Palladium-Catalyzed Isomerization of Aryl-Substituted Epoxides: A Selective Synthesis of Substituted Benzylic Aldehydes and Ketones

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Aryl-substituted epoxides bearing multiple methyl substituents on the epoxide ring isomerize in the presence of 5 mol % $Pd(OAc)_2/PR_3$ (R = *n*-Bu, Ph) to form the corresponding benzylic aldehyde or ketone, with complete regioselectivity for the carbonyl compound formed via cleavage of the benzylic C−O bond. No allylic alcohols or products arising from alkyl migration are observed. Rapid reaction rates and nearly quantitative yields are obtained, even with highly sterically hindered epoxides, using tri-*n*-butylphosphine as ligand and *tert*-butyl alcohol as solvent. 2-Aryl-substituted epoxides with two methyl substituents on C3 are completely unreactive, consistent with an oxidative addition/β-hydride elimination mechanism. Catalyst variation studies show that both $Pd(OAc)_2$ and PR_3 are essential for optimal activity and that palladium catalysts formed in this manner are superior to other Pd(0) catalysts (e.g., $Pd(PPh_3)_4$). The reactivity of catalytic $Pd(OAc)_2/PR_3$ toward multiply-substituted epoxides is compared to traditional Lewis acid catalysts; the former is found to be much more selective for isomerization without skeletal rearrangement. A mechanistic rationale involving turnover-limiting S_N2-like attack of Pd(0) at the benzylic carbon is proposed.

Introduction

Epoxides are one of the more versatile classes of organic compounds available to the synthetic chemist.[2] They can be prepared by a wide variety of methods,[3] often with high levels of relative and absolute stereocontrol,[4] and also undergo numerous modes of subsequent transformation. While epoxides are frequently employed as electrophiles in ring-opening nucleophilic addition reactions,[2a,3] another common, useful, and atom-economical reaction is isomerization to form other functional groups. In the presence of a strong, bulky base, an epoxide may undergo a deprotonation−elimination sequence to form an allylic alcohol,[5] frequently with high stereoselectivity. More commonly, epoxides react with Lewis acids to form carbonyl compounds, generally via hydride, alkyl, or aryl 1,2-migration pathways.[6] The synthetic applications of epoxides have been the subject of a number of recent and thorough reviews.[2a,3,7]

In recent years, the promise of increased chemo-, regio-, and stereoselectivity available via transition metal catalysis[8] has led investigators to study the interactions of epoxides with transition metal complexes, and a number of interesting and useful isomerization reactions have been reported. Notably, epoxides activated by adjacent aryl, vinyl, silyl, or carbonyl substituents are isomerized to carbonyl compounds or allylic alcohols by complexes of Rh,[9] Pd,[10] Mo,[11] Sm,[12] and Fe.[13] For example, Milstein studied the rearrangement of *trans*-stilbene oxides to 1,2-diarylethanones by $RhCl(PPh_3)_3$,[9b] and Vankar described the isomerization of aryl-substituted epoxides to carbonyl compounds with $Pd(PPh_3)_4$;[10d] both observed electronic influences on the regioselectivity of attack. Vinyl epoxides are commonly employed as precursors to alkoxy-substituted π-allylpalladium intermediates, which are useful in Pd-catalyzed allylic alkylations.[14] Suzuki et al. demonstrated that the chemoselectivity in isomerization of vinyl epoxides depends on the substrate structure: highly-substituted vinyl epoxides tend to form allylic alcohols (presumably via β-hydride elimination in a (π-allyl)palladium intermediate), while cyclic epoxides (such as cyclopentadiene monoepoxide) afford β,γ-unsaturated ketones.[10a] The same workers also reported the Pd-catalyzed rearrangement of α,β-epoxy ketones to the corresponding β-diketones.[10b]

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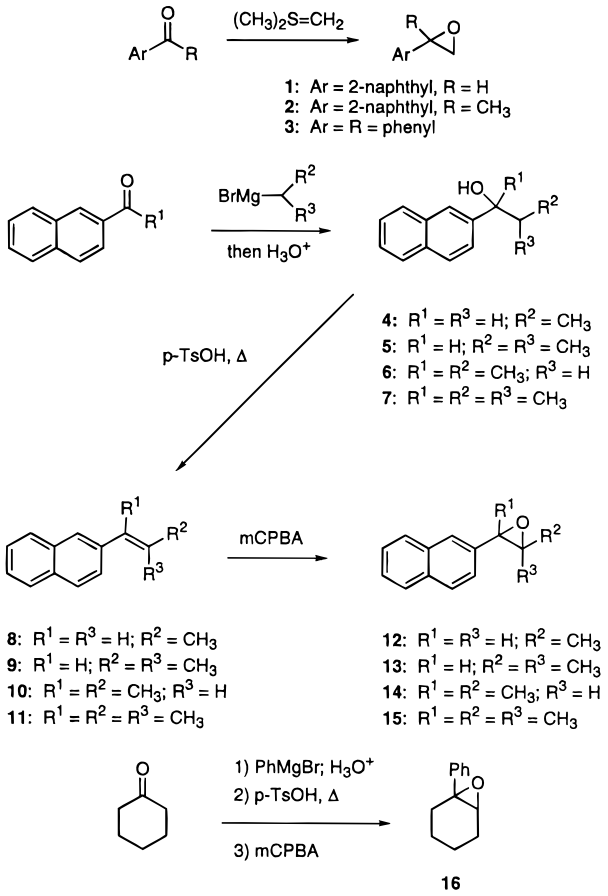
Less commonly observed are transition metal-catalyzed isomerizations of unactivated epoxides (i.e., those bearing only alkyl substituents). One of the earliest reports of such a reaction described the simple rearrangement of propylene oxide to acetone, catalyzed by dicobalt octacarbonyl.[15] Kagan showed that Mn-, Co-, Ce-, and Sm-based catalysts are effective for the isomerization of simple alkyl-substituted epoxides to carbonyl compounds.[12] Miyashita and co-workers have reported the rearrangement of alkyl- and aryl-substituted epoxides with a variety of Ni-based catalysts and observed variable chemoselectivity in product formation.[16] More recently, Cabrera et al. demonstrated that the chemoselectivity for catalytic rearrangement of propylene oxide to acetone vs propanal by $Sn[Co(CO)_4]_4$ can be controlled by external CO pressure.[17] In some cases, tandem isomerization/carbonylation sequences are possible.[18]

Our general interest in the metal-mediated transformations of small-ring heterocycles led us to investigate the reactivity of low-valent, electron-rich transition metal complexes toward several different classes of epoxides. Recently, we reported the selective, palladium-catalyzed conversion of monoalkyl-substituted epoxides to methyl ketones and aryl-substituted epoxides to carbonyl compounds via benzylic C−O cleavage.[19] While epoxide isomerization processes employing both main-group Lewis acids (as described in a recent excellent review by Rickborn)[6a] and d-block metal catalysts are well-precedented, many of them suffer from a lack of regioselectivity, giving more than one isomeric carbonyl compound. Many such isomerization reactions also exhibit low chemoselectivity, resulting in skeletal rearrangements concomitant with simple functional group transformation. In the present study, we have investigated the rearrangement of epoxides with multiple aryl and alkyl substituents, because these substrates are particularly prone to unselective reactions with traditional Lewis acid catalysts. We now report that $Pd(OAc)_2/PR_3$ smoothly catalyzes the isomerization of many multiply-substituted epoxides to afford carbonyl compounds, via exclusive benzylic C−O cleavage, under mild conditions, in good to excellent yields, representing an efficient route to substituted benzylic aldehydes and ketones.

Results and Discussion

Substrate Synthesis. The aryl-substituted epoxides employed in this study were synthesized either by methylenation of aryl ketones or aldehydes or via epoxidation of the appropriate vinylarene, as depicted in Schemes 1 and 2. Reaction of 2-naphthaldehyde, 2-acetonaphthenone, and benzophenone with dimethylsulfonium methylide[20] gave the 2-substituted epoxides **1**−**3** in excellent yield. Aryl-substituted epoxides with multiple methyl groups were prepared by a three-step protocol involving Grignard addition to the appropriate

Scheme 1. Synthesis of Aryl-Substituted Epoxides



carbonyl compound, acid-catalyzed dehydration to provide the vinylarene, and then epoxidation with MCPBA. Thus, addition of ethyl- and isopropylmagnesium bromide to 2-naphthaldehyde gave secondary alcohols **4** and **5**, respectively, while addition to 2-acetonaphthenone gave tertiary alcohols **6** and **7**. Dehydration of these benzylic alcohols with substoichiometric *p*-toluenesulfonic acid in refluxing benzene afforded the vinylarenes **8**−**11**; alkenes **8** and **10** were formed as the (*E*) isomers exclusively. Finally, epoxidation with MCPBA in CH_2Cl_2 provided the epoxides **12**−**15** in good yields. 1-Phenyl-1,2-epoxycyclohexane (**16**) was synthesized by a similar three-step route, from cyclohexanone and phenylmagnesium bromide.

Aryl-substituted epoxides bearing a variety of functionalized side chains were prepared as shown in Scheme 2. A common precursor to each of the functionalized epoxides, 1-phenyl-10-undecen-1-ol (**17**), was prepared via addition of phenylmagnesium bromide to 10-undecenal. Acid-catalyzed dehydration of **17** and subsequent epoxidation with MCPBA gave a separable mixture of epoxide **18** and the previously reported diepoxide.[19] Hydroboration of **17**, followed by acid-catalyzed dehydration, gave (*E*)-11-phenyl-10-undecen-1-ol, the primary hydroxyl group of which was elaborated into a variety of functional groups (cyano, ethoxycarbonyl, acetyl, alkynyl, and bromo) as depicted. Epoxidation of the resulting vinylarenes gave the functionalized epoxides **19**−**24**.

Isomerization of Multiply-Substituted Epoxides. Our preliminary investigations[19] showed that the Pd(0) complexes generated *in situ* from $Pd(OAc)_2$ and PR_3 (R = *n*-Bu, Ph)[21] are active catalysts for the isomerization of naphthyl epoxides **1** and **12** to 2-naphthylacetaldehyde

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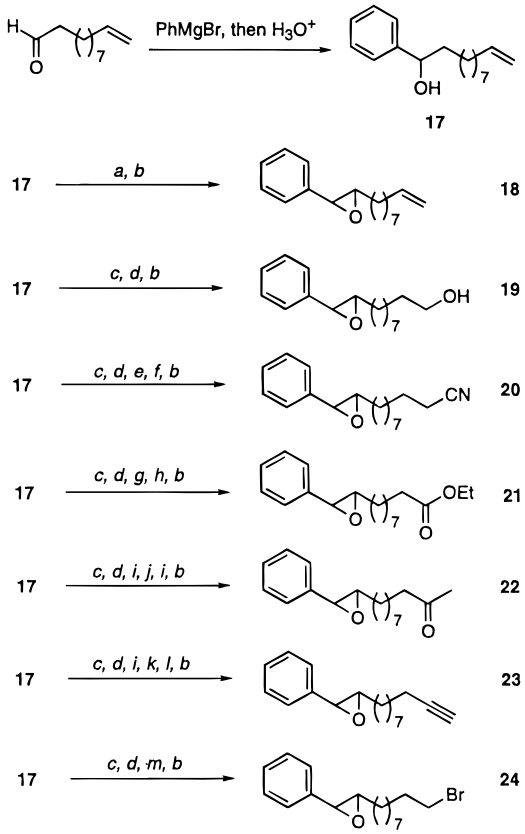
(20) Trost, B. M.; Melvin, L. R. *Sulfur Ylides: Emerging Synthetic Intermediates*; Academic Press: New York, 1975; pp 51−76.

Scheme 2. Synthesis of Functionalized Epoxides[a]

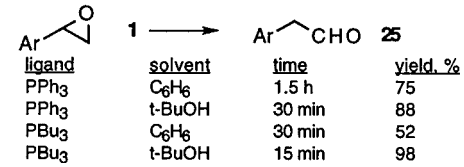


[a] Reagents and conditions: (a) *p*-TsOH, C_6H_6, Δ; (b) MCPBA, CH_2Cl_2; (c) BH_3−THF, then $NaOH-H_2O_2$; (d) H_3PO_4, THF, Δ; (e) *p*-TsCl, py; (f) NaCN, DMF, Δ; (g) CrO_3, H_2SO_4; (h) EtOH, *p*-TsOH, Δ; (i) PCC/Celite, CH_2Cl_2; (j) CH_3MgI, Et_2O, then H_3O^+; (k) CBr_4, PPh_3, CH_2Cl_2; (l) *n*-BuLi, THF, −78 °C, then H_3O^+; (m) NBS, PPh_3, DMF.

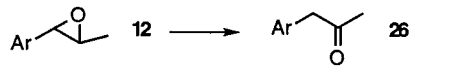
and 1-(2-naphthyl)propanone, respectively, in refluxing benzene. We also saw that sterically hindered epoxides (e.g., *trans*-stilbene oxide) require the more electron-rich tributylphosphine for efficient isomerization. We quickly learned that generation of the Pd(0) catalyst and subsequent catalytic epoxide isomerization may be carried out in many common organic solvents (*vide infra*).

In order to determine precisely how the solvent, phosphine ligand, and epoxide substitution pattern influence the efficiency of the Pd-catalyzed isomerization reaction, we treated epoxides **1**, **2**, and **12**−**15** with $Pd(OAc)_2/PR_3$ in refluxing benzene and *tert*-butyl alcohol. These two test solvents were chosen because they differ widely in polarity[22] but have similar boiling points. We also studied the effect of the phosphine ligand by employing PBu_3 and PPh_3, which differ significantly in steric and electronic properties.[23] In all cases, the isomerization reactions were carried out by generating the Pd(0) catalyst from $Pd(OAc)_2$ (5%) and PR_3 (15 mol %), adding the epoxide substrate, and refluxing under N_2 until the epoxide was consumed, or until no further catalytic turnovers were observed. The results are presented in Table 1.

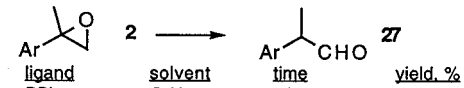
Table 1. Isomerization of Multiply-Substituted Epoxides with $Pd(OAc)_2-PR_3$[a]



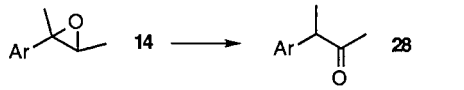
entry	ligand	solvent	time	yield, %
1	PPh_3	C_6H_6	1.5 h	75
2	PPh_3	t-BuOH	30 min	88
3	PBu_3	C_6H_6	30 min	52
4	PBu_3	t-BuOH	15 min	98



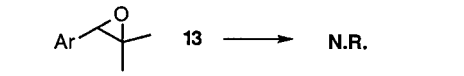
entry	ligand	solvent	time	yield, %
5	PPh_3	C_6H_6	2 h	92
6	PPh_3	t-BuOH	5 min	95
7	PBu_3	C_6H_6	30 min	96
8	PBu_3	t-BuOH	10 min	96



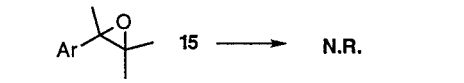
entry	ligand	solvent	time	yield, %
9	PPh_3	C_6H_6	1 h	91
10	PPh_3	t-BuOH	30 min	93
11	PBu_3	C_6H_6	1 h	69
12	PBu_3	t-BuOH	30 min	99



entry	ligand	solvent	time	yield, %
13	PPh_3	C_6H_6	24 h	0 (90)
14	PPh_3	t-BuOH	20 h	0 (66)
15	PBu_3	C_6H_6	1 h	69
16	PBu_3	t-BuOH	30 min	96



entry	ligand	solvent	time	yield, %
17	PBu_3	t-BuOH	24 h	0 (85)



entry	ligand	solvent	time	yield, %
18	PBu_3	t-BuOH	24 h	0 (92)

[a] All isomerization reactions were carried out using 5 mol % $Pd(OAc)_2$, 15 mol % PR_3, in refluxing solvent. Times required for complete consumption of starting material (or time after which reaction stopped) are indicated. Yields refer to isolated, pure product; number in parentheses refers to percentage of unreacted starting material recovered after the indicated time period. In all cases, Ar = 2-naphthyl.

