z* calcd for $C_{17}H_{33}O_2Si$ $(M - C_3H_7)^+$ 297.2250, found 297.2256.

(1*R*,3*S*,5*S*,6*S*)-6-Ethyl-3-(*tert*-butyldiphenylsilyl)oxy-8-oxabicyclo-[3.2.1]octane (26). A solution of substrate **24** (15 mg, 0.08 mmol), Pd((*R*)-Tol-BINAP)Cl_2 (3.9 mg, 0.004 mmol), and Zn$(OTf)_2$ (3.0 mg, 0.008 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 1 h. To this solution was added Et_2Zn (125 μL, 1.0 M in toluene, 0.125 mmol). The resulting mixture was stirred for 6 h at room temperature. The reaction was quenched by addition of several drops of water. This was stirred vigorously for 10 min to allow the precipitation of zinc salts. $MgSO_4$ was added to dry the solution, and then it was filtered and evaporated to give crude product. The crude product was purified by flash chromatography on silica gel (15% Et_2O in hexanes) to give the product **26** (13 mg, 76%) as an oil. The ee was determined to be 94% by HPLC analysis on a CHIRACEL OD column, λ = 254 nm, flow rate 1 mL/min. Retention times in 1% *i*-PrOH in hexanes were 4.7 and 5.0 (major) min. IR (neat) 2937, 1592, 1069, 1009 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (m, 4H), 7.38 (m, 6H), 4.31 (dd, J = 7.2, 4.1 Hz, 1H), 4.10 (t, J = 4.3 Hz, 1H), 3.91 (d, J = 3.7 Hz, 1H), 2.74−2.70 (m, 1H), 2.62 (dd, J = 11.6, 8.7 Hz, 1H) 1.86 (m, 2H), 1.66−1.28 (m, 5H), 1.09 (s, 9H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 134.1, 129.6, 127.6, 79.0, 74.5, 65.8, 43.8, 38.8, 38.6, 36.4, 29.9, 27.0, 19.1, 12.6; HRMS *m*/*z* calcd for $C_{21}H_{25}O_2Si$ $(M - C_4H_9)^+$ 337.1624, found 337.1631.

(1*S*,2*R*,3*S*,4*S*,7*S*)-4-Ethyl-1-(triisopropylsilyl)oxy-2,7-dimethylcyclohept-5-en-3-ol (27). A solution of substrate **23** (60 mg, 0.2 mmol), Pd((*R*)-Tol-BINAP)Cl_2 (8.6 mg, 0.01 mmol), and Zn$(OTf)_2$ (7.2 mg, 0.02 mmol) in dichloroethane or CH_2Cl_2 (4 mL) was stirred at room temperature for 1 h. To this solution was added Et_2Zn (300 μL, 1.0 M in toluene, 0.3 mmol). The resulting mixture was stirred for 4 h at room temperature. Addition of EtMgBr (200 μL, 3.0 M, 0.6 mmol) to the reaction at room temperature was followed by stirring for 30 min. The reaction was quenched by addition of several drops of water. This was stirred vigorously for 10 min to allow the precipitation of salts. $MgSO_4$ was added to dry the solution, and then it was filtered and evaporated to give crude product. The crude product was purified by flash chromatography on silica gel (15% Et_2O in hexanes) to give the product **27** (57 mg, 84%) as an oil. The ee was determined to be 98% by conversion to the benzoate ester and HPLC analysis on a CHIRACEL OD column, λ = 254 nm, flow rate 0.5 mL/min. Retention times in 0.2% *i*-PrOH in hexanes were 11.8 and 12.2 (major) min. IR (neat) 3381, 2958, 2868, 1462, 1381, 1089, 1012 cm^{-1}; ^{1}H NMR (400

MHz, $CDCl_3$) δ 5.72 (ddd, J = 11.5, 7.5, 2.0 Hz, 1H), 5.36 (dd, J = 11.5, 5.0 Hz, 1H), 4.18 (dd, J = 4.9, 3.8 Hz, 1H), 3.68 (t, J = 6.9 Hz, 1H), 2.52 (m, 2H), 2.27 (m, 1H), 1.63 (m, 2H), 1.47 (m, 1H), 1.15 (d, J = 7.1 Hz, 3H), 1.13 (d, J = 7.1 Hz, 3H), 1.08 (m, 21H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3, 130.7, 76.1, 71.1, 46.0, 42.8, 42.3, 25.7, 18.2, 15.7, 14.3, 12.7, 12.5; HRMS *m*/*z* calcd for $C_{17}H_{33}O_2Si$ (M − C_3H_7)$^+$ 297.2250, found 297.2242.

