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Titanocene catalyzed opening of oxetanes

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ABSTRACT

The reductive opening of oxetanes by Cp_2TiCl was investigated by a combined synthetic and computational study. The activation and reaction energies predict a more difficult reaction than the related epoxide opening. Synthetically, the γ-titanoxy radicals obtained behave like typical free radicals. Their reactions are not controlled by the metal and its ligands. This is highlighted by the dimerization of phenyl substituted oxetane derived radicals.

1. Introduction

Strained heterocycles that can be opened through radical chemistry are highly versatile and often readily available radical precursors. This is because a large driving force for the ring opening is provided by the release of strain. It is possible to generate three important intermediates in this manner: heteroatom-centered radicals, carbon-centered radicals, and radical anions. While numerous efficient applications of classical radical chain reactions have emerged, the opening of heterocycles through electron transfer has attracted attention only more recently.[1]

In this context, epoxides were first opened by solvated electrons.[2] This concept has been further developed by Bartmann,[3] Cohen,[4] and Yus[5] who have employed aromatic radical anions as the reducing agents in many synthetically useful applications. However, the initially formed radical is rapidly reduced further to give carbanionic species. The mechanism of this epoxide opening through electron transfer has been studied computationally.[6]

Oxetane opening proceeds much slower under these conditions[7,8] but can be accelerated through activation by Lewis acids. The radicals initially formed are reduced to organolithium species. These intermediates can be used in the typical manner. The advantages of radical chemistry remain untapped by this approach.

With respect to the utilization of the intermediate radicals for organic synthesis the use of low valent metal complexes is more promising.[9] This was first demonstrated by Nugent and Rajan-Babu,[10] who introduced Cp_2TiCl as a reagent for reductive epoxide opening. Typical radical reactions, such as 5-*exo* cyclizations,[10a] intermolecular additions to acrylates,[10b] and H-atom abstraction from 1,4-cyclohexadiene,[10c] were realized. The mechanistic idea (Fig. 1) is based on the similarity of the metal bound epoxide with the cyclopropylcarbinyl radical that swiftly opens the ring.[11]

After the introduction of reaction conditions catalytic in titanocene[12] the field has developed rapidly in the last decade[1,13] and a number of unusual and pertinent applications, such as enantioselective radical generation,[14] unusual cyclizations,[15] tandem processes,[16] and epoxypolyene cyclizations via radicals,[17] have appeared. Other reagents have, as yet, proven to be inferior.[18] Moreover, Cp_2TiCl has been used as reagent or catalyst in a number of other important reactions, such as transformations of ketyl radicals,[19] allylations,[20] benzylations,[20,21] Reformatsky type transformations,[22] and reductive couplings of allyl halides.[23]

The mechanism of epoxide opening has been studied by a combination of computational, electrochemical, and synthetic methods.[24] Surprisingly, the exothermicity of ring opening that proceeds via a homolytic substitution is rather low. In the absence of the release of strain as driving force for C–O bond cleavage, C–O bonds can indeed be formed by attack of alkyl radicals on Ti–O bonds as has been demonstrated by the synthesis of tetrahydrofuran derivatives.[25] This unusual homolytic substitution reaction that is shown in Figure 2 may even be regarded as an organometallic analog of the oxygen-rebound step of the P450 enzymes.[26]

Here, we report on the use of oxetanes as substrates in titanocene catalyzed electron transfer reactions as shown in Figure 3. This

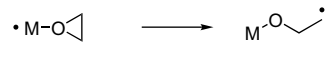

Figure 1. Analogy of epoxide opening to cyclopropylcarbinyl radical opening.

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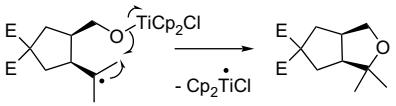

Figure 2. THF formation via homolytic substitution.

transformation is interesting for two reasons. First, it is important to understand how oxetanes behave in metal mediated electron transfer reactions compared to epoxides and tetrahydrofurans and second, for applications in synthesis, the γ-titanoxy radicals generated through ring opening constitute a potentially interesting class of functionalized radicals. To achieve both goals, we carried out a combined experimental and theoretical study of oxetane opening. To the best of our knowledge no such study has appeared in the literature, as yet.