Entries 1−4 (Table 1) show the isomerization of a simple aryl-substituted epoxide to the corresponding arylacetaldehyde (**25**). In all cases, reaction times were short and yields of the aldehyde were moderate to excellent. A clear preference for *tert*-butyl alcohol solvent is seen; when combined with PBu_3 as ligand, a near quantitative yield of 2-naphthylacetaldehyde is obtained. With this substrate, however, it is essential that the reaction be stopped as soon as the epoxide is completely consumed, or subsequent aldol condensation of the product aldehyde to form the 2,4-diaryl-2-butenal ensues, as we have recently described.[24] In all cases, no other isomeric carbonyl compounds were observed (i.e., 2-acetonaphthenone) by capillary GC or ^1H NMR. Using the 2-aryl-3-methyl-substituted epoxide **12** (entries 5−8), excellent yields of benzylic ketone **26** were obtained under all conditions investigated. However, the advantage of

(21) Mandai, T.; Matsumoto, T.; Tsuji, J.; Saito, S. *Tetrahedron Lett.* **1993**, *34*, 2513−2516.

(22) (a) Dielectric constants:[22b] benzene = 2.27; *t*-BuOH = 12.47. (b) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: Weinheim, 1988; pp 408−411.

(23) (a) Cone angles:[23b] PBu_3 = 132°, PPh_3 = 145°. Tolman electronic parameters:[23b] PBu_3 = 2060.3 cm^{-1}; PPh_3 = 2068.9 cm^{-1}. (b) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313−348.

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tert-butyl alcohol is evident in comparing the times required in entries 5 and 6: the isomerization is distinctly faster in the alcohol solvent compared to benzene. This effect is not noticeable, however, when the more electron-rich trialkylphosphine is used as ligand (entries 7 and 8). Again, only one regioisomeric carbonyl compound was formed in all cases.

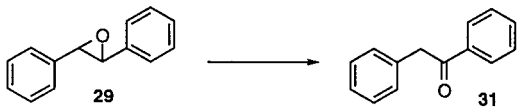
Disubstitution at the benzylic position is tolerated, as shown in entries 9−12, in which the 2-arylpropanal **27** is cleanly formed. A nearly quantitative yield is obtained in *t*-BuOH with PBu_3. The greater reactivity of Pd(0) catalysts bearing electron-rich trialkylphosphines is most clearly exemplified in entries 13−16, in which the highly-substituted epoxide **14** rearranges to the 3-aryl-2-butanone **28** only using $Pd(OAc)_2/PBu_3$ as catalyst. With PPh_3 as ligand, no isomerization occurs, and only starting material is recovered. Again, improved yields are obtained with the tertiary alcohol solvent, and no isomeric carbonyl compounds (for example, as might be formed via alkyl migration) were observed.

The limitations of this isomerization methodology are apparent in entries 17 and 18. Here we applied the most forcing isomerization conditions ($Pd(OAc)_2/PBu_3$ in refluxing *t*-BuOH) but observed no traces of isomerization product after 24 h, recovering only starting epoxide. While the unreactivity of tetrasubstituted epoxide **15** is perhaps to be expected, the trisubstituted epoxide **13** does not appear to be significantly more sterically encumbered than **14**, which undergoes isomerization cleanly and efficiently. The key appears to be the position of the two methyl substituents: with two alkyl groups located β to the aryl ring, epoxides **13** and **15** lack hydrogen atoms capable of migrating in order to form benzylic carbonyl compounds. The implications for this unreactivity on the mechanism of the isomerization reaction are discussed below.

We also investigated the reactivity of epoxides bearing two aryl substituents, under the catalytic conditions described above; the results of these experiments are depicted in Table 2. Both *trans*-stilbene oxide (**29**, entries 1−4) and *cis*-stilbene oxide (**30**, entries 5−8) isomerize to form deoxybenzoin (**31**) in the presence of $Pd(OAc)_2/PR_3$; only a trace (<3%) of *cis* to *trans* isomerization is observed by GC during the isomerization of **30**. The *trans* isomer gives good yields using PBu_3 in either solvent, or PPh_3 in *t*-BuOH; with PPh_3 in benzene, however, only a small amount of ketone is formed, with recovery of a significant amount of unreacted epoxide. A similar situation holds with the *cis* isomer: $Pd(OAc)_2/PPh_3$ affords only partial conversion of the epoxide after 1−2 days reflux, with significantly better reactivity in *t*-BuOH. With PBu_3 as ligand, nearly quantitative yields of isomerization product are obtained, but again, the reaction is noticeably faster in alcoholic solvent. The mechanistic implications of this particular observation are discussed below. The isomeric epoxide with both phenyl rings at the same position (**3**) is largely unreactive under our most forcing conditions (entries 9 and 10), affording only a trace of diphenylacetaldehyde (**32**) after prolonged reflux. In this case, the increased steric hindrance of two aryl groups at the reactive site appears to be too great to permit reaction, even with the more reactive trialkylphosphine ligand.

The relative reactivities of *cis*- and *trans*-stilbene oxide were compared directly by monitoring the isomerization of an equimolar mixture of **29** and **30** by capillary gas chromatography, using $Pd(OAc)_2/PBu_3$ as catalyst in refluxing benzene and hexadecane as an internal standard. The relative isomerization rates were estimated by calculating the initial rate constants (measured over 2 half-lives of the reaction). Using standard pseudo-first-order treatment of the kinetic data, plots of $\ln([\text{epoxide}]_0/[\text{epoxide}]_t)$ vs time are linear ($r^2 \geq 0.97$) and give rate constants of $5.34(\pm0.33) \times 10^{-2}$ h^{-1} for **29** and $8.07(\pm0.58) \times 10^{-2}$ h^{-1} for **30**. The greater reactivity of *cis*-stilbene oxide (by a factor of 50%) is not surprising, considering that this isomer should experience a greater degree of intrinsic steric strain, which is relieved upon isomerization to the ketone. Additionally, an external reagent (such as a metal catalyst) attacking the oxirane moiety should encounter less steric hindrance in approaching the *cis* isomer than the *trans*. This observation, plus the fact that both substrates show clean first-order kinetics in epoxide concentration, are consistent with a mechanism involving turnover-limiting attack of a metal catalyst on the epoxide, as discussed in detail below.

Table 2. Isomerization of Diphenyloxiranes with $Pd(OAc)_2-PR_3$[a]



entry	ligand	solvent	time	yield, %
1	PPh_3	C_6H_6	48 h	27 (61)
2	PPh_3	t-BuOH	5.5 h	80
3	PBu_3	C_6H_6	43 h	83
4	PBu_3	t-BuOH	5 min	84

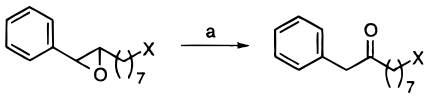
entry	ligand	solvent	time	yield, %
5	PPh_3	C_6H_6	48 h	46 (45)
6	PPh_3	t-BuOH	24 h	66 (32)
7	PBu_3	C_6H_6	30 h	99
8	PBu_3	t-BuOH	10 min	97

entry	ligand	solvent	time	yield, %
9	PPh_3	t-BuOH	24 h	3 (84)
10	PBu_3	t-BuOH	24 h	3 (73)

[a] All isomerization reactions were carried out using 5 mol % $Pd(OAc)_2$, 15 mol % PR_3, in refluxing solvent. Times required for complete consumption of starting material (or time after which reaction stopped) are indicated. Yields refer to isolated, pure product; number in parentheses refers to percentage of unreacted starting material present after the indicated time period (either isolated or quantified spectroscopically).

Functional Group Tolerance. In order to investigate the chemoselectivity of the palladium(0) catalyst toward epoxide isomerization, we have studied the reaction of a number of aryl-substituted epoxides bearing reactive functional groups. Epoxides **18**−**24**, prepared as outlined in Scheme 2, were subjected to the optimal conditions identified above (5 mol % $Pd(OAc)_2$, 3 equiv of PBu_3 per Pd, refluxing *t*-BuOH); the results of these experiments are depicted in Table 3. The Pd(0) catalyst clearly tolerates the terminal alkenyl (entry 1), primary alcohol (entry 2), nitrile (entry 3), ester (entry 4), and

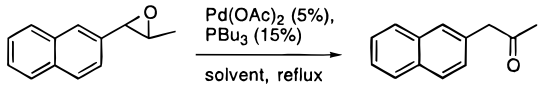
Table 3. Functional Group Tolerance in Epoxide Isomerization



entry	X (substrate)	time[b]	yield (%)[c]
1	$CH{=}CH_2$ (**18**)	1 h	80 (**33**)
2	CH_2CH_2OH (**19**)	30 min	90 (**34**)
3	$CH_2CH_2C{\equiv}N$ (**20**)	40 min	80 (**35**)
4	$CH_2CO_2CH_2CH_3$ (**21**)	45 min	96 (**36**)
5	CH_2COCH_3 (**22**)	25 min	98 (**37**)
6	$CH_2C{\equiv}CH$ (**23**)	24 h	0 (90)[d]
7	CH_2CH_2Br (**24**)	24 h	0 (98)[d]

[a] $Pd(OAc)_2$ (5 mol %), PBu_3 (15 mol %), *t*-BuOH, reflux. [b] Time required for complete consumption of epoxide. [c] Yields refer to isolated, pure product; compound number follows. [d] Amount in parentheses refers to unreacted starting material recovered after 24 h.

Table 4. Influence of Solvent on Isomerization Yield



12 26

entry	solvent	time (min)[a]	yield (%)[b]
1	2-butanone	5	99
2	*t*-BuOH	10	96
3	C_6H_6	30	93
4	dioxane	5	93
5	THF	10	92
6	CH_3CN	60	80
7	DMF[c]	5	71

[a] Time required for complete consumption of starting material. [b] Yields refer to isolated, pure product. [c] Reaction carried out at 120 °C.

ketone (entry 5) functionalities, providing the functionalized benzylic ketones **33**−**37** in excellent yields, within reasonable time periods. Limitations on the range of reactive functionality are clearly seen in entries 6 and 7, in which epoxides **23** and **24**, bearing terminal alkynyl and primary bromoalkyl groups, respectively, are completely unreactive. Although we have not determined the fate of the Pd catalyst in the presence of these substrates, catalyst poisoning via oxidative addition of C−H or C−Br is a reasonable hypothesis, since these bonds are known to react with Pd(0).[25]

Solvent Effects. Although the substrate studies described above were performed only in benzene and *tert*-butyl alcohol, we have also investigated a number of other reaction media for the isomerization reaction. We find that the Pd(0) catalyst may be generated, and the subsequent isomerization efficiently carried out, in several common organic solvents. Table 4 shows the yields of 1-(2-naphthyl)propanone (**26**) obtained by refluxing epoxide **12** with $Pd(OAc)_2$ (5 mol %) and PBu_3 (15 mol %) in the indicated solvent, for the specified time period. As shown, nearly quantitative yields of **26** are obtained using ketone (entry 1), alcohol (entry 2), aromatic (entry 3), and ethereal (entries 4 and 5) solvents. Reaction in refluxing acetonitrile requires a somewhat longer reaction time for complete conversion; both acetonitrile and *N*,*N*-dimethylformamide (entries 6 and 7) give noticeably lower yields of ketone, possibly due to catalyst decomposition.

To obtain a more quantitative picture of the influence of solvent on the rate of isomerization, we monitored the initial rates of conversion of **12** to **26** at ambient temperature, in *t*-BuOH, benzene and acetonitrile. The catalyst loading and substrate concentrations were identical in all cases, and the extent of reaction was determined by capillary gas chromatography, determining the amount of remaining substrate at time intervals by integration vs internal hexadecane. In the cases of benzene and acetonitrile, plots of $\ln([\text{epoxide}]_0/[\text{epoxide}]_t)$ vs time are linear ($r^2 \geq 0.97$) for over 3 half-lives of the reaction and pseudo-first order rate constants of $1.44(\pm 0.11) \times 10^{-2}$ min^{-1} and $1.53(\pm 0.08) \times 10^{-2}$ min^{-1}, respectively, are obtained from the slopes. With *t*-BuOH, it was not possible to obtain an accurate rate constant, because the isomerization reaction was essentially complete by the time the first measurement was taken (ca. 10 min), indicating a rate constant of at least 7×10^{-2} min^{-1}, several times greater than those measured for benzene and acetonitrile.

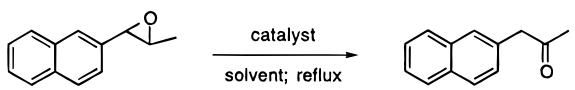
These experiments demonstrate a distinct solvent effect on the rate of the isomerization reaction. Although the observed reaction rates vary with solvent polarity, they do not correlate directly with the dielectric constants of the media. The isomerization reaction proceeds at identical rates (within experimental error) in benzene and acetonitrile, two solvents with widely differing dielectric constants (2.27 and 35.94, respectively).[22b] However, the reaction is much faster in *tert*-butyl alcohol, a solvent of intermediate dielectric constant (12.47). We suggest that the increased rate of the isomerization reaction in *t*-BuOH is not a function of the polarity of the solvent *per se* but rather a result of its ability to serve as a hydrogen bond donor. The implications of this suggestion for the mechanism of the isomerization reaction are discussed below. From a synthetic standpoint, the observation of fast isomerization in *t*-BuOH at room temperature indicates that, at least with substrates such as **12**, the reflux temperature used in Table 1 is not necessary and that ambient temperature suffices for rapid reaction.

Catalyst Effects. Our method for the *in situ* generation of a zero-valent Pd complex as catalyst is based directly on literature precedent. The reduction of $Pd(OAc)_2$ by PPh_3 has been known for some time,[26] but our use of PBu_3 to generate a catalyst presumed to be $Pd(PBu_3)_n$ (where $n = 1-3$) is inspired by the recent work of Mandai et al.,[21] who showed by ^{31}P NMR and comparative reactivity studies that formation of a Pd(0) complex is highly likely under these conditions. Our first question, then, was whether both components of the catalyst "recipe" are indeed necessary for maximum efficiency or whether the active catalyst might instead be traces of Pd(II) or tertiary phosphine present in the reaction mixture. To address this issue, we carried out a series of control experiments using $Pd(OAc)_2$ and PBu_3 alone, in both benzene and *tert*-butyl alcohol. The results of these experiments are depicted in Table 5.

(25) (a) For a report on the direct oxidative addition of the C−H bond of a terminal alkyne to Pd(0), see: Chukhadzhyan, G. A.; Evoyan, Z. K.; Melkonyan, L. N. *Zh. Obshch. Khim.* **1975**, *45*, 1114−1117; *Chem. Abstr.* 83, 97535c. (b) For a recent report on Pd-catalyzed reactions of terminal alkynes that proceed via C−H activation, see: Trost, B. M.; Matsubara, S.; Caringi, J. *J. Am. Chem. Soc.* **1989**, *111*, 8745−8746. (c) For oxidative addition reactions of Pd(0) with organic bromides, see: Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434−442.

(26) (a) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985. (b) Heck, R. F. *Org. React. (N.Y.)* **1982**, *27*, 345−390.