(1*S*,2*R*,3*R*,4*R*,5*R*,6*R*,7*R*)-6-Ethyl-7-iodo-2,4-dimethyl-3-(triisopropylsilyl)oxy-8-oxabicyclo[3.2.1]octane (28). A solution of substrate **23** (60 mg, 0.2 mmol), Pd((*R*)-Tol-BINAP)Cl_2 (8.6 mg, 0.01 mmol), and Zn$(OTf)_2$ (7.2 mg, 0.02 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 1 h. To this solution was added Et_2Zn (300 μL, 1.0 M in toluene, 0.3 mmol). The resulting mixture was stirred for 4 h at room temperature. To the reaction was added iodine (126 mg, 0.5 mmol). This was stirred for 6 h at room temperature. The reaction was then quenched with water. The aqueous layer was extracted with ether two times. The combined organics were washed with $Na_2S_2O_3$ solution, dried with $MgSO_4$, filtered, and evaporated to give crude product. The crude product was purified by flash chromatography on silica gel (15% Et_2O in hexanes) to give the product **28** (52 mg, 58%) as a white solid. Mp 91−94 °C; $[\alpha]_D$ = −15.3° (c = 1.3, $CHCl_3$); IR (neat) 2880, 1460, 1379, 1255, 1020 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (d, J = 7.9 Hz, 1H), 4.46 (d, J = 3.5 Hz, 1H), 4.04 (t, J = 3.8 Hz, 1H), 3.66 (d, J = 2.8 Hz, 1H), 2.39 (m, 1H), 2.01 (m, 2H), 1.52 (m, 1H), 1.35 (m, 1H), 1.19−1.10 (m, 21H), 1.07 (d, J = 7.3 Hz, 3H), 0.96 (d, J = 7.3 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 91.7, 82.8, 73.9, 42.9, 41.5, 39.5, 35.6, 35.5, 18.6, 18.5, 14.2, 13.8, 13.7, 13.4; HRMS *m*/*z* calcd for $C_{17}H_{32}O_2SiI$ (M − C_3H_7)$^+$ 423.1216, found 423.1214.

(1*R*,2*S*,3*R*,4*R*,5*S*,6*S*,7*R*)-7-Allyl-6-ethyl-2,4-dimethyl-3-(triisopropylsilyl)oxy-8-oxabicyclo[3.2.1]octane (29). A solution of substrate **23** (60 mg, 0.2 mmol), Pd((*R*)-Tol-BINAP)Cl_2 (8.6 mg, 0.01 mmol), and Zn$(OTf)_2$ (7.2 mg, 0.02 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 1 h. To this solution was added Et_2Zn (300 μL, 1.0 M in toluene, 0.3 mmol). The resulting mixture was stirred for 4 h at room temperature. The reaction was cooled to −10 °C and a solution of CuCN·2LiCl in THF added [made from addition of CuCN (54 mg, 0.6 mmol) to a THF (1 mL) solution of LiCl (50 mg, 1.2 mmol), which had been dried in vacuo for 2 h at 150 °C]. This was stirred for 10 min at −10 °C and then allyl bromide (85 μL, 1 mmol) added. This was stirred at 0 °C for 2 h. The reaction was then quenched with saturated NH_4Cl solution. The aqueous layer was extracted with ether two times. The combined organics were washed with $Na_2S_2O_3$ solution, dried with $MgSO_4$, filtered, and evaporated to give crude product. The crude product was purified by flash chromatography on silica gel (15% Et_2O in hexanes) to give the product **29** (49 mg, 64%) as an oil. $[\alpha]_D$ = −34.4° (c = 2.4, $CHCl_3$); IR (neat) 2949, 1639, 1458, 1377, 1255, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (m, 1H), 4.98 (m, 2H), 4.05 (t, J = 3.9 Hz, 1H), 3.64 (t, J = 4.1 Hz, 1H), 2.68 (m, 1H), 2.53 (m, 1H), 2.23 (m, 1H), 2.01 (m, 2H), 1.89 (m, 1H), 1.59 (m, 1H), 1.19−1.10 (m, 22H), 0.95 (d, J = 7.3 Hz, 3H), 0.90 (d, J = 7.5 Hz, 3H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 115.4, 84.1, 83.6, 74.2, 42.5, 40.1, 40.0, 39.9, 34.4, 22.5, 18.6, 14.0, 13.8, 13.7, 13.6; HRMS *m*/*z* calcd for $C_{20}H_{37}O_2Si$ (M − C_3H_7)$^+$ 337.2563, found 337.2568.