2. Results

2.1. Computational investigations

In order to obtain data that can be readily compared to our study of the titanocene mediated epoxide opening, the same computational methods were employed. Thus, the complexation of two oxetanes by Cp_2TiCl, the activation and reaction energies of ring opening, and the structures of all pertinent intermediates, transition states, and products were studied by density functional theory (DFT) calculations with the BP functional and a TZVP basis set.[27] This pure density functional is suited for the description of reactions of transition metal compounds and has been successfully used in the literature for chemically similar systems.[28] One must be aware, however, that the absolute barriers of radical reactions predicted by this method are usually too low.[29] Since we are mainly interested in the comparison of reactivities of various oxetanes, this systematic error seems acceptable and does not affect the conclusions of our work. We did not investigate the reactions of the half-open Cp_2TiCl dimer[30] with oxetanes as the results with this species did not provide additional qualitative insight into the mechanism of epoxide opening.

The results of these DFT calculations of the complexation of 2,2-dimethyl oxetane (**1**) and 2-methyl-2-phenyl oxetane (**2**) and the ring opening of their respective complexes **1a** and **2a** are summarized in Figure 4.

As expected, replacement of THF from Cp_2TiCl is more favorable for the sterically less demanding **1** than for **2** containing the larger phenyl substituent.

The activation energies of ring opening to yield the primary radicals **1b** and **2b** (19.0 and 17.1 kcal mol^{-1}) are substantially higher than those calculated for generation of primary radicals from epoxides (about 9 kcal mol^{-1}). This constitutes a clear reflection of the stronger steric interaction of the substituents of the tertiary carbon with the cyclopentadienyl ligands in both transition structures of oxetane opening. The activation energy for the formation of the tertiary radical **1c** (9.7 kcal mol^{-1}) is much lower than that for **1b** but still noticeably higher for the corresponding epoxide (7.0 kcal mol^{-1}).[24]

Due to the very low activation energies, the generation of the benzylic radical **2c** will be substantially faster than the formation of

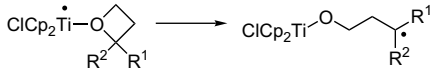

Figure 3. Titanocene mediated oxetane opening investigated in this study.

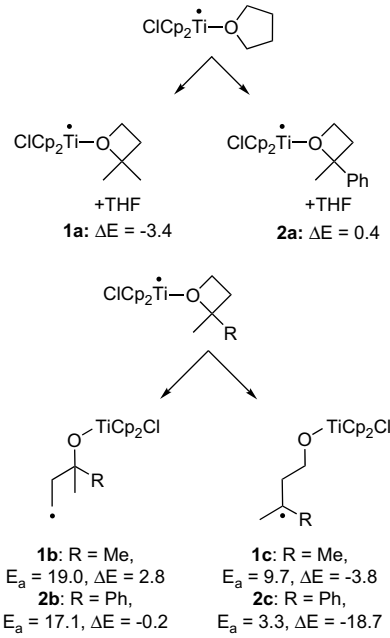

Figure 4. Computational results of the complexation and opening of **1** and **2**. All energies are in kcal mol^{-1}.

1c. The transition states **TS2b** and **TS2c** (Fig. 5) are relatively early and hence the C–O bonds are to a large degree still intact. Of course, in **TS2b** the C–O distance is longer (1.98 Å) than in **TS2c** (1.82 Å). Thus, only some but not the full stabilization of the benzylic radical is available for rendering **TS2c** more favorable. The second contribution to the lowering of **TS2c**, that is shown in Figure 5, is constituted by the reduction of steric interactions between the phenyl group and the upper cyclopentadienyl ligand. At present it is not possible to quantify the relative magnitude of the steric and electronic effects on **TS2c**.

In summary, oxetane opening is predicted to proceed slower but more selectively than the corresponding reactions of the epoxides. Moreover, under the reaction conditions used here oxetane cleavage will occur irreversibly as typical radical transformations are much faster than ring closure of the γ-titanoxy radicals.