Table 5. Catalyst Control Experiments

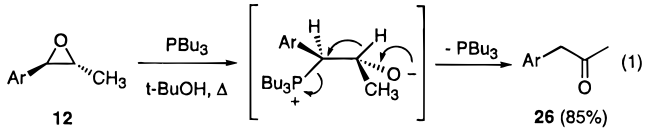


12 **26**

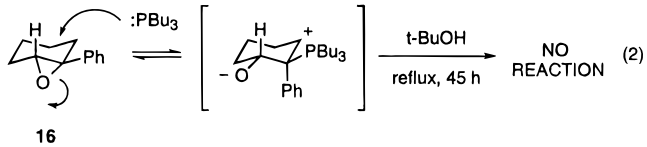
entry	catalyst	solvent	time	**12** (%)[a]	**26** (%)[a]
1	$Pd(OAc)_2$ (5%)	C_6H_6	45 h	100	0
2	PBu_3 (15%)	C_6H_6	95 h	85	0
3	$Pd(OAc)_2$ (5%)	*t*-BuOH	45 h	76	23
4	PBu_3 (15%)	*t*-BuOH	45 h	0	85
5	none	*t*-BuOH	72 h	96	0
6	$Pd(OAc)_2$ (5%) + PBu_3 (15%)	*t*-BuOH	10 min	0	96

[a] Yields refer to isolated, pure products.

Reaction of disubstituted epoxide **12** with substoichiometric amounts of either $Pd(OAc)_2$ (entry 1) or tributylphosphine (entry 2) in refluxing benzene led to no observable isomerization to form ketone **26**; in both cases, only starting material was recovered, in high yield. In contrast, when the same catalysts were employed in *tert*-butyl alcohol, we observed slow but significant formation of ketone **26** with $Pd(OAc)_2$ (entry 3) and complete conversion of the epoxide with PBu_3, leading to a quite nice yield of the benzylic ketone (entry 4). In the former case, we suspect that palladium(II) acetate, which is quite soluble in alcoholic solvents, behaves as a simple Lewis acid catalyst and that the ketone is formed by the traditional acid-catalyzed isomerization mechanism.[6] In the latter case, we suggest that the phosphine-catalyzed isomerization may proceed as described in eq 1. Nucleo-



philic attack of the phosphine at the benzylic carbon can lead to the betaine intermediate; rapid 1,2-hydride migration, with concomitant C=O bond formation and phosphine expulsion, may afford ketone **26**. Interestingly, the intermediate betaine is the same as would be expected from addition of a phosphorus ylide to an aldehyde; however, we see no evidence of alkene formation via phosphine oxide elimination. In contrast, the deoxygenation of stilbene oxide and other aryl-substituted epoxides by PR_3 (R = Ph, *n*-Bu) is well-known,[27] although the conditions employed differ considerably from ours. Support for the mechanistic proposal in eq 1 arises from the attempted PBu_3-catalyzed isomerization of bicyclic epoxide **16** (eq 2). In contrast to the monocyclic



case, **16** is completely inert toward PBu_3 in refluxing *t*-BuOH; after 45 h, 88% of the unreacted epoxide was recovered, with no trace of 2-phenylcyclohexanone, the expected isomerization product. We propose that this unreactivity is due to the inability of the β-hydrogen and PBu_3 substituents to attain a mutually antiperiplanar arrangement, thus preventing the concerted 1,2-hydride migration suggested in eq 1. We believe that traces of free PBu_3 are not responsible for the catalytic epoxide isomerization observed in the experiments described in Tables 1−4 above primarily because the rate of isomerization of epoxide **12** using $Pd(OAc)_2/PBu_3$ (Table 1, entry 8) is significantly greater than that observed using only PBu_3. Furthermore, while PBu_3 does not isomerize cyclic epoxide **16**, $Pd(OAc)_2/PBu_3$ does so quite efficiently (*vide infra*), arguing in favor of a direct role for the Pd(0) complex. The nucleophilic properties of tertiary phosphines have been exploited in a number of other useful catalytic (but metal-free) processes,[28] and we are continuing to explore this potentially useful transformation.

The remaining control experiment depicted in Table 5 (entry 5) demonstrates that the polar solvent alone is not responsible for the isomerization of **12**. In contrast, however, extremely electron-rich epoxides, such as *p*-methoxystyrene oxide, are known to rearrange spontaneously in aqueous medium.[29] Finally, the catalytic efficiency of $Pd(OAc)_2/PBu_3$ is depicted in entry 6 for comparison to the control experiments and is clearly much higher than any of the other conditions tested.

The next question to be addressed concerns the nature of the catalyst formed from $Pd(OAc)_2$ and PPh_3. While the reduction of $Pd(OAc)_2$ to zero-valent palladium by tertiary phosphines is fairly well-accepted,[26] the precise nature of the reduction product (and, in fact, the active catalyst in the Heck reaction) has only recently been identified by Amatore et al. as $Pd(PPh_3)_3(OAc)^-$, in equilibrium with the bis-phosphine complex via PPh_3 dissociation.[30] Since our methodology involves generation of Pd(0) under the same conditions studied by Amatore, it is reasonable to suspect that the catalytically active species in the epoxide isomerization reaction is also the anionic acetoxypalladium(0) complex. In order to determine precisely how the mode of preparation of a $Pd(0)-PPh_3$ catalyst influences its reactivity toward catalytic epoxide isomerization, we studied the rearrangement of epoxide **12** to ketone **26** using a variety of palladium(0) catalysts, all with triphenylphosphine as the supporting ligand. Isomerization reactions were carried out in DMF (in order to closely approximate the conditions employed by Amatore et al.) at ambient temperature. After 24 h, the product ketone **26** and any unreacted epoxide **12** present were isolated and quantified. The results of these experiments are depicted in Table 6.

Entries 1−3 demonstrate that the catalysts obtained via reduction of $Pd(OAc)_2$ with 3, 4, or 5 equiv of PPh_3, respectively, are all about equally effective for the isomerization of **12** to **26**; in each case, 80−90% of the product ketone is formed, with <10% of unreacted epoxide recovered. Significantly, the preformed catalyst

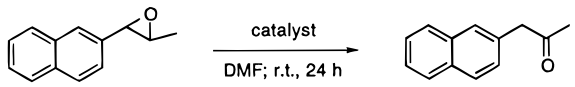
(27) Bissing, D. E.; Speziale, A. J. *J. Am. Chem. Soc.* **1965**, *87*, 2683−2690. In these studies, the intermediacy of a betaine and its reversible fragmentation to phosphorane and benzaldehyde were proven by the isolation of *m*-chlorostilbene from the deoxygenation reaction of stilbene oxide with PBu_3 in the presence of *m*-ClC_6H_4CHO, thus implicating exchange with added aldehyde. However, all of the deoxygenation reactions were carried out neat, and at temperatures exceeding 100 °C.

(28) (a) Ono, N.; Miyake, H.; Kaji, A. *J. Chem. Soc., Chem. Commun.* **1983**, 875−876. (b) Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933−7935. (c) Vedejs, E.; Diver, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 3358−3359. (d) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 10819−10820.

(29) For a recent example, see: Blumenstein, J. J.; Ukachukwu, V. C.; Mohan, R. S.; Whalen, D. L. *J. Org. Chem.* **1993**, *58*, 924−932.

(30) Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. A.; Meyer, G. *Organometallics* **1995**, *14*, 5605−5614.

Table 6. Epoxide Isomerization using Pd(0)-PPh_3 Catalysts



12 26

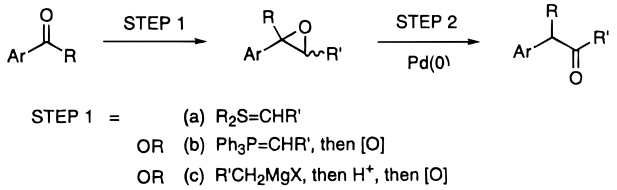
entry	catalyst	**12** (%)[a]	**26** (%)[a]
1	5% $Pd(OAc)_2$, 15% PPh_3	0	82
2	5% $Pd(OAc)_2$, 20% PPh_3	6	86
3	5% $Pd(OAc)_2$, 25% PPh_3	3	91
4	5% $Pd(PPh_3)_4$	28	61
5	5% $Pd(PPh_3)_4$ + 5% KOAc	18	76
6	5% $Pd(PPh_3)_4$ + 5% HOAc	14	59
7	2.5% $Pd_2(dba)_3$ + 20% PPh_3	89	0

[a] Yields refer to isolated, purified product.

$Pd(PPh_3)_4$ is much less reactive (entry 4) even than the catalyst mixture formed from 5 equiv of PPh_3 per Pd, which, presumably, still has 4 equiv of unoxidized PPh_3 present (based on the hypothesis that reduction of $Pd(OAc)_2$ with PPh_3 affords Pd(0), O=PPh_3, and HOAc, in the presence of trace water).[30] Clearly, the mode of preparation of the Pd(0) catalyst has a major effect on its reactivity. In order to probe whether the presence of acetate leads to higher catalytic activity, we repeated the experiment in entry 4, except with 1 equiv of anhydrous potassium acetate per Pd. Interestingly, the reactivity increased (entry 5) compared to $Pd(PPh_3)_4$, but not quite to the level observed in entry 3. This observation contrasts with Amatore's work,[30] in which $Pd(OAc)_2/PPh_3$ and $Pd(PPh_3)_4 + OAc^-$ displayed *identical* physicochemical properties. Thus, although acetate increases the reactivity of $Pd(PPh_3)_4$ in catalytic epoxide isomerization, possibly by formation of the anionic acetoxypalladate anion identified by Amatore, the catalyst mixture is *not* identical to that obtained by reduction of $Pd(OAc)_2$ with PPh_3. Acetic acid (5 mol %), in contrast, has little effect on the catalytic efficiency of $Pd(PPh_3)_4$ (entry 6); although less unreacted epoxide was recovered, the yield of ketone **25** was about the same as with $Pd(PPh_3)_4$ alone. As we have no direct evidence concerning the nature of the catalyst formed in our experiments, we can only surmise that some other component present in the mixtures formed in entries 1−3 but absent from the $Pd(PPh_3)_4$ reaction facilitates the epoxide isomerization but has no influence on the rate of the Heck reaction. Finally, in entry 7, we show that the catalyst obtained by treatment of the palladium(0)-dibenzylideneacetone complex with PPh_3 (4 equiv/Pd) is completely unreactive in epoxide isomerization. Clearly, displacement of dba by PPh_3 is incomplete,[31] and the resulting enone− or phosphine−enone complexes that may be present are simply insufficiently nucleophilic to activate epoxides. This observation, as well as those in entries 3−5, should serve as a warning to those who might mistakenly assume that all $Pd(0)/PPh_3$ catalysts are equivalent in reactivity.

The high efficiency of isomerization observed using $Pd(OAc)_2/PBu_3$ in *t*-BuOH prompted us to question whether 5 mol % Pd per epoxide, as was employed throughout this study, was really necessary for maximum yield. In order to determine the maximum possible turnover number (i.e., moles of isomerization product formed per mole of catalyst) prior to catalyst deactivation, we treated a solution of $Pd(OAc)_2/PBu_3$ with a large excess (1000 equiv per Pd) of disubstituted epoxide **12** and carried out the isomerization reaction as described previously. After 48 h of reflux under N_2, the isolated yield of isomerization product **26** was 93%, with no unreacted epoxide observed, indicating that at least 930 catalytic turnovers are achievable. Clearly, although 5 mol % Pd(0) works conveniently for a number of substitution patterns, some substrates can be isomerized quite efficiently with a much lower catalyst loading.

Scheme 3. Two-Step Synthesis of Benzylic Carbonyl Compounds



Synthetic Utility of Pd-Catalyzed Epoxide Isomerization. The primary goal of this research is to develop a selective and efficient synthesis of carbonyl compounds from epoxides. In general, our reaction can be viewed as the key process in a two-step protocol for the homologation of an aryl aldehyde or ketone to a higher carbonyl compound. This protocol involves (1) conversion of the aryl aldehyde or ketone to an epoxide followed by (2) selective isomerization of the epoxide to a benzylic aldehyde or ketone, as depicted in Scheme 3. The first step may be carried out in a number of ways. The shortest route (method a) involves addition of an alkylidene fragment to the starting carbonyl compound, via sulfur ylide technology,[20] providing the epoxide in one step. Alternatively (path b), a Wittig or other olefination,[32] followed by epoxidation with any of a variety of oxygen-atom transfer reagents,[2−4] affords the epoxide in two steps. In this case, the stereochemistry of olefination is not important, since the β-carbon eventually attains sp^2-hybridization. Finally (path c), the three-step sequence demonstrated in Scheme 1 (Grignard addition, dehydration, epoxidation) is also a viable route.

The crucial step, however, is the Pd-catalyzed epoxide isomerization. As mentioned previously, Lewis acids have long been known to catalyze the rearrangement of epoxides to carbonyl compounds.[6] Although certain epoxide substrates reliably give a single isomeric carbonyl compound upon rearrangement with Lewis acids, some classes of epoxides are notoriously prone to unselective reactions. For example, House showed that *trans*-stilbene oxide undergoes isomerization with catalytic $MgBr_2$ to afford a mixture of deoxybenzoin and diphenylacetaldehyde[33a] and that 2,3-epoxybutane also gives mixtures of products arising from competitive hydride and alkyl migration.[33b] Likewise, Rickborn and coworkers found that lithium salts rearrange simple monoalkyl-substituted epoxides to give both the methyl ketone and the corresponding aldehyde.[34] More recently, Yamamoto investigated the use of bulky aluminum-based

(31) Amatore et al. have also shown that excess PPh_3 is necessary for complete displacement of dibenzylideneacetone from $Pd(dba)_2$. Amatore, C.; Jutand, A.; Khalil, F.; M'Barki, M. A.; Mottier, L. *Organometallics* **1993**, *12*, 3168−3178.

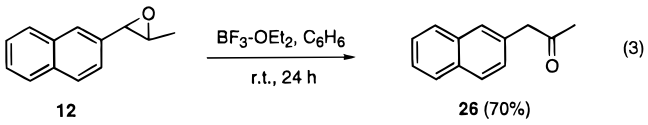
(32) (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927. (b) For an excellent overview of carbonyl olefination reactions, see: Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 1, Chapter 3.1.

(33) (a) House, H. O. *J. Am. Chem. Soc.* **1955**, *77*, 3070−3075. (b) House, H. O. *J. Am. Chem. Soc.* **1955**, *77*, 5083−5089.

(34) Rickborn, B.; Gerkin, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 1693−1700.

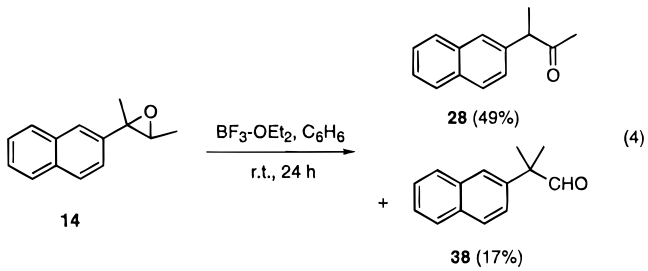
Lewis acids for rearrangement of both aryl- and alkyl-substituted epoxides and found that trisubstituted epoxides consistently form aldehydes by selective alkyl group (rather than hydride) migration.[35]

In contrast to these results, we find that all of our aryl-substituted epoxide substrates that react with $Pd(OAc)_2/PBu_3$ (i.e., those bearing at least one hydrogen β to the aryl ring) do so with *complete regioselectivity for formation of a single carbonyl compound, via cleavage of the benzylic C−O bond*. In order to make a direct comparison between our catalyst system and a traditional Lewis acid catalyst, boron trifluoride etherate, we reacted epoxides **12** and **14** with the latter reagent. With the disubstituted epoxide **12** (eq 3), we obtained ketone **26** in 70% yield.