(1*S*,2*R*,3*S*,4*S*,7*S*)-4-Ethyl-1-(triisopropylsilyl)oxy-2,7-dimethylcyclohept-5-en-3-yl Benzoate (30). A solution of substrate **23** (60 mg, 0.2 mmol), Pd((*R*)-Tol-BINAP)Cl_2 (8.6 mg, 0.01 mmol), and Zn$(OTf)_2$ (7.2 mg, 0.02 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 1 h. To this solution was added Et_2Zn (300 μL, 1.0 M in toluene, 0.3 mmol). The resulting mixture was stirred for 4 h at room temperature. To the reaction was then added PhCOCl (116 μL, 1 mmol), and stirring was continued 30 min at room temperature. The reaction was quenched by addition of DMAP (122 mg, 1 mmol) and then water. The aqueous layer was extracted with ether two times, and the combined organics were dried with $MgSO_4$, filtered, and evaporated to give crude product. The crude product was purified by flash chromatography on silica gel (5% Et_2O in hexanes) to give the product **30** (57 mg, 84%) as an oil. The ee was determined to be 98% by HPLC analysis on a CHIRACEL OD column, λ = 254 nm, flow rate 0.5 mL/min. Retention times in 0.2% *i*-PrOH in hexanes were 11.8 and 12.2 (major) min. IR (neat) 2942, 2868, 1718, 1459, 1272, 1095, 1066 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.0 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.43 (d, J = 7.6 Hz, 2H), 5.67 (ddd, J = 11.7, 7.1, 1.5 Hz, 1H), 5.51 (dd, J = 11.7, 5.5 Hz, 1H), 5.28 (dd, J = 7.5, 2.2 Hz, 1H), 4.25 (dd, J = 4.8, 3.3 Hz, 1H), 2.59 (m, 2H), 2.50 (m, 1H), 1.64 (m, 1H), 1.48 (m, 1H), 1.20 (d, J = 7.1 Hz, 3H), 1.18 (d, J = 7.0 Hz, 3H), 1.04 (m, 21H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.2, 132.7, 130.8, 130.3, 129.6, 128.3, 78.1, 72.2, 42.7, 42.2, 41.9, 25.1, 18.2, 16.5, 14.3, 12.8, 12.6; HRMS *m*/*z* calcd for $C_{24}H_{37}O_3Si$ (M − C_3H_7)$^+$ 401.2512, found 401.2508.

(1*S*,2*S*,3*S*,4*S*,7*S*)-4-Ethyl-1-(triisopropylsilyl)oxy-2,7-dimethyl-3-(trimethylsilyl)oxycyclohept-5-ene (31). A solution of substrate **23** (60 mg, 0.2 mmol), Pd((*R*)-Tol-BINAP)Cl_2 (8.6 mg, 0.01 mmol), and Zn$(OTf)_2$ (7.2 mg, 0.02 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 1 h. To this solution was added Et_2Zn (300 μL, 1.0 M in toluene, 0.3 mmol). The resulting mixture was stirred for 4 h at room temperature. To the reaction was then added (TMS)Cl (64 μL, 1 mmol) at −20 °C, and stirring was continued for 30 min. The reaction was quenched by addition of water. The aqueous layer was extracted with ether two times, and the combined organics were dried with $MgSO_4$, filtered, and evaporated to give crude product. The crude product was purified by flash chromatography on silica gel (2.5% Et_2O in hexanes) to give the product **31** (52 mg, 65%) as an oil. $[\alpha]_D$ = +110.1° (c = 0.8, $CHCl_3$); IR (neat) 2944, 1463, 1380, 1253, 1061 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (dd, J = 11.6, 6.7 Hz, 1H), 5.48 (dd, J = 11.6, 6.6 Hz, 1H), 4.19 (dd, J = 5.3, 3.1 Hz, 1H), 3.75 (dd, J = 7.8, 2.5 Hz, 1H), 2.48 (m, 1H), 2.23 (m, 1H), 2.15 (m, 1H), 1.71 (m, 1H), 1.37 (m, 1H), 1.12 (d, J = 7.9 Hz, 3H), 1.10 (d, J = 7.5 Hz, 3H), 1.07 (m, 21H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.1, 130.9, 76.3, 72.2, 46.0, 45.2, 42.5, 24.1, 18.3, 18.2, 16.6, 14.9, 13.1, 12.8, 0.4; HRMS *m*/*z* calcd for $C_{22}H_{45}O_2Si_2$ (M − CH_3)$^+$ 397.2958, found 397.2962.