Thermodynamically, formation of the primary radicals is clearly disfavored and thermoneutral (**1b**, −0.2 kcal mol^{-1}) or even endothermic (**2b**, +2.8 kcal mol^{-1}). The generation of the tertiary radical **1c** is slightly exothermic (−3.8 kcal mol^{-1}). As expected for electronic reasons, formation of the benzylic radical **2c** is substantially more advantageous. Again, ring opening of the corresponding epoxides is more favorable. An important structural

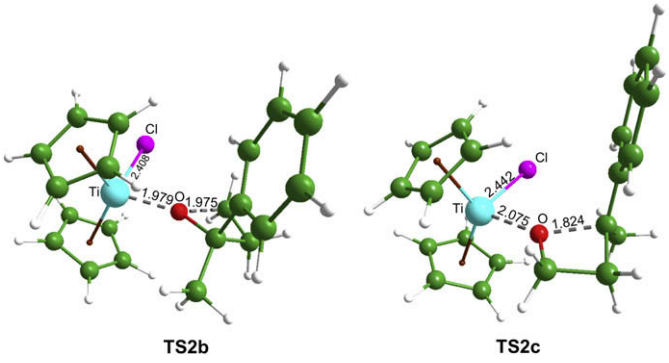

Figure 5. Transition states **TS2b** and **TS2c**.

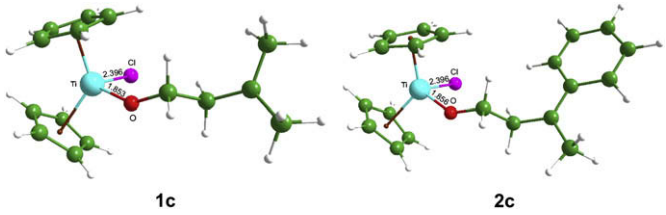

Figure 6. Calculated structures of **1c** and **2c**.

difference of the γ-titanoxy radicals **1c** and **2c** to epoxide derived β-titanoxy radicals is apparent from Figure 6.

The most favorable conformations of **1c** and **2c** are fairly stretched out to avoid steric interactions between the cyclopentadienyl ligands and the radicals. Hence, the γ-titanoxy radicals investigated here are not shielded by titanocene as the β-titanoxy radicals are. Therefore, their reactions will most likely resemble those of classical free radicals and are predicted not to be controlled by the metal and its ligands.

2.2. Synthetic investigations

As the computational results suggest that ring opening with aryl substituted oxetanes proceeds swiftly, we decided to employ such substrates first. However, the formation of benzylic radicals in titanocene mediated or catalyzed reactions may also lead to problems. This is because the typically employed trapping reagents, such as 1,4-cyclohexadiene or acrylates, react only slowly with these stabilized intermediates.[10,12] Hence, potentially undesired pathways, such as radical reduction by a second equivalent of the titanocene, may interfere.

Our results with the three aryl substituted oxetanes **3**–**5** are summarized in Figure 7. In the absence of external trapping agents, such as 1,4-cyclohexadiene or *tert*-butyl acrylate a reductive oxetane dimerization to **6**–**8** was observed that proceeded with low diastereoselectivity.

Thus, the intermediate γ-titanoxy radicals are not reduced by a second Cp_2TiCl but combine fast enough to form a hexasubstituted

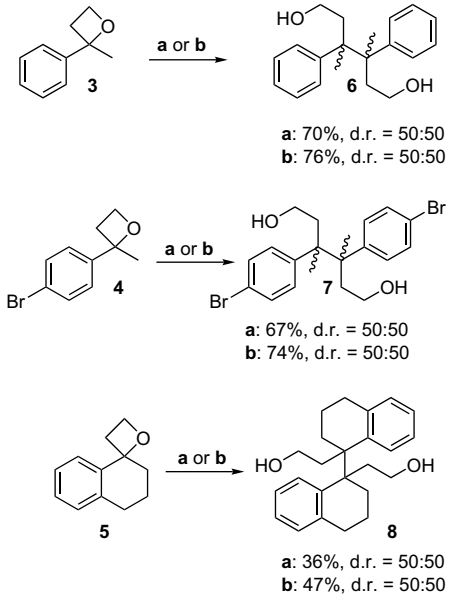

Figure 7. Reductive dimerization of oxetanes. (**a**) 20 mol % Cp_2TiCl_2, Mn, 2.5 equiv Coll·HCl; (**b**) 20 mol % Cp_2TiCl_2, Mn, 7 equiv Coll, 4 equiv Me_3SiCl.