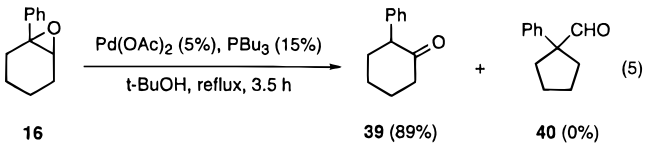
(3)

Although the chemoselectivity with respect to product formation is very high, the yield is considerably lower than we observe using $Pd(OAc)_2/PR_3$ (compare to Table 1, entries 5−8), which gives a near quantitative yield of ketone within minutes. Furthermore, the Pd catalyst operates under nearly neutral (or, in fact, Lewis basic) conditions and thus may be preferable with substrates that are sensitive to strong Lewis acids. With trisubstituted epoxide **14**, however, a very different picture emerges. Isomerization with $BF_3{\cdot}OEt_2$ (eq 4) gave ketone



(4)

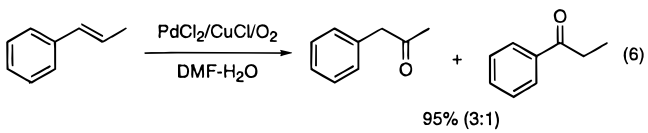
28, formed via hydride migration, as well as aldehyde **38**, via methyl migration. The overall isolated yield was only 66%, and the chemoselectivity was a mere 2.8:1, slightly favoring the hydride migration pathway. This result stands in stark contrast to that obtained with $Pd(OAc)_2/PBu_3$ in *t*-BuOH, wherein we saw formation of ketone **28** as the only isomerization product, in a satisfying 96% yield (Table 1, entry 16). Clearly, the palladium(0) route is the method of choice for rearrangement of highly substituted epoxides which are otherwise prone to isomerization via alkyl migration. Finally, isomerization of the cyclic, trisubstituted epoxide **16** using $Pd(OAc)_2/PBu_3$ in *t*-BuOH provided 2-phenylcyclohexanone (**39**) in 89% yield (eq 5), again as the only isomerization product



(5)

observed. In contrast, Yamamoto's work showed that treatment of epoxide **16** with a variety of Lewis acids, such as $BF_3{\cdot}OEt_2$, SbF_5, and methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR), led to isolation of the ring-contracted aldehyde **40** with complete selectivity, and in high yield.[35] In fact, all trisubstituted epoxides tested with MABR showed complete selectivity for the high-yield formation of aldehyde via alkyl-group migration. Thus, the present study demonstrates the complementary nature of our Pd(0) system to Lewis acid catalysts: the latter give variable amounts of alkyl migration (in some cases, such as with MABR, with complete selectivity), while the former operates only via hydride migration, even with multiply-substituted substrates. It should be noted that Sankararaman and colleagues have recently reported the use of 5 M $LiClO_4-Et_2O$ as a catalyst for the isomerization of epoxides to carbonyl compounds.[36] These workers observe high selectivity for rearrangement via C−O cleavage at the more substituted oxirane carbon, followed by hydride (rather than alkyl or aryl) migration, regardless of whether that position is aryl- or alkyl-substituted. The high selectivity of $LiClO_4-Et_2O$ system for substituted oxiranes (monoalkyl-substituted epoxides are inert) also makes it highly complementary to the two isomerization catalysts discussed above.

The extremely high regioselectivity we observe in the isomerization of aryl-substituted epoxides to benzylic carbonyl compounds offers a synthetic advantage over another possible pathway to aldehydes and ketones, namely, Wacker oxidation of vinylarenes. Although such compounds do undergo direct aerobic oxidation with $PdCl_2/CuCl$ to form carbonyl compounds, the selectivity is generally poor. For example, Keinan observed that Wacker oxidation of β-methylstyrene gave a 3:1 mixture of 1-phenyl-2-propanone and 1-phenyl-1-propanone (eq 6).[37] In contrast, we find that the two-step protocol of



(6)

epoxidation of (*E*)-1-(2-naphthyl)-1-propene (**8**), followed by Pd-catalyzed isomerization, affords the 1-aryl-2-propanone **26** as the sole product (Table 1, entry 8), albeit in lower overall yield. This observation suggests that epoxidation/isomerization may be preferable to direct oxidation for the conversion of some alkenes to carbonyl compounds in a highly regioselective manner.

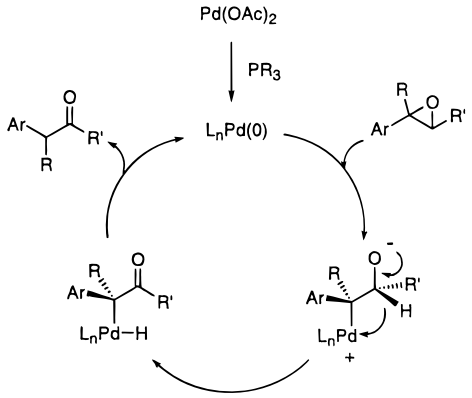
Mechanistic Rationale. The mechanism of epoxide isomerization by late-transition metal complexes is generally thought to involve cleavage of a C−O bond by an oxidative addition process, followed by β-hydride elimination to a metal hydrido−enolate complex, which reductively eliminates the carbonyl compound. In support of this general scenario, Milstein has shown that low-valent, electron-rich Ir and Rh complexes react with monosubstituted epoxides to form stable, isolable hydrido−enolate complexes *mer*-$(PMe_3)_3M(H)(Cl)(CH_2COR)$, one of which (M = Ir, R = H) was characterized by X-ray crystallography.[9c] The rhodium complex was shown to undergo a dissociative reductive elimination to form methyl ketones ($RCOCH_3$, where R = Me, Ph); in fact, the precursor to the Rh enolate complex, $RhCl(PMe_3)_3$,

(35) Maruoka, K.; Murase, N.; Bureau, R.; Ooi, T.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 3663−3672.

(36) Sudha, R.; Malola Narasimhan, K.; Geetha Saraswathy, V.; Sankararaman, S. *J. Org. Chem.* **1996**, *61*, 1877−1879.

(37) Keinan, E.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 3474−3480.

Scheme 4. Mechanistic Rationale



is a moderately active catalyst for the isomerization of mono-substituted epoxides to methyl ketones. Another possible intermediate in this process, a structurally characterized oxametallacyclobutane complex of Rh(III), was prepared via direct oxidative addition of a non-isomerizable epoxide (isobutylene oxide) to a Rh(I) precursor.[38] An exception to this general scenario of isomerization via C−O oxidative addition−β-hydride elimination arises in the earlier work of Milstein, Buchman, and Blum, who described the rearrangement of stilbene oxides to 1,2-diarylethanones via $RhCl(PPh_3)_3$.[9b] In contrast to the C−O cleavage route described above, this reaction was shown to proceed via initial insertion of Rh(I) into a C−H bond of the oxirane, followed by rate-determining 1,3-hydride migration from Rh to C2 of the oxiranyl ligand with concomitant ring-opening. In a similar vein, Wu and Bergman demonstrated that the reaction of a coordinatively unsaturated Rh(I) complex with ethylene oxide to generate a formylmethyl hydride complex also occurs via initial C−H insertion, followed in this case by ring opening and subsequent hydride migration from C2 of the oxiranyl ligand to C1, with concomitant enolate ligand formation.[39]

In order to rationalize the chemistry we observe between $Pd(OAc)_2/PR_3$ and aryl-substituted epoxides, we tentatively propose the mechanistic scenario depicted in Scheme 4. This rationale involves formation of a Pd(0) species as the active catalyst by reduction of $Pd(OAc)_2$ by tertiary phosphine; turnover-limiting attack of Pd(0) at the benzylic carbon in an S_N2-like process, generating a zwitterionic β-alkoxyalkylpalladium(II) intermediate; rapid β-hydride elimination to form a hydrido−enolate intermediate (which is depicted as carbon-bound for simplicity, but could instead be oxygen-bound); and rapid reductive elimination affording the carbonyl compound, with regeneration of Pd(0).

Although we have not yet completed a full mechanistic study of this reaction, the following preliminary observations support the above proposal. (1) The literature precedent for formation of Pd(0) from $Pd(OAc)_2$ and PR_3 (where R = *n*-Bu or Ph) has been discussed above;[26,30] the results of our catalysts studies (see Table 6) are consistent with the formation of a Pd(0) catalyst system that is distinctly more reactive than simple $Pd(PR_3)_4$. However, we have no direct evidence concerning the nature of the Pd(0) complex formed by reduction with PBu_3; we must rely on the observations of Mandai et al.,[21] who found the spectroscopy and reactivity of the catalysts formed *in situ* to be consistent with highly nucleophilic Pd(0)−tertiary phosphine complexes. (2) The turnover-limiting nature of the initial attack of Pd(0) on the epoxide is supported by the observation that more sterically hindered substrates react more slowly (compare, for example: entries 10 and 14 in Table 1; the greater reactivity of *cis*-stilbene oxide compared to *trans*-stilbene oxide; and the greater reactivity of either stilbene oxide vs 2,2-diphenyloxirane in Table 2). Our assertion that the structure of the initial oxidative addition product is a zwitterionic species rather than a palladaoxetane is based on the observation of increased reaction rates in polar, protic solvents (see discussion above). Indeed, the fastest isomerization reactions are observed in *t*-BuOH, in which $Pd(OAc)_2/PBu_3$-catalyzed isomerization of **12** to **26** occurs within minutes at ambient temperature, whereas the same reaction in benzene has a half-life of 48 min. It is easy to rationalize this phenomenon as a lowering of the activation barrier in the turnover-limiting step by stabilization of the transition state via hydrogen bonding of the incipient alkoxide anion with the protic solvent. The formation of a metallaoxetane on the isomerization pathway is unlikely on stereoelectronic grounds: such a coordination mode would preclude the Pd complex from attaining the syn-coplanar geometry of the Pd−C−C−H moiety necessary for β-H elimination. (3) Monitoring the catalytic isomerization of **12** to **26** by $Pd(OAc)_2/PBu_3$ using ^1H NMR (270 MHz, C_6D_6) revealed only signals attributable to **12**, **26**, and PBu_3. Specifically, we saw no aliphatic resonances that might arise from any of the other postulated intermediates in the reaction (for example, the alkoxyalkyl or hydrido−enolate complexes). In particular, we saw no evidence for metal hydrides (to −50 ppm). This suggests that the resting state of the catalyst is the simple Pd(0)−PR_3 complex and that none of the other intermediates are sufficiently long-lived to be observable by NMR. (4) The observed unreactivity of epoxides **13** and **15**, which have no hydrogens β to the aromatic ring capable of undergoing migration, is consistent with the mechanism depicted. While β-elimination of alkyl groups is not unknown in late transition metal chemistry, it is nevertheless uncommon, especially in the absence of any overwhelming driving force (such as aromatization or relief of ring strain).[40] Apparently the formation of a carbonyl group does not provide sufficient exothermicity to force the migration of a methyl group. This analysis assumes, of course, that initial attack and C−O cleavage actually occurs with **13** and **15**, which we have not yet rigorously proven, but infer from the reactivity of epoxides with similar steric profiles, such as **2** and **14**. It is also noteworthy that these latter substrates, which bear both a methyl group and an aryl substituent at C2, do not undergo competitive β-hydride elimination from the methyl group to form allylic alcohols, as is seen with certain types of epoxides and catalysts.[10a,e,13a,b] The full negative charge on the oxygen apparently induces preferential hydrogen migration from the alkoxyalkyl group rather than from the methyl group.

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(39) Wu, J.; Bergman, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 7628−7630.

(40) (a) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245−269. For specific examples, see: (a) Benfield, F. W. S.; Green, M. L. H. *J. Chem. Soc., Dalton Trans.* **1974**, 1324−1331. (b) Eilbracht, P.; Mayser, U. *Chem. Ber.* **1980**, *113*, 2211−2220. (c) Crabtree, R. H.; Dion, R. P. *J. Chem. Soc., Chem. Commun.* **1984**, 1260−1261.

The observed first-order dependence of the rate on epoxide concentration (at least during the initial period of the reaction), as demonstrated in the kinetic studies of the isomerization of epoxide **12**, does not necessitate that attack by Pd(0) be the turnover-limiting step, but is certainly consistent with such a hypothesis. We have not yet determined the order of the reaction with respect to Pd, but these and other experiments (including determination of activation parameters, isotopic labeling studies, and kinetic isotope effects) are in progress and will be reported in a forthcoming manuscript.

Conclusions

In summary, this work demonstrates a useful protocol for the high-yield, efficient, and selective synthesis of benzylic aldehydes and ketones by palladium(0)-catalyzed isomerization of the corresponding aryl-substituted epoxides. The reaction is applicable to epoxides with a variety of substitution patterns and functional groups and, when coupled with the preparation of the precursor epoxide (as depicted in Scheme 3), provides a convenient homologation of aryl aldehydes and ketones to benzylic aldehydes and ketones. The isomerization reaction is most efficient using $Pd(OAc)_2/PBu_3$ in refluxing *t*-BuOH or other polar solvents and provides the isomerization product with complete chemoselectivity for hydride migration rather than alkyl migration, in a manner that is complementary to commonly employed Lewis acidic isomerization catalysts.

Experimental Section

General Considerations. All reactions were carried out under an atmosphere of nitrogen using standard Schlenk techniques.[41] The isomerization reactions were carried out in Schlenk tubes with 19/22 outer joints and standard ground glass gas inlets; the main body of the tube was 1.5 (o.d.) × 14 cm, that is, of sufficient length that refluxing solvent was cooled by the ambient air (no condenser was required). Ether and tetrahydrofuran were distilled from blue or purple solutions of sodium benzophenone ketyl, and dichloromethane was distilled from CaH_2, immediately prior to use. Benzene, DMF, DMSO, acetonitrile, *t*-BuOH, and dioxane were distilled from CaH_2, stored over 3 Å molecular sieves, and deaerated by purging with nitrogen immediately before use. 2-Butanone was distilled and purged with nitrogen before use. All other solvents were used as received. Thin-layer chromatography was performed using Merck glass plates precoated with F_{254} silica gel 60; compounds were visualized by UV and/or with *p*-anisaldehyde stain solution. Flash chromatography was performed using EM Science silica gel 60, following the procedure of Still,[42] with the solvent mixtures indicated. Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Combustion analyses were performed by Desert Analytics of Tucson, AZ.

NMR spectra were measured on a Nicolet NT 270 spectrometer, modified with a Libra real-time NMR station, using MacNMR software, provided by Tecmag Inc. of Houston, TX; ^1H spectra were measured at 270 MHz and $^{13}C\{^1H\}$ NMR spectra were measured at 67.9 MHz; and chemical shifts are listed in δ (ppm) relative to Me_4Si. All spectra are recorded in $CDCl_3$. IR spectra were measured on a Mattson Galaxy 2020 Series FTIR, as neat films or Nujol mulls; absorption bands are reported in cm^{-1}. Gas chromatograms were measured on a Hewlett-Packard 5890 Series II instrument, using an Ultra 2 (cross-linked 5% Ph Me silicone) 50 m column (i.d 0.32 mm, film thickness 0.52 mm). Mass spectra were measured on a Fisons Instrument MD 800 quadrupole mass spectrometer, with 70 or 30 eV electron ionization, and a GC 8000 Series gas chromatograph inlet, using a J & W Scientific DB-5MS column of 15 m length, 0.25 mm i.d., and 0.25 mm film thickness. Mass spectral data are given as *m/e*, with the relative peak height following in parentheses.

Tri-*n*-butylphosphine, MCPBA (73.4%), *p*-toluenesulfonic acid hydrate, *p*-toluenesulfonyl chloride, trimethylsulfonium iodide, 2-naphthaldehyde, 2-acetonaphthenone, benzophenone, benzaldehyde, cyclohexanone, magnesium turnings, bromoethane, iodomethane, bromobenzene, 2-bromopropane, 10-undecenal (which was distilled prior to use), carbon tetrabromide, *n*-BuLi, *N*-bromosuccinimide, *trans*-stilbene, *cis*-stilbene, sodium hydride, BH_3·THF, and hexadecane were purchased from Aldrich Chemical Company. Chromium trioxide was purchased from Fisher Scientific, and pyridinium chlorochromate was from Lancaster Synthesis. Triphenylphosphine was purchased from Fluka and purified by recrystallization from 95% ethanol. Sodium cyanide was purchased from J. T Baker. Palladium acetate was from Strem Chemicals and was recrystallized from benzene prior to use. Palladium(II) chloride was purchased from Johnson Matthey and used directly in the synthesis of $Pd(PPh_3)_4$[43] and $Pd_2(dba)_3$.[44] All new compounds are fully characterized by standard spectroscopic and analytical or mass spectrometric techniques. Known compounds are identified by ^1H NMR and have literature references provided.

trans-Stilbene oxide (**29**),[45] *cis*-stilbene oxide (**30**),[45] and 1-phenyl-1,2-epoxycyclohexane (**16**)[35] were prepared according to the literature, and their identities and purities were verified by ^1H NMR.