2,5-Dimethyl-1,2-dihydronaphthalen-1-ol (33a) and 2,8-Dimethyl-1,2-dihydronaphthalen-1-ol (33b).[26] To a solution of **32** (50 mg, 0.31 mmol) and Pd((*S*)-*t*-Bu-POX)Cl_2 (8.9 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) was added Me_2Zn (0.31 mL, 2.0 M in toluene). This was stirred at room temperature for 16 h. The flask was then opened to air, and several drops of water were added. This solution was stirred for 20 min, allowing for precipitation of zinc salts. $MgSO_4$ was added as a drying agent followed by filtration and concentration to give the crude product. The crude product was purified by flash chromatography on silica gel (15% EtOAc in hexanes) to give the products **33a** and **33b** (45 mg, 81%) in a 1:1 ratio. The ee of both isomers was determined to be 95% using HPLC analysis on a CHIRACEL AD column, λ = 254 nm, flow rate 0.6 mL/min. Retention times in 2% *i*-PrOH in hexanes were 19.3, 25.7 (major), 26.8, and 27.7 (major) min. IR ($CHCl_3$) 3388, 3022, 2960, 1580, 1471, 1351 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−6.95 (m, 3H), 6.70 (dd, J = 9.9, 2.6 Hz, 1H), 6.50 (dd, J = 9.5, 3.1 Hz, 1H), 5.82 (dd, J = 9.8, 2.9 Hz, 1H), 5.67 (d, J = 9.5 Hz, 1H), 4.64 (dd, J = 8.6, 4.4 Hz, 1H), 4.49 (dd, J = 7.5, 4.8 Hz, 1H), 2.67−2.53 (m, 2H), 2.43 (s, 3H), 2.34 (s, 3H), 1.64 (d, J = 7.5 Hz, 1H), 1.40 (d, J = 7.5 Hz, 1H), 1.37 (d, J = 7.5 Hz, 3H), 1.23 (d, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 135.9, 134.5, 133.6, 132.4, 132.1, 131.6, 130.3, 130.2, 129.8, 128.2, 127.2, 127.1, 125.1, 124.7, 123.3, 72.1, 67.1, 35.4, 34.8, 18.9, 18.3, 15.3, 14.1; HRMS *m*/*z* calcd for $C_{12}H_{14}O$ (M)$^+$ 174.1044, found 174.1049.

1,3-Diphenylbut-1-enol Trimethylsilyl Ether (41). Dimethylzinc (215 μL, 2.0 M in toluene, 0.43 mmol) was added to a solution of substrate **40** (60 mg, 0.29 mmol) and Pd(dppf)Cl_2 (11.7 mg, 0.014

(26) Spectral data reported for the mixture.

mmol) in CH_2Cl_2 (4 mL) at 0 °C. To this was added (TMS)Cl (55 μL, 0.43 mmol), and the reaction was stirred at 0 °C for 1.5 h. To the reaction were added several drops of water to quench the reaction. This was stirred vigorously for 10 min to allow the precipitation of zinc salts. $MgSO_4$ was added to dry the solution, and then it was filtered and evaporated to give crude product. The crude product was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to give the product **41** (71 mg, 84%) as an oil. IR (neat) 3445, 2962, 1645, 1254, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49−7.14 (m, 10H), 5.38 (d, $J = 9.7$ Hz, 1H), 3.99 (m, 1H), 1.39 (d, $J = 7.0$ Hz, 3H), 0.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 146.9, 139.2, 128.3, 128.0, 127.6, 126.9, 125.8, 125.7, 116.3, 36.0, 22.6, 0.6; HRMS *m*/*z* calcd for $C_{19}H_{24}OSi$ $(M)^+$ 296.1596, found 296.1604.

1,3-Diphenylpent-1-enol Trimethylsilyl Ether (42). Diethylzinc (45 μL, 0.43 mmol) was added to a solution of substrate **40** (60 mg, 0.29 mmol) and Pd(dppf)Cl_2 (11.7 mg, 0.014 mmol) in CH_2Cl_2 (4 mL) at 0 °C. To this was added (TMS)Cl (55 μL, 0.43 mmol), and the reaction was stirred at 0 °C for 1.5 h. To the reaction were added several drops of water to quench the reaction. This was stirred vigorously for 10 min to allow the precipitation of zinc salts. $MgSO_4$ was added to dry the solution, and then it was filtered and evaporated to give crude product. The crude product was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to give the product **42** (61 mg, 69%) as an oil. IR (neat) 3445, 2961, 1645, 1254, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.12 (m, 10H), 5.35 (d, $J = 9.9$ Hz, 1H), 3.67 (m, 1H), 1.71 (m, 2H), 0.87 (t, $J = 7.3$ Hz, 3H), 0.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 145.7, 139.4, 128.3, 128.0, 127.5, 125.9, 125.8, 115.0, 43.8, 30.6, 12.2, 0.7; HRMS *m*/*z* calcd for $C_{20}H_{26}OSi$ $(M)^+$ 310.1753, found 310.1754.

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Supporting Information Available: Discussions on the attempts to add functionalized dialkylzincs, as well as attempted reaction of unstrained alkene and alkyne substrates, and crystallographic data and ORTEP diagram for the X-ray structure of compound **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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