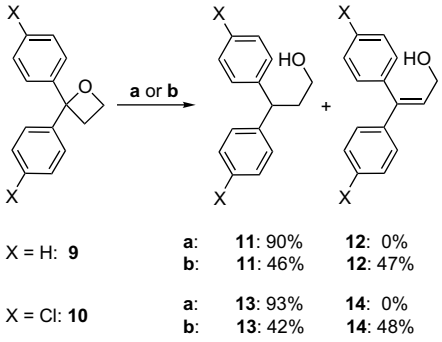

Figure 8. Reductive opening of diaryl substituted oxetanes in the presence or absence of collidine hydrochloride. (**a**) 20 mol % Cp_2TiCl_2, Mn, 2.5 equiv Coll·HCl; (**b**) 20 mol % Cp_2TiCl_2, Mn, 7 equiv Coll, 4 equiv Me_3SiCl.

C–C bond. It should be noted that this order of events is taking place under both conditions described for the regeneration of Cp_2TiCl from titanocene alkoxides.[12]

In order to understand the influence of the oxetane's substitution pattern on this peculiar reaction, we submitted the diaryl substituted oxetanes **9** and **10** to both catalytic conditions for ring opening (Fig. 8).

With the protic system for Cp_2TiCl generation (conditions **a**) the saturated alcohols **11** and **13** were obtained in high yield. Thus, the presence of the second aryl group effectively prevents dimerization. We suggest reductive trapping of the intermediate radical by a second equivalent of the titanocene and protonation of the Ti–C bond as mechanism for product formation.

Yet another reaction takes place in the presence of Coll·$SiMe_3Cl$ (conditions **b**), that silylates Ti–O bonds. In this case, mixtures of the saturated alcohols **11** and **13** with the respective allylic alcohols **12** and **14** were obtained that could be separated by column chromatography. As no source of protons is available under these conditions, the saturated alcohols must have formed through a H-atom abstraction. We suggest the mechanism shown in Figure 9 for the formation of **11** and **13** from **9**.

After the oxetane opening, that constitutes the slowest step in the sequence, and reductive trapping of **15** by Cp_2TiCl, the allylic alkoxide **16** is formed through β-hydride elimination. During this step, Cp_2TiClH is formed that should constitute a very powerful and fast H-atom donor. Reduction of radical **15** by this complex will be faster than reduction of **15** with Cp_2TiCl and generates **17**. In support of this proposal, we note that the closely related Schwartz reagent Cp_2ZrClH[31] has already been demonstrated to be a potent

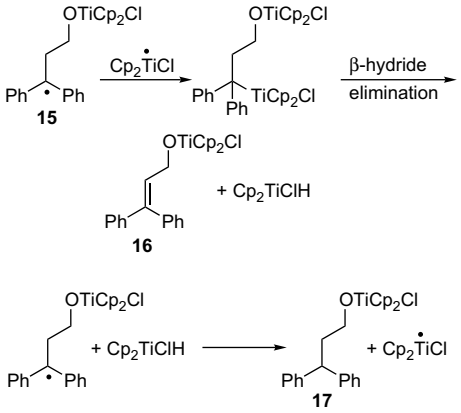

Figure 9. Mechanism of the formation of **16** and **17** from **15** in the absence of acid.

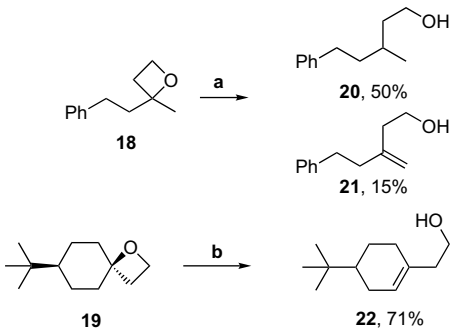

Figure 10. Reductive opening of the alkyl substituted oxetanes **18** and **19**. (**a**) 20 mol % Cp_2TiCl_2, Mn, 2.5 equiv Coll·HCl, 10 equiv 1,4-C_6H_8; (**b**) 20 mol % Cp_2TiCl_2, Mn, 7 equiv Coll, 4 equiv Me_3SiCl.