Preparation of Epoxides 1−3. General Method.[20] A solution of dimethylsulfonium methylide was prepared from trimethylsulfonium iodide and sodium hydride in DMSO−THF, and a solution of the appropriate carbonyl compound in THF was added at 0 °C. After completion of reaction, as determined by TLC, the mixture was worked up by diluting with water and extracting with diethyl ether; the epoxide was purified by flash chromatography.

2-(2-Naphthyl)oxirane (1):[46] prepared from trimethylsulfonium iodide (2.61 g, 13 mmol), NaH (0.31 g, 13 mmol), DMSO (19.0 mL), THF (11.7 mL), and 2-naphthaldehyde (1.0 g, 6.4 mmol); yield = 0.873 g (80%), R_f = 0.45 (6:1 hexane−ethyl acetate), mp 57−58 °C. ^1H NMR: δ 7.88−7.72 (m, 4H), 7.63−7.50 (m, 2H), 7.37−7.29 (m, 1H), 4.03 (dd, J = 4.0, 2.4 Hz, 1H), 3.23 (dd, J = 4.2, 5.6 Hz, 1H), 2.91 (dd, J = 2.4, 5.5 Hz, 1H).

2-Methyl-2-(2-naphthyl)oxirane (2):[47] prepared from trimethylsulfonium iodide (2.41 g, 12 mmol), NaH (0.29 g, 12 mmol), DMSO (15 mL), THF (11 mL), and 2-acetonaphthenone (1.0 g, 5.9 mmol); yield = 0.976 g (90%), R_f = 0.50 (6:1 hexane−ethyl acetate), mp 79−81 °C. ^1H NMR: δ 7.91−7.81 (m, 3H), 7.49−7.46 (m, 4H), 3.07 (d, J = 5.1 Hz, 1H), 2.90 (d, J = 5.4 Hz, 1H), 1.57 (s, 3H).

2,2-Diphenyloxirane (3):[48] prepared from trimethylsulfonium iodide (2.24 g, 11 mmol), NaH (0.26 g, 11 mmol), DMSO (15 mL), THF (10.5 mL), and benzophenone (1.0 g, 5.5 mmol); yield = 0.973 g (90%), R_f = 0.56 (6:1 hexane−ethyl acetate). ^1H NMR: δ 7.51−7.26 (m, 10H), 3.28 (s, 2H).

Preparation of Benzylic Alcohols 4−7. General Method. A solution of Grignard reagent was prepared from the bromoalkane and magnesium in ether, cooled to 0 °C, and treated with a solution of the appropriate carbonyl compound. The mixture was warmed to room temperature and quenched with water, and the phases were separated. The ethereal layer

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(47) Matsumoto, T.; Takeda, Y.; Iwata, E.; Sakamoto, M.; Ishida, T. *Chem. Pharm. Bull.* **1994**, *42*, 1191−1197.
(48) Lopez, L.; Troisi, L. *Tetrahedron Lett.* **1989**, *30*, 3097−3100.

was washed with saturated solutions of $NaHSO_4$, $NaHCO_3$, and brine, dried ($MgSO_4$), and evaporated to afford the crude alcohol, which was purified by flash chromatography.

1-(2-Naphthyl)-1-propanol (4):[49] prepared from magnesium (1.49 g, 61.4 mmol), bromoethane (3.8 mL, 51.2 mmol), 2-naphthaldehyde (4.0 g, 25.6 mmol), and ether (40 mL); yield = 4.07 g (85%), R_f = 0.38 (6:1 hexane−ethyl acetate). ^{1}H NMR: δ 7.85−7.78 (m, 4H), 7.51−7.45 (m, 3H), 4.78 (dt, J = 3.1, 6.6 Hz, 1H), 1.94−1.82 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H).

2-Methyl-1-(2-naphthyl)-1-propanol (5):[50] prepared from magnesium (0.88 g, 36 mmol), 2-bromopropane (2.8 mL, 30 mmol), 2-naphthaldehyde (2.34 g, 15 mmol), and ether (15 mL); yield = 2.1 g (70%), R_f = 0.42 (6:1 hexane−ethyl acetate). ^{1}H NMR: δ 7.84−7.75 (m, 4H), 7.49−7.44 (m, 3H), 4.54 (dd, J = 7.1, 2.9 Hz, 1H), 2.14 (m, 1H), 1.94 (d, J = 3.2 Hz, 1H), 1.05 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H).

2-(2-Naphthyl)-2-butanol (6):[51] prepared from ethylmagnesium bromide (11.0 mL of a 1.28 M ethereal solution, 14 mmol), 2-acetonaphthenone (2.0 g, 12 mmol), and ether (15 mL); yield = 2.30 g (96%), R_f = 0.38 (6:1 hexane−ethyl acetate). ^{1}H NMR: δ 7.97 (m, 1H), 7.90−7.82 (m, 3H), 7.58 (dd, J = 1.7, 8.7 Hz, 1H), 7.52−7.49 (m, 2H), 1.96 (dq, J = 2.7, 7.3 Hz, 2H), 1.67 (s, 3H), 0.88 (t, J = 7.3 Hz, 3H).

3-Methyl-2-(2-naphthyl)-2-butanol (7): prepared from magnesium (1.03 g, 42.2 mmol), 2-bromopropane (3.3 mL, 35.2 mmol), 2-acetonaphthenone (3.0 g, 17.6 mmol), and ether (15 mL); yield = 1.89 g (50%), R_f = 0.39 (8:1 hexane−ethyl acetate). ^{1}H NMR: δ 7.88−7.36 (m, 7H), 2.08 (m, 1H), 2.02 (s, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H). ^{13}C NMR: δ 145.5, 133.2, 132.3, 128.2, 127.5, 127.4, 125.9, 125.6, 124.1, 123.7, 76.9, 38.5, 26.9, 17.6, 17.3. IR: 3478, 3060, 2978, 2876, 1923, 1678, 1630, 1599, 1504, 1459, 1385, 1273, 1132, 1080, 1037, 903, 819, 746. MS: 214 (M^+, 78.0), 196 (78.0), 181 (81.6), 171 (100.0), 165 (74.9), 155 (80.0), 141 (70.2), 128 (94.9), 115 (63.5), 101 (31.4), 89 (43.5), 77 (6.8), 63 (38.0), 51 (29.8). Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.13; H, 8.31.

Preparation of Vinylarenes 8−11. General Method. A solution of benzylic alcohol (ca. 0.5−0.7 M) and *p*-toluenesulfonic acid hydrate (10 mol %) in benzene was refluxed under N_2 until the starting material was no longer visible by TLC (ca. 0.5 h). The solution was cooled, diluted with ether, washed with saturated aqueous $NaHCO_3$ and water, dried over $MgSO_4$, and purified by flash chromatography.

***(E)*-1-(2-Naphthyl)propene (8):**[49] prepared from a solution of crude 1-(2-naphthyl)-1-propanol (**4**, 4.0 g, 21.0 mmol) and *p*-toluenesulfonic acid hydrate (0.39 g, 2.1 mmol) in benzene (30 mL); yield = 3.18 g (90%), R_f = 0.76 (9:1 hexane−ethyl acetate), mp 40−42 °C. ^{1}H NMR: δ 7.83−7.35 (m, 7H), 6.56 (dq, J = 15.8, 1.8 Hz, 1H), 6.37 (dq, J = 15.8, 6.6 Hz, 1H), 1.94 (dd, J = 6.6, 1.8 Hz, 3H).

2-Methyl-1-(2-naphthyl)propene (9):[52] prepared from a solution of 2-methyl-1-(2-naphthyl)-1-propanol (**5**, 5.48 g, 27.4 mmol) and *p*-toluenesulfonic acid hydrate (0.52 g, 2.7 mmol) in benzene (30 mL); yield = 4.9 g (91%), R_f = 0.49 (hexane). ^{1}H NMR: δ 7.81−7.66 (m, 4H), 7.45−7.35 (m, 3H), 6.42 (s, 1H), 1.96 (d, J = 1.5 Hz, 3H), 1.94 (d, J = 1.2 Hz, 3H).

***(E)*-2-(2-Naphthyl)-2-butene (10):**[53] prepared from a solution of 2-(2-naphthyl)-2-butanol (**6**, 1.0 g, 5.0 mmol) and *p*-toluenesulfonic acid hydrate (0.095 g, 0.5 mmol) in benzene (10 mL); yield = 0.69 g (76%), R_f = 0.87 (8:1 hexane−ethyl acetate). ^{1}H NMR: δ 7.95−7.41 (m, 7H), 6.02 (qq, J = 6.8, 1.4 Hz, 1H), 2.12 (pseudo dq, J = 0.97 Hz, 3H), 1.85 (dq, J = 6.8, 0.98 Hz, 3H).

3-Methyl-2-(2-naphthyl)-2-butene (11):[50] prepared from 3-methyl-2-(2-naphthyl)-2-butanol (**7**, 1.0 g, 4.7 mmol) and *p*-toluenesulfonic acid hydrate (0.09 g, 0.47 mmol) in benzene (10 mL); yield = 0.75 g (82%), R_f = 0.51 (petroleum ether). ^{1}H NMR: δ 7.83−7.79 (m, 3H), 7.68 (m, 1H), 7.51−7.43 (m, 2H), 7.31 (dd, J = 8.4, 1.9 Hz, 1H), 2.02 (s, 3H), 1.88 (s, 3H), 1.65 (s, 3H).

Preparation of Epoxides 12−15. General Method. A solution of the vinylarene in CH_2Cl_2 (0.2−0.4 M) was cooled to 0 °C, treated with MCPBA, and allowed to stir while warming to room temperature for approximately an hour. When TLC indicated completion of reaction, the mixture was worked up by diluting with diethyl ether, separating phases, and washing the organic phase with saturated aqueous $Na_2S_2O_3$ (2 × 10 mL), $NaHCO_3$ (3 × 10 mL), 5% NaOH (10 mL), and brine (10 mL), followed by drying over $MgSO_4$. After evaporation, the epoxide was purified by flash chromatography.

***trans*-3-Methyl-2-(2-naphthyl)oxirane (12):**[19] prepared from (*E*)-1-(2-naphthyl)propene (**8**, 0.50 g, 2.9 mmol) and MCPBA (0.84 g, 3.6 mmol, 73.4% pure) in CH_2Cl_2 (10 mL); yield = 0.45 g (81%), R_f = 0.53 (9:1 hexane−ethyl acetate), mp 56−57 °C. ^{1}H NMR: δ 7.83−7.76 (m, 4H), 7.50−7.45 (m, 2H), 7.32 (dd, J = 1.5, 8.6 Hz, 1H), 3.74 (d, J = 2.2 Hz, 1H), 3.14 (dq, J = 2.2, 5.3 Hz, 1H), 1.50 (d, J = 5.3 Hz, 3H).

3,3-Dimethyl-2-(2-naphthyl)oxirane (13): prepared from 2-methyl-1-(2-naphthyl)propene (**9**, 0.67 g, 3.7 mmol) and MCPBA (1.0 g, 4.4 mmol, 73.4% pure) in CH_2Cl_2 (10 mL); yield = 0.63 g (86%), R_f = 0.61 (6:1 hexane−ethyl acetate), mp 52−55 °C. ^{1}H NMR: δ 7.84−7.75 (m, 4H), 7.49−7.43 (m, 3H), 4.03 (s, 1H), 1.54 (s, 3H), 1.11 (s, 3H). ^{13}C NMR: δ 138.7, 133.2, 132.8, 128.1, 127.9, 127.6, 126.2, 125.9, 124.4, 123.2, 64.8, 61.4, 24.8, 18.1. IR: 2934, 2856, 1928, 1801, 1597, 1460, 1377, 1304, 1243, 1125, 954, 887, 756. MS: 198 (M^+, 98.0), 183 (74.5), 169 (84.7), 155 (94.9), 140 (100.0), 127 (89.4), 115 (46.3), 101 (23.9), 89 (49.8), 77 (50.6), 63 (47.8), 51 (26.7). Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.79; H, 7.22.

***trans*-2,3-Dimethyl-2-(2-naphthyl)oxirane (14):** prepared from (*E*)-2-(2-naphthyl)-2-butene (**10**, 0.43 g, 2.4 mmol) and MCPBA (0.67 g, 2.9 mmol, 73.4% pure) in CH_2Cl_2 (10 mL); yield = 0.33 g (75%), R_f = 0.53 (8:1 hexane−ethyl acetate), mp 51−53 °C. ^{1}H NMR: δ 8.09 (m, 1H), 7.89 (m, 3H), 7.50 (m, 3H), 4.28 (q, J = 6.8 Hz, 1H), 2.19 (s, 3H), 1.08 (d, J = 6.8 Hz, 3H). ^{13}C NMR: δ 140.6, 132.6, 128.2, 127.9, 127.6, 126.1, 125.8, 123.9, 123.2, 76.6, 62.5, 60.6, 21.5, 17.6, 14.5. IR: 2924, 2853, 1943, 1647, 1599, 1507, 1459, 1377, 1274, 1195, 1129, 1071, 858, 808, 744. MS: 198 (M^+, 67.6), 169 (77.6), 155 (100.0), 141 (48.9), 128 (51.0), 115 (29.5), 102 (4.8), 89 (4.1), 77 (12.7), 63 (6.9), 43 (12.1). Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.91; H, 6.96.

2,3,3-Trimethyl-2-(2-naphthyl)oxirane (15): prepared from 3-methyl-2-(2-naphthyl)-2-butene (**11**, 0.75 g, 3.8 mmol) and MCPBA (1.07 g, 4.6 mmol, 73.4% pure) in CH_2Cl_2 (10 mL); yield = 0.60 g (74%), R_f = 0.70 (6:1 hexane−ethyl acetate), mp 37−38 °C. ^{1}H NMR: δ 7.82−7.73 (m, 3H), 7.46−7.38 (m, 4H), 1.68 (s, 3H), 1.49 (s, 3H), 0.97 (s, 3H). ^{13}C NMR: δ 133.1, 132.5, 128.0, 127.8, 127.7, 127.6, 126.1, 125.6, 124.7, 124.4, 69.1, 63.9, 21.7, 21.4, 20.8. IR: 2978, 2863, 1989, 1636, 1603, 1460, 1377, 1190, 1069, 911. MS: 212 (M^+, 93.3), 197 (76.9), 169 (87.1), 152 (100.0), 141 (73.7), 127 (86.7), 115 (62.8), 101 (35.7), 89 (24.6), 77 (63.1), 63 (46.3), 51 (36.1). Anal. Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.83; H, 7.45.

1-Phenyl-10-undecen-1-ol (17).[19] A solution of phenylmagnesium bromide was prepared from magnesium (0.56 g, 23.0 mmol), bromobenzene (2.0 mL, 19.0 mmol), and diethyl ether (20 mL). The solution was cooled to 0 °C and treated dropwise with freshly distilled 10-undecenal (1.98 mL, 9.5 mmol) via syringe. The mixture was allowed to warm to room temperature with stirring, over 30 min, at which point no aldehyde was observed by TLC (the product alcohol showed R_f = 0.36 in 6:1 hexane−ethyl acetate). The mixture was poured onto ice, and the phases were separated; the organic layer was washed with saturated $NaHSO_4$ (20 mL), $NaHCO_3$ (3 × 20 mL), and brine (20 mL). After drying ($MgSO_4$) and evaporation, the crude product was distilled (155 °C at 5 mm) to afford 1.8 g (79%) of the alcohol. ^{1}H NMR: δ 7.33 (m, 5H), 5.81 (ddt, J = 17.1, 6.6, 7.0 Hz, 1H), 4.98 (d of m, J = 17.1 Hz, 1H), 4.92 (d of m, J = 12.3, 1H), 4.66 (t, J = 7.0 Hz, 1H), 2.03 (m, 2H), 1.74 (m, 2H), 1.26 (m, 12H).