H-atom donor.[32] Silylation and protic work-up yields **11** and **12**. An alternative mechanism based on the mixed disproportionation of radicals has recently been proposed by Cuerva et al.[33] Currently, we are unable to rule out either of these two pathways.

The final reductive openings of oxetanes were carried out with **18** and **19** under the conditions shown in Figure 10.

In the case of the reaction of **18** that was carried out under similar conditions as typical reductive epoxide openings a relatively low yield of 50% **20** was obtained. Moreover, the product of the β-hydride elimination pathway **21** was also obtained in 15% yield together with 20% of recovered starting material. Thus, even in the presence of 10 equiv of 1,4-cyclohexadiene radical reduction by Cp_2TiCl is competing. With lower amounts of titanium the conversion is even worse. This is a clear indication of the relatively difficult oxetane opening as predicted by the computational results. As reductive trapping of the radicals by titanium is rather efficient, we also investigated the aprotic conditions for oxetane with the sterically less hindered substrate **19**. Gratifyingly, **22** could be obtained as the sole product of the reaction in 71% isolated yield. However, this result also suggests that the formation of C–C bonds either by intermolecular addition to acrylates or by cyclization reactions will be difficult.

To test this notion, we investigated the reaction of **18** with *tert*-butyl acrylate under the protic and silylating conditions for Cp_2TiCl regeneration as summarized in Figure 11.

Under both conditions the yield of the desired **23** is only modest and **21** was also obtained in 10–20% yield. Even with 10 equiv of radical trap the usually very swift addition to acrylates is not able to fully suppress the reductive trapping of the intermediate radical. Thus, as opposed to the epoxide derived β-titanoxy radicals, oxetane derived γ-titanoxy radicals are not suitable for the efficient formation of C–C bonds. Unfortunately, this was also observed in a number of attempted 5-*exo* cyclizations.

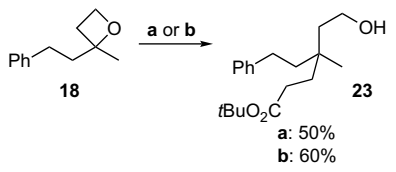

Figure 11. Reductive opening of the alkyl substituted oxetanes **18** and **19**. (**a**) 20 mol % Cp_2TiCl_2, Mn, 2.5 equiv Coll·HCl, 10 equiv *tert*-butyl acrylate; (**b**) 20 mol % Cp_2TiCl_2, Mn, 7 equiv Coll, 4 equiv Me_3SiCl, 10 equiv *tert*-butyl acrylate.

3. Conclusion

In summary, we have described the first opening of oxetanes by a low valent metal complex and have studied the mechanism of ring opening with the aid of computational chemistry. Oxetane opening proceeds slower and less exothermic than the related epoxide opening. The resulting γ-titanoxy radicals are not shielded by the metal and its ligands and therefore behave like typical free radicals. This was demonstrated by their dimerization reactions, reductions, and additions to acrylates.

4. Experimental section

All reactions were performed in oven-dried (100 °C) glassware under Ar. THF was freshly distilled from K. CH_2Cl_2 was freshly distilled from CaH_2. The products were purified by flash chromatography on Merck silica gel 50 (eluents given in brackets, EA refers to ethyl acetate, CH to cyclohexane) according to the procedure of Still.[34] Yields refer to analytically pure samples. Isomer ratios were determined by suitable ^1H NMR integrals of cleanly separated signals. NMR: Bruker DRX 300, AMX 300, AM 400; DRX500 ^1H NMR, $CHCl_3$ (7.26 ppm) or C_6D_5H (7.16 ppm) in the indicated solvent as internal standard in the same solvent; ^{13}C NMR, $CDCl_3$ (77.16 ppm) or C_6D_6 (128.06 ppm) as internal standard in the same solvent;[35] integrals in accordance with assignments, coupling constants are measured in hertz and always constitutes *J*(H,H) coupling constants. IR spectra: Perkin–Elmer 1600 series FT-IR and Thermo Nicolet 380 as neat films on KBr plates or via ATR measurements. Mass Spectrometry: EI Thermoquest Finningan MAT 95 XL, calibration against PFK; ESI Bruker Daltonics microTOF-Q, calibration against HCO_2Na. Combustion analytics was performed on a vario microcube from Elementar, Hanau.

Oxetanes **3**,[36] **9**,[36] and **19**[36] were prepared according to literature procedures. Alcohol **11** is commercially available.

4.1. General procedures for the preparation of oxetanes

4.1.1. GP1

A solution of *t*-BuOK (4.848 g, 40.0 mmol) and trimethylsulfoxonium iodide (8.803 g, 40.0 mmol) in dry *t*-BuOH (30 mL) was stirred at 50 °C for 1 h. Then, a solution of the ketone (10.0 mmol) in 5 mL of dry *t*-BuOH was added, and the new mixture was heated at 50 °C for 2 days. Then, the solvent was removed, water was added and the mixture was extracted with *t*-BuOMe, dried over $MgSO_4$, and the solvent was removed. The residue was purified by flash chromatography (mixtures of CH–EA).

4.1.2. GP2

To a stirred suspension of NaH (791 mg, 33.0 mmol) in 100 mL of dry DMSO, *S,S*-dimethyl-*N*-(4-tolylsulfonyl)sulfoximine (8.155 g, 33.0 mmol) was added and the suspension was stirred for 2 h at 47 °C. The ketone (10.0 mmol) was dissolved in 30 mL of dry DMSO and then was added to the mixture, and the stirring was continued for 48 h at 55 °C. Then, the reaction was cooled at rt, water was added, and the mixture was extracted with Et_2O (3×50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed. The residue was purified by flash chromatography (mixtures of CH–EA).

*4.1.3. 2-(4-Bromophenyl)-2-methyloxetane (**4**)*

(CH–EA 90:10) GP1: (1.596 g, 7.0 mmol, 70%), colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ=7.48 (d, *J*=8.7 Hz, 2H), 7.26 (d, *J*=8.7 Hz, 2H), 4.62 (ddd, *J*=8.6, 6.4, 6.3 Hz, 1H), 4.50 (ddd, *J*=8.6, 6.9, 6.0 Hz, 1H), 2.80 (ddd, *J*=10.7, 8.6, 6.9 Hz, 1H), 2.69 (ddd, *J*=10.7, 8.7, 6.6 Hz, 1H), 1.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=147.3, 131.3, 125.6, 120.6, 86.2, 64.5, 35.6, 30.5; IR (film) ν=2975, 2880, 1485, 1395, 1260, 1085, 1010, 820; EIHRMS calcd for $C_{10}H_{11}OBr$ 225.9993, found 225.9990.

*4.1.4. 3,4-Dihydro-2H-spiro(naphthalene-1,2′-oxetane) (**5**)*

(CH–EA 90:10) GP1: (1.010 g, 5.8 mmol, 58%), colorless oil. ^{1}H NMR (400 MHz, C_6D_6) δ=8.01 (d, J=7.8 Hz, 1H), 7.22 (dd, J=7.6, 7.6 Hz, 1H), 7.08 (dd, J=7.5, 7.5 Hz, 1H), 6.88 (d, J=7.8 Hz, 1H), 4.35–4.46 (m, 2H), 2.35–2.53 (m, 3H), 2.14 (ddd, J=10.8, 8.3 Hz, J=6.2 Hz, 1H), 2.08 (ddd, J=12.5, 6.3, 3.0 Hz, 1H), 1.97 (ddd, J=12.3, 12.1, 3.1 Hz, 1H), 1.55–1.65 (m, 1H), 1.35–1.45 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ=142.6, 136.3, 128.5, 127.6, 127.2, 126.7, 84.9, 64.4, 37.2, 32.2, 29.5, 19.7; IR (film) ν=2930, 1485, 1455, 1305, 1225, 980, 850, 755. HRMS (EI, 70 eV) calcd for $C_{15}H_{14}O$ [M] 174.1045, found 174.1047.