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1,2-Epoxy-1-phenyl-10-undecene (18). A solution of **17** (1.0 g, 4.1 mmol) and *p*-TsOH (77.3 mg, 0.41 mmol) in benzene (10 mL) was refluxed for 2.5 h. The solution was cooled and diluted with diethyl ether and water (10 mL each), and the phases were separated. The organic layer was washed with $NaHCO_3$ (3 × 15 mL) and brine (20 mL), dried ($MgSO_4$), and evaporated. Chromatography gave 805 mg (86%) of 1-phenyl-1,10-undecadiene,[19] R_f = 0.64 (hexane). ^{1}H NMR: δ 7.32 (m, 5H), 6.37 (d, J = 15.8 Hz, 1H), 6.22 (dt, J = 15.8, 6.6 Hz, 1H), 5.81 (ddt, J = 17.1, 6.6, 7.0 Hz, 1H), 4.98 (d of m, J = 17.1 Hz, 1H), 4.92 (d of m, J = 12.3 Hz, 1H), 2.20 (dt, J = 7.9, 14.5 Hz, 2H), 2.04 (dt, J = 7.0, 14.1 Hz, 2H), 1.36 (m, 10H). 1,2-Epoxy-1-phenyl-10-undecene was prepared from the above diene (554 mg, 2.3 mmol) and MCPBA (0.81 g, 4.7 mmol, 73% pure) in CH_2Cl_2 (7 mL) using the general procedure described above; yield = 272 mg (46%) of the diepoxide, R_f = 0.38 (6:1 hexane−ethyl acetate), and 251 mg (43%) of the monoepoxide (**18**), R_f = 0.69 (6:1 hexane−ethyl acetate). ^{1}H NMR: δ 7.38−7.24 (m, 5H), 5.81 (ddt, J = 17.1, 6.6, 7.0 Hz, 1H), 4.98 (d of m, J = 17.1 Hz, 1H), 4.92 (d of m, J = 12.3 Hz, 1H), 3.60 (d, J = 2.2 Hz, 1H), 2.95 (dt, J = 2.2, 5.4 Hz, 1H), 2.05 (m, 2H), 1.67 (m, 2H), 1.51−1.34 (m, 10H). ^{13}C NMR: δ 139.2, 138.1, 128.5, 127.9, 125.6, 114.2, 63.1, 58.7, 33.8, 32.4, 29.4, 29.3, 29.1, 28.9, 25.9. IR: 3074, 3036, 2977, 2927, 2856, 1947 (w), 1891 (w), 1819 (w), 1640, 1605, 1497, 1461, 1437, 1351, 1308, 1247, 1202, 1072, 1020, 994, 909, 880, 750, 697. MS: 244 (M^+, 1.1), 228 (6.6), 153 (7.5), 135 (18.2), 117 (65.8), 104 (68.4), 91 (100), 83 (12.3), 69 (17.8), 55 (29.4). Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.59; H, 9.58.

***(E)*-11-Phenyl-10-undecen-1-ol.** A solution of alcohol **17** (1.7 g, 6.9 mmol) in THF (8 mL) was cooled to 0 °C in a Schlenk flask under nitrogen. BH_3·THF (17.0 mL, 1 M, 17 mmol) was added to the solution dropwise, and the mixture was warmed to room temperature. After 30 min at room temperature, the mixture was cooled to 0 °C, aqueous sodium hydroxide (3 M, 2.4 mL) was added, and the mixture was stirred at 0 °C for a further 30 min. Then 30% H_2O_2 (2.8 mL) was added to the mixture, which was then heated to 60 °C for 1 h, at which point TLC showed only the product. The reaction mixture was diluted with diethyl ether (20 mL) and washed with 1 M HCl (2 × 20 mL), water (3 × 10 mL), and brine (10 mL). The organic phase was dried ($MgSO_4$) to afford 1.8 g (99%) of crude product, which was recrystallized from 20 mL of 3:1 hexane−diethyl ether to provide 1.4 g (74%, mp 55 °C) of 1-phenyl-1,11-undecanediol.[54] ^{1}H NMR: δ 7.33 (m, 5H), 4.65 (t, J = 7.3 Hz, 1H), 3.63 (t, J = 6.6 Hz, 2H), 1.86−1.25 (m, 18H). A solution of the above diol (525 mg, 1.9 mmol) in 5 mL of THF and 5 mL of H_3PO_4 (85%) was refluxed for 45 min. After cooling, the mixture was diluted with diethyl ether (15 mL) and water (15 mL) and washed with $NaHCO_3$ (15 mL) and brine (15 mL). After drying ($MgSO_4$) and evaporation, the crude product was chromatographed (R_f = 0.48, 1:1 hexane−diethyl ether) to give 272 mg (56%) of (*E*)-11-phenyl-10-undecen-1-ol; mp 35−37 °C. ^{1}H NMR: δ 7.36−7.15 (m, 5H), 6.37 (d, J = 15.6 Hz, 1H), 6.21 (dt, J = 15.8, 6.6 Hz, 1H), 3.61 (t, J = 6.6 Hz, 2H), 2.19 (q, J = 6.6 Hz, 2H), 1.30 (m, 14H). ^{13}C NMR: δ 137.9, 131.1, 129.7, 128.4, 126.7, 125.9, 62.8, 32.9, 32.6, 29.7, 29.4, 29.3, 29.2, 29.0, 25.6. IR: 3251, 3025, 2923, 2853, 1947−1811 (w), 1664, 1599, 1577, 1466, 1377, 1073, 964, 898, 735, 691. MS: 246 (M^+, 100), 228 (7.7), 171 (2.9), 157 (4.2), 144 (6.4), 137 (2.9), 129 (13.7), 117 (12.6), 104 (48.9), 96 (4.6), 82 (7.4). Anal. Calcd for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 83.09; H, 10.82.

10,11-Epoxy-11-phenyl-1-undecanol (19): prepared from (*E*)-11-phenyl-10-undecen-1-ol (197 mg, 0.801 mmol), MCPBA (226 mg, 73.4%, 0.96 mmol), and CH_2Cl_2 (5 mL), using the general procedure described above; yield = 162 mg (77%); R_f = 0.29 (1:1 hexane−diethyl ether), mp 50−53 °C. ^{1}H NMR: δ 7.28 (m, 5H), 3.63 (t, J = 6.3 Hz, 2H), 3.61 (d, J = 2.2 Hz, 1H), 2.95 (dt, J = 2.2, 5.9 Hz, 1H), 1.69−1.17 (m, 16H). ^{13}C NMR: δ 137.8, 128.3, 127.8, 125.4, 63.1, 62.9, 58.6, 32.7, 32.3, 29.4, 29.3, 29.2, 29.1, 25.8, 25.7. IR: 3247, 3020, 2925, 2853, 1945−1811, 1599, 1466, 1377, 1073, 964, 898, 735, 691. MS: 244 ($M^+ - H_2O$, 3.9), 216 (25.7), 171 (45.8), 153 (92.9), 135 (65.1), 107 (100), 95 (21.1), 81 (26.8). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 78.21; H, 10.15.

11,12-Epoxy-12-phenyldodecanenitrile (20). A solution of (*E*)-11-phenyl-10-undecen-1-ol (1.3 g, 5.3 mmol) in pyridine (15 mL) was cooled to 0 °C and treated with *p*-toluenesulfonyl chloride (2.02 g, 11 mmol). The mixture was maintained at 0 °C for 1 h at which point TLC showed only the product (R_f = 0.44, 6:1 hexane−ethyl acetate). The mixture was poured onto 50 g of ice, which was extracted with diethyl ether (2 × 25 mL). The organic layer was washed with saturated $NaHSO_4$ (2 × 25 mL) and water (25 mL), dried ($MgSO_4$), and evaporated to give 1.87 g (89%) of crude (*E*)-11-phenyl-10-undecen-1-yl *p*-toluenesulfonate, which was sufficiently pure for the next step. ^{1}H NMR: δ 7.81−7.18 (m, 9H), 6.38 (d, J = 15.6 Hz, 1H), 6.22 (dt, J = 15.6, 6.6 Hz, 1H), 4.02 (t, J = 6.6 Hz, 2H), 2.44 (s, 3H), 2.19 (q, J = 6.8 Hz, 2H), 1.63−1.17 (m, 14H). ^{13}C NMR: δ 144.6, 137.9, 133.4, 131.1, 129.8, 129.7, 128.5, 127.9, 126.7, 125.9, 70.6, 32.9, 29.4, 29.2, 29.1, 28.9, 28.7, 28.6, 25.2, 21.4. IR: 3025, 2922, 2849, 1933, 1886, 1654, 1597, 1494, 1467, 1352, 1312, 1189, 1098, 1069, 959, 915, 864, 822, 746, 691, 662, 581, 552. MS: 246 ($M^+ - SO_2C_6H_4CH_3$, 6.0), 157 (22.0), 144 (4.3), 129 (11.8), 117 (24.9), 104 (100), 96 (5.9), 82 (11.2). A solution of the crude tosylate (1.72 g, 4.3 mmol) and NaCN (0.32 g, 6.5 mmol) in DMF (13 mL) was refluxed for 1 h, whereupon TLC showed only the nitrile (R_f = 0.38, 6:1 hexane−ethyl acetate). The mixture was partitioned between water and hexane (50 mL each) and separated; the organic layer was washed with water (25 mL), dried ($MgSO_4$) and evaporated to yield 970 mg (88%) of crude (*E*)-12-phenyl-11-dodecenenitrile, which was used directly in the next step. ^{1}H HMR: δ 7.37−7.19 (m, 5H), 6.38 (d, J = 15.4 Hz, 1H), 6.22 (dt, J = 15.9, 6.6 Hz, 1H), 2.32 (t, J = 7.1 Hz, 2H), 2.21 (q, J = 6.8 Hz, 2H), 1.70−1.17 (m, 14H). ^{13}C NMR: δ 137.9, 131.1, 129.7, 128.4, 126.6, 125.8, 119.7, 32.8, 29.1, 29.0, 28.9, 28.6, 28.5, 28.4, 25.1, 16.9. IR: 3025, 2926, 2854, 2245, 1945, 1875, 1802, 1650, 1598, 1494, 1465, 1351, 1086, 965, 744, 693. MS: 227 (M^+ − HCN − H, 1.7), 212 (3.4), 164 (12.4), 151 (27.5), 145 (7.2), 131 (22.5), 117 (44.9), 104 (100.0), 97 (2.6). A solution of the olefinic nitrile (943 mg, 3.7 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C and treated with MCPBA (1.05 g, 73%, 4.44 mmol). After warming to room temperature over 2 h, the mixture was worked up as described above, and the product was purified by flash chromatography (R_f = 0.29, 6:1 hexane−ethyl acetate), affording 520 mg (88%) of 11,12-epoxy-12-phenyldodecanenitrile (**20**). ^{1}H NMR: δ 7.38−7.25 (m, 5H), 3.61 (d, J = 1.9 Hz, 1H), 2.94 (dt, J = 2.2, 5.4 Hz, 1H), 2.33 (t, J = 6.8 Hz, 2H), 1.69−1.68 (m, 16H). ^{13}C NMR: δ 137.9, 128.3, 127.8, 125.4, 119.7, 63.0, 62.9, 58.4, 32.1, 29.2, 28.9, 28.4, 25.7, 25.5, 25.1, 16.8. IR: 3029, 2930, 2855, 2245, 1954, 1890, 1811, 1719, 1604, 1497, 1462, 1426, 1370, 1309, 1201, 1072, 1027, 882, 752, 699. MS: 271 (M^+, 4.1), 180 (100.0), 152 (39.2), 135 (7.4), 119 (14.1), 107 (38.8), 97 (13.6), 83 (5.1). Anal. Calcd for $C_{18}H_{25}NO$: C, 79.66; H, 9.28. Found: C, 79.95; H, 8.81.

Ethyl 10,11-Epoxy-11-phenylundecanoate (21). Using the general procedure reported in the literature,[55] a solution of chromium trioxide (0.77 g, 7.7 mmol) in 1 M H_2SO_4 (20 mL) was maintained between 5 and 10 °C while a solution of (*E*)-11-phenyl-10-undecen-1-ol (0.5 g, 2.03 mmol) in acetone (20 mL) was slowly added. The reaction mixture was stirred at rt for 4 h. Ether (50 mL) was added, and the mixture was washed with brine (3 × 50 mL). The organic phase was concentrated under reduced pressure and then taken up in ether (50 mL), which was extracted with 1 M NaOH (2 × 30 mL). The combined basic extracts were acidified with 6 M H_2SO_4 and back-extracted with ether (3 × 50 mL). The combined ethereal extracts were washed with water and brine, dried over $MgSO_4$, and concentrated to give 362 mg (69%) of crude (*E*)-11-phenyl-10-undecenoic acid. ^{1}H NMR: δ 7.34−7.13 (m, 5H), 6.36 (d, J = 15.6 Hz, 1H), 6.20 (dt, J = 15.9, 6.6 Hz, 1H), 4.04 (t, J = 6.6 Hz, 1H), 2.28 (t, J = 7.3 Hz, 2H), 2.18 (m, 2H), 1.69−1.17 (m, 12H). ^{13}C NMR: δ 173.7, 137.8, 130.9, 129.7, 128.3, 126.6, 125.8, 64.3, 34.3, 32.9, 29.3, 29.1, 28.6, 25.9,

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24.9. IR: 3500−2600 (broad), 3028, 2927, 2854, 1962−1885 (w), 1704, 1603, 1494, 1451, 1411, 1288, 1241, 1187, 1094, 1048, 964, 744, 693. MS: 242 ($M^+ - H_2O$, 5.0), 159 (2.5), 145 (6.8), 131 (20.3), 117 (25.0), 104 (100.0), 91 (7.3), 78 (3.7). A solution of this carboxylic acid (1.97 g, 7.58 mmol) in anhydrous ethanol (0.79 g, 1.0 mL, 0.017 mol) was treated with *p*-toluenesulfonic acid hydrate (0.29 g, 1.52 mmol) and refluxed for 1 h. After cooling, the mixture was diluted with ether and water (10 mL each) and washed with $NaHCO_3$ (10 mL) and brine (10 mL). After drying and evaporation, the crude product was chromatographed (R_f = 0.77, 6:1 hexane−ethyl acetate) to give 1.13 g (52%) of ethyl (*E*)-11-phenyl-10-undecenoate. ^{1}H NMR: δ 7.35−7.26 (m, 5H), 6.37 (d, J = 15.9 Hz, 1H), 6.22 (dt, J = 15.9, 6.6 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 2.29 (t, J = 7.1 Hz, 2H), 2.19 (m, 2H), 1.31−1.22 (m, 12 H), 1.25 (t, J = 7.1 Hz, 3H). IR: 3061, 3028, 2928, 2854, 1946, 1874, 1738, 1689, 1598, 1494, 1453, 1371, 1249, 1180, 1099. 1029, 964, 910, 735, 701. MS: 242 ($M^+ - C_2H_5OH$, 58.9), 224 (6.6), 214 (3.3), 200 (3.9), 173 (2.4), 155 (11.4), 145 (9.8), 131 (21.5), 117 (41.0), 104 (100.0), 91 (6.3). The ester (1.13 g, 3.92 mmol) was epoxidized with MCPBA (1.11 g, 4.71 mmol, 73% pure) in CH_2Cl_2 (10 mL) according to the above procedure; the usual workup and chromatography gave 950 mg (80%) of ethyl 10,11-epoxy-11-phenylundecanoate (**21**); R_f = 0.81 (6:1, hexane−ethyl acetate). ^{1}H NMR: δ 7.37−7.23 (m, 5H), 4.11 (q, J = 7.1 Hz, 2H), 3.59 (d, J = 1.9 Hz, 1H), 2.94 (td, J = 5.5, 2.2 Hz, 1H), 2.28 (t, J = 7.3 Hz, 2H), 1.71−1.19 (m, 16H), 1.24 (t, J = 7.3 Hz, 3H). ^{13}C NMR: δ 173.8, 137.9, 128.2, 127.8, 125.3, 63.0, 62.9, 59.9, 58.4, 34.1, 32.1, 29.1, 28.9, 25.7, 24.7, 23.6, 14.0. IR: 3062, 3029, 2931, 2855, 1950, 1881, 1730, 1689, 1604, 1497, 1452, 1371, 1303, 1246, 1180, 1099, 1029, 880, 752, 700. MS: 241 ($M^+ - C_2H_5O - H_2O$, 2.5), 213 (100.0), 199 (10.8), 183 (5.8), 167 (22.6), 155 (17.2), 134 (17.5), 121 (22.9), 108 (20.2), 91 (46.5).

11,12-Epoxy-12-phenyl-2-dodecanone (22). To a suspension of pyridinium chlorochromate (3.13 g, 0.145 mol) and Celite (6.3 g) in CH_2Cl_2 (20 mL) was added (*E*)-11-phenyl-10-undecen-1-ol (2.38 g, 9.67 mmol); the oxidation was complete after 2 h at rt, by TLC. The reaction mixture was diluted with 100 mL of pentane−ether (1:1) and filtered. After evaporation, chromatography gave 1.86 g (79%) of (*E*)-11-phenyl-10-undecenal;[56] R_f = 0.58 (6:1 hexane−ethyl acetate), mp 48−49 °C. ^{1}H NMR: δ 9.74 (t, J = 1.9 Hz, 1H), 7.36−7.17 (m, 5H), 6.37 (d, J = 15.9, 1H), 6.22 (dt, J = 15.9, 6.6 Hz, 1H), 2.19 (m, 2H), 1.42−1.30 (m, 14H), 1.17 (d, J = 6.1 Hz, 3H). To a cooled solution of methylmagnesium iodide (10 mL, 1.9 M in ether, 0.019 mol) was slowly added a solution of the above aldehyde (1.86 g, 7.59 mmol) in ether (5 mL). The reaction mixture was stirred at rt for 30 min at which point TLC indicated only the product alcohol (R_f = 0.28, 6:1 hexane−ethyl acetate). The reaction mixture was quenched with 15 mL of ice water, washed with saturated aqueous $NaHSO_4$ (3 × 15 mL), $NaHCO_3$ (3 × 15 mL), and brine (15 mL), and dried ($MgSO_4$). Evaporation of solvent gave 1.42 g (72%) of crude (*E*)-12-phenyl-11-dodecen-2-ol, which was sufficiently pure to continue with the next step. ^{1}H NMR: δ 7.35−7.15 (m, 5H), 6.37 (d, J = 15.9 Hz, 1H), 6.22 (dt, J = 15.9, 6.6 Hz, 1H), 2.19 (m, 2H), 1.42−1.30 (m, 14H), 1.17 (d, J = 6.1 Hz, 3H). ^{13}C NMR: δ 137.9, 131.1, 129.7, 128.4, 126.7, 125.9, 68.1, 68.0, 39.3, 33.0, 29.5, 29.4, 29.3, 29.2, 25.7, 23.4. IR: 3378, 3025, 2927, 2854, 1941−1798 (w), 1651, 1598, 1494, 1449, 1373, 1308, 1119, 1071, 963, 743, 692. MS: 243 ($M^+ - H_2O$, 18.2), 199 (3.1), 185 (8.4), 171 (9.1), 158 (8.1), 143 (15.6), 138 (86.1), 129 (69.1), 117 (23.5), 104 (67.9), 96 (44.2), 82 (26.7). The above alcohol (1.42 g, 5.44 mmol) was added to a mixture of PCC (1.76 g, 8.16 mmol) and Celite (3.52 g) in CH_2Cl_2 (10 mL). After 20 h at rt, the reaction mixture was worked up as described above; chromatography gave 867 mg (62%) of (*E*)-12-phenyl-11-dodecen-2-one; R_f = 0.59 (6:1 hexane−ethyl acetate). ^{1}H NMR: δ 7.36−7.15 (m, 5H), 6.37 (d, J = 15.9 Hz, 1H), 6.22 (dt, J = 15.9, 6.6 Hz, 1H), 2.41 (t, J = 7.3 Hz, 2H), 2.19 (m, 2H), 2.12 (s, 3H), 1.59−1.24 (m, 12H). ^{13}C NMR: δ 209.1, 137.8, 131.0, 129.6, 128.3, 126.5, 125.7, 43.7, 32.9, 29.7, 29.3, 29.2, 29.1, 29.0, 23.8, 23.7. IR: 3034, 2927, 2850, 1954, 1885, 1715, 1598, 1494, 1461, 1375, 1161, 1082, 965, 742, 694. MS: 242 ($M^+ - OH$, 100.0), 227 (4.6), 202 (4.0), 186 (8.9), 171 (7.8), 157 (9.4), 143 (20.2), 138 (31.4), 129 (68.6), 117 (37.3), 104 (86.8), 95 (36.3), 82 (60.3). The ketone (867 mg, 3.35 mmol) was dissolved in CH_2Cl_2 (10 mL), cooled to 0 °C, and epoxidized with MCPBA (950 mg, 73% pure, 4.02 mmol). After stirring at rt for 3 h, the mixture was worked up as described above; chromatography gave 718 mg (78%) of pure 11,12-epoxy-12-phenyl-2-dodecanone (**22**); R_f = 0.39 (6:1 hexane−ethyl acetate). ^{1}H NMR: δ 7.34−7.23 (m, 5H), 3.59 (d, J = 1.9 Hz, 1H), 2.93 (td, J = 5.5, 1.9 Hz, 1H), 2.41 (t, J = 7.6 Hz, 2H), 2.12 (s, 3H), 1.71−1.29 (m, 14H). ^{13}C NMR: δ 209.0, 137.8, 128.3, 127.8, 125.5, 63.1, 62.9, 58.5, 43.6, 32.2, 29.7, 29.2, 29.1, 29.0, 25.8, 23.7. IR: 2922, 2849, 1940−1790 (w), 1715, 1653, 1499, 1461, 1373, 1207, 1161, 1128, 870, 782, 757, 741, 700. MS: 241 ($M^+ - C_2H_4 - H_2O$, 1.7), 228 (19.7), 217 (6.5), 183 (100.0), 165 (6.4), 147 (12.8), 133 (3.3), 121 (6.0), 107 (10.1), 95 (6.2), 81 (5.4). Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 79.20; H, 9.58.

11,12-Epoxy-12-phenyl-1-dodecyne (23). The general procedure is taken from the literature.[57] To a clear solution of carbon tetrabromide (985 mg, 2.97 mmol) in CH_2Cl_2 (7 mL) in a Schlenk flask under a positive flow of N_2 was added triphenylphosphine (1.56 g, 5.94 mmol) to give an orangish red mixture. (*E*)-11-Phenyl-10-undecenal (364 mg, 1.49 mmol; see first step in the preparation of **22**) dissolved in CH_2Cl_2 (1 mL) was added, causing the color to change from orange to yellow. After stirring at rt for 30 min, TLC showed no starting material. The reaction mixture was diluted with pentane (30 mL) followed by filtration to remove triphenylphosphine oxide and evaporation of solvent. This step was repeated twice. The crude product was purified by chromatography to give (*E*)-1,1-dibromo-12-phenyl-1,11-dodecadiene (327 mg, 55%); R_f = 0.66 (6:1 hexane−ethyl acetate). ^{1}H NMR: δ 7.36−7.17 (m, 5H), 6.38 (t, J = 16.6 Hz, 1H), 6.22 (dt, J = 15.9, 6.6 Hz, 1H), 2.21 (m, 2H), 2.08 (m, 2H), 1.53−1.25 (m, 12H). ^{13}C NMR: δ 180.0, 138.7, 137.9, 130.9, 129.7, 128.3, 126.6, 125.8, 32.9, 32.8, 29.3, 29.2, 29.1, 29.0, 28.9, 27.7. IR: 3025, 2925, 2854, 1941−1796 (w), 1728, 1598, 1494, 1454, 1071, 1028, 963, 799, 743, 692. MS: 239 ($M^+ - Br_2$, 4.5), 185 (3.1), 171 (12.2), 157 (16.5), 143 (10.7), 131 (24.7), 117 (60.4), 104 (100.0), 91 (13.1). A solution of the dibromoalkene (296 mg, 0.74 mmol) in THF (4 mL) at −78 °C under nitrogen was treated with *n*-butyllithium (1.2 mL, 1.3 M in hexane, 1.6 mmol). After being stirred for 1 h at −78 °C, the reaction mixture was warmed to rt and maintained at rt for a further hour, at which point TLC showed only the product; R_f = 0.90 (6:1 hexane−ethyl acetate). The reaction mixture was diluted with hexane and water (10 mL each). The organic layer was separated, washed with brine (10 mL), and dried ($MgSO_4$). After evaporation of solvent, 177 mg (99%) of crude (*E*)-12-phenyl-11-dodecen-1-yne was obtained. ^{1}H NMR: δ 7.36−7.15 (m, 5H), 6.38 (d, J = 15.9 Hz, 1H), 6.22 (dt, J = 15.9, 6.6 Hz, 1H), 2.24−2.15 (m, 4H), 1.93 (t, J = 2.7 Hz, 1H), 1.52−1.26 (m, 12H). ^{13}C NMR: δ 137.9, 131.0, 129.7, 128.3, 126.6, 125.8, 97.4, 84.6, 67.9, 32.8, 29.2, 28.9, 28.6, 28.5, 28.4, 18.2. IR: 3312, 3095, 3061, 3028, 2932, 2855, 2118, 1944−1801 (w), 1649, 1598, 1494, 1449, 1071, 1029, 964, 743, 692, 631. MS: 240 (M^+, 35.2), 225 (2.0), 197 (7.7), 183 (23.9), 169 (33.2), 155 (33.7), 149 (68.3), 130 (86.1), 117 (89.6), 104 (100.0), 94 (41.6), 81 (35.2). The above enyne (149 mg, 0.62 mmol) was epoxidized with MCPBA (176 mg, 73% pure, 0.75 mmol) in CH_2Cl_2 (5 mL) according to the above procedure; chromatography gave 107 mg (67%) of pure 11,12-epoxy-12-phenyl-1-dodecyne (**23**); R_f = 0.76 (6:1 hexane−ethyl acetate). ^{1}H NMR: δ 7.38−7.24 (m, 5H), 3.60 (d, J = 1.9 Hz, 1H), 2.95 (td, J = 5.5, 2.2 Hz, 1H), 2.19 (td, J = 6.8, 2.9 Hz, 2H), 1.94 (t, J = 2.9 Hz, 1H), 1.69−1.25 (m, 14H). ^{13}C NMR: δ 137.9, 128.3, 127.8, 125.4, 97.4, 84.5, 67.9, 62.9, 58.4, 32.1, 29.2, 28.8, 28.5, 28.3, 25.7, 18.2. IR: 3310, 2931, 2856, 2117, 1962−1729 (w), 1605, 1497, 1462, 1071, 1027, 880, 750, 698, 627. MS: 199 ($M^+ - CH_2CCH - H_2O$, 1.7), 173 (9.9), 157

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(21.1), 143 (16.4), 131 (26.8), 107 (100.0), 93 (47.5), 81 (81.9). Anal. Calcd for $C_{18}H_{24}O$: C, 84.32; H, 9.43. Found: C, 84.11; H, 9.12.

1-Bromo-10,11-epoxy-11-phenylundecane (24). The general procedure is taken from the literature.[58] *N*-Bromosuccinimide (566 mg, 3.18 mmol) was slowly added to a solution of (*E*)-11-phenyl-10-undecen-1-ol (391 mg, 1.59 mmol) and triphenylphosphine (834 mg, 3.18 mmol) in DMF (3 mL). After 5 min at rt, TLC showed completion of reaction (the new product was observed at R_f = 0.86 in 6:1 hexane−ethyl acetate). Methanol (2 mL) was added to destroy the excess reagent. After a further 5 min, ether was added and the organic layer was washed with water, saturated $NaHCO_3$ (10 mL), and brine (10 mL) and dried ($MgSO_4$). After evaporation of solvent, the product was extracted twice into hexane, leaving a residue of triphenylphosphine oxide. After evaporation of solvent, 383 mg (78%) of crude (*E*)-1-bromo-11-phenyl-10-undecene was obtained, which was sufficiently pure for the next step. ^{1}H NMR: δ 7.36−7.15 (m, 5H), 6.38 (d, J = 15.9, 1H), 6.22 (dt, J = 15.9, 6.6 Hz, 1H), 3.41 (t, J = 6.8 Hz, 2H), 2.21 (m, 2H), 1.85 (m, 2H), 1.31−1.28 (m, 12H). ^{13}C NMR: δ 137.9, 131.1, 129.6, 128.3, 126.5, 125.8, 33.9, 32.8, 32.7, 29.3, 29.2, 29.0, 28.6, 28.0, 25.7. IR: 3070, 3025, 2927, 2854, 1948−1811 (w), 1727, 1654, 1598, 1494, 1448, 1369, 1308, 1259, 1199, 1070, 1027, 964, 743, 694. MS: 173 ($M^+ - C_4H_9Br$, 1.4), 159 (3.6), 145 (5.6), 131 (14.9), 117 (74.9), 104 (100.0), 91 (11.9), 81 (3.0). The above alkene (383 mg, 1.24 mmol) was epoxidized with MCPBA (350 mg, 73% pure, 1.48 mmol) in CH_2Cl_2 (5 mL) according to the general procedure described above; chromatography gave 356 mg (88%) of pure 1-bromo-10,11-epoxy-11-phenylundecane (**24**); R_f = 0.75 (9:1 hexane−ethyl acetate). ^{1}H NMR: δ 7.38−7.24 (m, 5H), 3.60 (d, J = 2.2 Hz, 1H), 3.40 (t, J = 6.8 Hz, 2H), 2.95 (td, J = 5.4, 2.2 Hz, 1H), 1.85 (m, 2H), 1.67 (m, 2H), 1.51−1.31 (m, 12H). ^{13}C NMR: δ 137.9, 128.3, 127.8, 125.4, 62.9, 58.5, 33.7, 32.8, 32.3, 29.3, 29.2, 29.1, 28.7, 28.1, 25.8. IR: 3031, 2929, 2855, 1962−1819 (w), 1728, 1617, 1497, 1461, 1378, 1307, 1260, 1175, 1072, 1027, 881, 751, 698. MS: 233 ($M^+ - CH_3Br$, 29.4), 217 (13.2), 175 (3.9), 161 (14.7), 133 (29.3), 107 (100.0), 91 (54.3), 83 (30.7). Anal. Calcd for $C_{17}H_{25}BrO$: C, 62.77; H, 7.75. Found: C, 62.74; H, 7.74.

Isomerization of Epoxides in Tables 1−3 General Method. To a small Schlenk flask was added $Pd(OAc)_2$ (0.05 equiv per substrate) and distilled, deoxygenated solvent (enough to make the final solution 0.1−0.3 M in substrate), followed by tri-*n*-butylphosphine (3 equiv per Pd) via microliter syringe. In the case of PPh_3, solid ligand was added to the flask prior to dissolution. The substrate was then added to the solution of the Pd(0) catalyst, and the mixture was refluxed under N_2, until TLC or GC indicated complete consumption of the substrate, or no further conversion. The product was isolated and purified by flash chromatography on silica gel, using the indicated solvent mixture. In some cases, mixtures of unreacted starting material and product were isolated by chromatography and analyzed by GC or ^{1}H NMR to determine extent of conversion. Specific amounts of reagents used for a representative synthesis of each carbonyl compound shown in Tables 1−3 are given below; spectroscopic characterization data follow.

2-Naphthylacetaldehyde (25):[59] prepared as in Table 1, entry 4, from 2-(2-naphthyl)oxirane (**1**, 50 mg, 0.29 mmol), $Pd(OAc)_2$ (3.3 mg, 14.7 μmol), PBu_3 (11.0 μL, 44.1 μmol), and *t*-BuOH (0.5 mL); yield = 49 mg (98%), R_f = 0.36 (6:1 hexane−ethyl acetate). ^{1}H NMR: δ 9.82 (t, J = 2.2 Hz, 1H), 7.86−7.79 (m, 3H), 7.68 (m, 1H), 7.52−7.45 (m, 2H), 7.32 (dd, J = 8.4, 1.8 Hz, 1H), 3.84 (d, J = 2.2 Hz, 2H).

1-(2-Naphthyl)propanone (26):[60] prepared as in Table 1, entry 5, from *trans*-3-methyl-2-(2-naphthyl)oxirane (**12**, 50 mg, 0.27 mmol), $Pd(OAc)_2$ (3.1 mg, 13.6 μmol), PPh_3 (10.7 mg, 40.8 μmol), and benzene (0.5 mL); yield = 46.0 mg (92%), R_f = 0.34 (6:1 hexane−ethyl acetate). ^{1}H NMR: δ 7.81−7.28 (m, 7H), 3.83 (s, 2H), 2.16 (s, 3H).

2-(2-Naphthyl)propanal (27):[61] prepared as in Table 1, entry 10, from 2-methyl-2-(2-naphthyl)oxirane (**2**, 50 mg, 0.27 mmol), $Pd(OAc)_2$ (3.1 mg, 13.6 μmol), PPh_3 (10.7 mg, 40.8 μmol), and *t*-BuOH (0.5 mL); yield = 46.3 mg (93%), R_f = 0.54 (6:1 hexane−ethyl acetate). ^{1}H NMR: δ 9.77 (d, J = 1.5 Hz, 1H), 7.88−7.81 (m, 3H), 7.68 (m, 1H), 7.51−7.48 (m, 2H), 7.32 (dd, J = 8.4, 1.9 Hz, 1H), 3.81 (dq, J = 1.5, 7.8 Hz, 1H), 1.54 (d, J = 7.1 Hz, 3H).

3-(2-Naphthyl)-2-butanone (28):[62] prepared as in Table 1, entry 15, from *trans*-2,3-dimethyl-2-(2-naphthyl)oxirane (**14**, 50 mg, 0.25 mmol), $Pd(OAc)_2$ (2.9 mg, 12.7 μmol), PBu_3 (9.5 μL, 38.1 μmol), and benzene (0.5 mL); yield = 34.5 mg (69%), R_f = 0.46 (6:1 hexane−ethyl acetate). ^{1}H NMR: δ 7.83−7.79 (m, 1H), 7.51−7.43 (m, 2H), 7.31 (dd, J = 8.4, 1.9 Hz, 1H), 3.89 (q, J = 6.8 Hz, 1H), 2.06 (s, 3H), 1.47 (d, J = 6.8 Hz, 3H).

1,2-Diphenylethanone (31):[9b] prepared as in Table 2, entry 7, from *cis*-stilbene oxide (**29**, 50 mg, 0.26 mmol), $Pd(OAc)_2$ (2.9 mg, 12.7 μmol), PBu_3 (9.5 μL, 38.2 μmol), and benzene (0.5 mL); yield = 49.7 mg (99%), R_f = 0.48 (6:1 hexane−ethyl acetate). ^{1}H NMR: δ 8.03−8.00 (m, 5H), 7.59−7.22 (m, 5H), 4.29 (s, 2H).

Diphenylacetaldehyde (32):[63] prepared as in Table 2, entry 9, from 2,2-diphenyloxirane (**3**, 50 mg, 0.26 mmol), $Pd(OAc)_2$ (2.9 mg, 12.8 μmol), PPh_3 (10.1 mg, 38.4 μmol), and *t*-BuOH (0.5 mL); yield = 1.3 mg (3%) of aldehyde (identified and quantified by ^{1}H NMR) and 41.8 mg (84%) of epoxide; R_f = 0.65 (6:1 hexane−ethyl acetate). ^{1}H NMR: δ 9.91 (d, J = 1.7 Hz, 1H), 4.89 (d, J = 1.7 Hz, 1H), 7.50−7.15 (m, 10H).

1-Phenyl-10-undecen-2-one (33). Isomerization of 1,2-epoxy-1-phenyl-10-undecene (**18**, 50 mg, 0.19 mmol) using $Pd(OAc)_2$ (2.1 mg, 9.5 mmol) and PBu_3 (7.1 mL, 28.6 mmol) in *t*-BuOH (0.5 mL) for 1 h gave the ketone (44 mg, 80%), R_f = 0.60 (6:1 hexane−ethyl acetate). ^{1}H NMR: δ 7.36−7.19 (m, 5H), 5.81 (ddt, J = 17.1, 6.6, 7.0 Hz, 1H), 4.98 (d of m, J = 17.1 Hz, 1H), 4.92 (d of m, J = 12.3 Hz, 1H), 3.67 (s, 2H), 2.44 (t, J = 7.1 Hz, 2H), 2.02 (m, 2H), 1.54 (m, 2H), 1.27−1.23 (m, 10H). ^{13}C NMR: δ 208.3, 138.9, 134.3, 129.3, 128.6, 126.8, 114.0, 50.0, 49.9, 41.8, 33.6, 28.8, 28.7, 23.6, 23.4. IR: 3065, 3030, 2958, 2857, 1946 (w), 1878 (w), 1825 (w), 1714, 1640, 1603, 1496, 1454, 1412, 1359, 1187, 1087, 1031, 995, 909, 699. MS: 244 (M^+, 1.7), 153 (84.5), 135 (100), 107 (36.7), 91 (87.4), 83 (69.6), 69 (80.7), 55 (77.8). Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.48; H, 9.99.

11-Hydroxy-1-phenyl-2-undecanone (34). Isomerization of 10,11-epoxy-11-phenyl-1-undecanol (**19**, 30 mg, 0.114 mmol) using $Pd(OAc)_2$ (1.3 mg, 5.7 μmol) and PBu_3 (4.3 μL, 17.2 μmol) in *t*-BuOH (0.5 mL) for 1 h gave the ketone (29 mg, 97%), R_f = 0.21 (1:1 hexane−diethyl ether). ^{1}H NMR: δ 7.35−7.18 (m, 5H), 3.68 (s, 2H), 3.63 (t, J = 6.4 Hz, 2H), 2.44 (t, J = 7.3 Hz, 2H), 1.54−1.16 (m, 14H). ^{13}C NMR: δ 208.4, 134.3, 129.3, 128.5, 126.8, 62.9, 60.1, 50.1, 41.9, 32.7, 29.2, 29.1, 28.9, 25.6, 23.7. IR: 3280, 2925, 2850, 1950, 1889, 1708, 1463, 1418, 1377, 1118, 1073, 1036, 1007, 952, 910, 750, 701. MS: 171 ($M^+ - C_6H_5CH_2$, 52.5), 153 (100.0), 135 (64.7), 111 (18.4), 97 (16.2), 83 (9.9).

11-Oxo-12-phenyldodecanenitrile (35). Isomerization of 11,12-epoxy-12-phenyldodecanenitrile (**20**, 50 mg, 0.185 mmol) using $Pd(OAc)_2$ (2.1 mg, 9.2 μmol) and PBu_3 (6.9 μL, 27.7 μmol) in *t*-BuOH (0.5 mL) for 40 min gave the ketone (40 mg, 80%), R_f = 0.19 (6:1 hexane−ethyl acetate). ^{1}H NMR: δ 7.36−7.19 (m, 5H), 3.68 (s, 2H), 2.44 (t, J = 7.3 Hz, 2H), 2.32 (t, J = 6.8 Hz, 2H), 1.71−1.24 (m, 14H). ^{13}C NMR: δ 208.3, 134.3, 129.3, 128.6, 126.8, 119.7, 50.1, 50.0, 41.9, 29.1, 28.9, 28.6, 25.3, 25.2, 23.6, 17.1. IR: 3064, 3030, 2931, 2858, 2245, 1970−1829 (w), 1731, 1603, 1498, 1463, 1425, 1364, 1187, 1113, 1066, 1031, 916, 730, 700. MS: 181 ($M^+ - C_6H_5CH_2 + H$, 37.3), 152 (78.9), 135 (8.5), 110 (4.6), 96 (6.2), 82 (2.8).

Ethyl 10-Oxo-11-phenylundecanoate (36). Isomerization of ethyl 10,11-epoxy-11-phenylundecanoate (**21**, 47 mg, 0.155 mmol) using $Pd(OAc)_2$ (1.7 mg, 7.8 μmol) and PBu_3 (5.8

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μL, 23.3 μmol) in *t*-BuOH (0.5 mL) for 45 min gave the ketone (45 mg, 96%), R_f = 0.80 (9:1 hexane−ethyl acetate). ^{1}H NMR: δ 7.36−7.19 (m, 5H), 4.12 (q, J = 7.3 Hz, 2H), 4.08 (s, 2H), 2.43 (t, J = 7.3 Hz, 2H), 2.27 (t, J = 7.3 Hz, 2H), 1.69−1.22 (m, 12H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 208.3, 173.7, 134.4, 129.3, 128.6, 126.8, 59.9, 49.9, 41.7, 34.1, 29.1, 29.0, 28.8, 25.6, 24.7, 23.4, 13.9. IR: 2932, 2856, 1968−1890 (w), 1732, 1603, 1498, 1371, 1181, 1098, 1032, 916, 733, 700. MS: 214 ($M^+ - C_6H_5CH_2 + H$, 12.4), 213 (100.0), 185 (3.1), 167 (6.3), 149 (7.5), 139 (16.3), 121 (8.0).

1-Phenyl-2,11-dodecanedione (37). Isomerization of 11,12-epoxy-12-phenyl-2-dodecanone (**22**, 50 mg, 0.182 mmol) using $Pd(OAc)_2$ (2.0 mg, 9.1 μmol) and PBu_3 (6.8 μL, 27.3 μmol) in *t*-BuOH (0.5 mL) for 25 min gave the ketone (49 mg, 98%), R_f = 0.27 (6:1 hexane−ethyl acetate); mp 50−52 °C. ^{1}H NMR: δ 7.36−7.18 (m, 5H), 3.67 (s, 2H), 2.43 (t, J = 7.3 Hz, 2H), 2.39 (t, J = 7.6 Hz, 2H), 2.13 (s, 3H), 1.53−1.24 (m, 12H). ^{13}C NMR: δ 209.1, 208.4, 134.3, 129.3, 128.5, 126.7, 50.1, 43.6, 41.8, 29.7, 29.2, 29.1, 29.0, 28.9, 23.7, 23.6. IR: 3031, 2930, 2856, 1956, 1895, 1713, 1603, 1481, 1454, 1409, 1365, 1259. MS: 274 (M^+, 3.6), 183 (100.0), 165 (3.9), 14.7 (15.1), 121 (4.1), 107 (10.2), 91 (64.9), 71 (19.1), 55 (48.0), 43 (81.4).

Kinetic Studies of the Isomerization of 29 and 30 to 31. A mixture of *trans*-stilbene oxide (**29**, 25 mg, 0.13 mmol), *cis*-stilbene oxide (**30**, 25 mg, 0.13 mmol), and hexadecane (3.7 μL) was isomerized as described above using the Pd(0) catalyst formed from $Pd(OAc)_2$ (2.9 mg, 12.7 μmol) and PBu_3 (9.5 μL, 38.1 μmol) in benzene (0.5 mL). Aliquots were removed periodically using a TLC pipet, filtered through silica gel, and analyzed by capillary GC. Amounts of **29**, **30**, and **31** were normalized by dividing the integrated area for each compound by the area of the internal standard. The data were subjected to a standard first-order kinetic treatment by plotting $\ln([\text{epoxide}]_0/[\text{epoxide}]_t)$ vs time; using the plotting program MacCurveFit (version 1.1), a slope was calculated, from which the pseudo-first-order rate constants were determined. The uncertainties on the rate constants were estimated by least-squares curve fitting available on the same program.

Kinetic Studies of the Isomerization of 12 to 26. Rate constants for the isomerization of *trans*-3-methyl-2-(2-naphthyl)oxirane (**12**) to 1-(2-naphthyl)propanone (**26**) were obtained as described above, in benzene and acetonitrile. In both cases, 29.5 mg (0.16 mmol) of substrate, 1.8 mg (8.1 μmol) of $Pd(OAc)_2$, 6.1 μL (24.4 μmol) of PBu_3, and 0.5 mL of solvent were employed.

Epoxide Isomerization Studies in Tables 4−6. General Method. For each entry in Tables 4−6, the appropriate catalyst or catalyst precursors were placed in a Schlenk tube and dissolved in the indicated solvent, the substrate was added, and the mixture was allowed to react at the specified temperature (ambient or reflux) for the indicated time period. The product and any unreacted starting material were isolated by flash chromatography on silica gel, quantified, and identified by the ^{1}H NMR data provided above.

Isomerization of 12 with BF_3·OEt_2. *trans*-3-Methyl-2-(2-naphthyl)oxirane (**12**, 50 mg, 0.27 mmol) was dissolved in benzene (2 mL) and stirred at room temperature under a positive flow of nitrogen. Freshly distilled boron trifluoride etherate (50 μL, 0.41 mmol) was added to the flask, and the reaction was left for 24 h. The reaction mixture was quenched with 1 M NaOH and extracted with ether; the extracts were dried ($MgSO_4$) and evaporated and the product purified by flash chromatography (6:1 hexane−ethyl acetate); yield = 35 mg (70%) of ketone **26**, identified by ^{1}H NMR.

Isomerization of 14 with BF_3·OEt_2. *trans*-2,3-Dimethyl-2-(2-naphthyl)oxirane (**14**, 50 mg, 0.25 mmol) was dissolved in benzene (2 mL) and treated with BF_3·OEt_2 (50 μL, 0.41 mmol) under the same conditions as described above. Purification by flash chromatography (6:1 hexane−ethyl acetate) gave 33.0 mg (66%) of a mixture of ketone **28** (R_f = 0.46) and aldehyde **38** (R_f = 0.41). The product ratio was estimated as 74% ketone **28** (49% yield) and 26% aldehyde **38** (17% yield) by capillary GC, and the products were identified by ^{1}H NMR. Characterization of **38**. ^{1}H NMR: δ 9.61 (s, 1H), 7.89−7.26 (m, 7H), 1.57 (s, 6H). MS: 198 (M^+, 83.1), 169 (100), 155 (100), 141 (81.9), 128 (79.6), 115 (69), 101 (13.2), 89 (11.5), 77 (45.5), 63 (24.3), 51 (16.4), 43 (51.8).

2-Phenylcyclohexanone (39).[64] 1-Phenyl-1,2-epoxycyclohexane (**16**, 50 mg, 0.29 mmol) was isomerized as described above, using $Pd(OAc)_2$ (8.9 mg, 14.3 μmol) and PBu_3 (10.7 μL, 42.9 μL) in refluxing *t*-BuOH (0.5 mL) for 3.5 h, giving 44.6 mg (89%) of 2-phenylcyclohexanone, R_f = 0.41 (6:1 hexane−ethyl acetate), as identified by ^{1}H NMR: δ 7.42−7.11 (m, 5H), 3.61 (dd, J = 5.1, 5.6 Hz, 1H), 2.51 (m, 2H), 2.35−1.81 (m, 6H).

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Supporting Information Available: Additional spectroscopic data for known compounds described in this work (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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