*4.1.5. 2,2-Bis(4-chlorophenyl)oxetane (**10**)*

(CH–EA 90:10) GP1: (1.956 g, 7.0 mmol, 70%), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.32 (s, 8H), 4.65 (t, J=7.7 Hz, 2H), 3.17 (t, J=7.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=144.9, 133.3, 128.7, 126.6, 88.1, 65.5, 36.0; IR (film) ν=2965, 2895, 1490, 1400, 1235, 1090, 1010, 975, 810; EIHRMS calcd for $C_{15}H_{12}OCl_2$ 278.0265, found 278.0270.

*4.1.6. 2-Methyl-2-phenethyloxetane (**18**)*

(CH–EA 85:15) GP2: (1.058 g, 6.0 mmol, 60%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.31–7.26 (mdd, J=7.5, 7.4 Hz, 2H), 7.25–7.16 (mdd, J=7.7, 7.1 Hz, 3H), 4.53 (ddd, J=12.9, 8.8, 6.2 Hz, 1H), 4.47 (ddd, J=12.6, 8.8, 6.2 Hz, 1H), 2.74 (ddd, J=12.6, 6.2, 2.5 Hz, 1H), 2.72 (ddd, J=12.6, 6.2, 2.5 Hz, 1H), 2.50 (ddd, J=10.9, 8.8, 6.8 Hz, 1H), 2.36 (ddd, J=10.9, 8.8, 6.8 Hz, 1H), 2.03–1.97 (md, J=6.7 Hz, 2H), 1.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=142.3, 128.5, 128.4, 125.8, 86.3, 64.3, 44.0, 32.4, 30.0, 27.4; IR (film) ν 3445, 3025, 2965, 2875, 1605, 1495, 1450, 1375, 1255, 1065, 960, 855, 750, 700; EIHRMS calcd for $C_{12}H_{16}O$ 176.1201, found 176.1197.

4.2. General procedures for the opening of oxetanes

4.2.1. GP3

Strictly deoxygenated THF (15 mL) was added to a mixture of Cp_2TiCl_2 (50 mg, 0.2 mmol), Mn dust (440 mg, 8.0 mmol), and collidine hydrochloride (396 mg, 2.5 mmol) under Ar atmosphere and the suspension was stirred at rt until it turned green (about 15 min). Then, a solution of oxetane (1.0 mmol) in THF (5 mL) was added and the mixture was stirred at 60 °C overnight. Then, a solution of 2 N of HCl was added and the mixture was extracted with AcOEt. The organic layer was dried over $MgSO_4$ and the solvent removed. The residue was purified by flash chromatography (mixtures of CH–EA).

4.2.2. GP4

Strictly deoxygenated THF (15 mL) was added to a mixture of Cp_2TiCl_2 (50 mg, 0.2 mmol) and Mn dust (440 mg, 8.0 mmol) under Ar atmosphere and the suspension was stirred at rt until it turned green (about 15 min). Then, a solution of 2,4,6-collidine (925 μl, 7.0 mmol) and Me_3SiCl (510 μl, 4.0 mmol) in THF (4 mL) was added and the mixture was stirred for 5 min. Then, a solution of oxetane (1.0 mmol) in THF (5 mL) was added and the mixture was stirred at 60 °C overnight. Then, a solution 2 N of HCl was added and the mixture was extracted with AcOEt. The organic layer was dried over $MgSO_4$ and the solvent removed. The residue was purified by flash chromatography (mixtures of CH–EA).

*4.2.3. 3,4-Dimethyl-3,4-diphenylhexane-1,6-diol (**6**)*

(CH–EA 10:90) GP3: (105 mg, 0.35 mmol, 70%); GP4: (114 mg, 0.38 mmol, 76%), colorless solid. mp 159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.16–7.07 (md, J=7.3 Hz, 6H), 6.99–6.94 (md, J=8.2 Hz, 4H), 3.39 (ddd, J=10.1, 9.9, 6.0 Hz, 2H), 3.23 (ddd, J=10.1, 10.1, 4.6 Hz, 2H), 2.24 (ddd, J=13.5, 9.9, 4.6 Hz, 2H), 1.87 (ddd, J=13.5, 10.1, 6.0 Hz, 2H), 1.21 (s, 6H), 0.87 (br s, –OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ=145.3, 131.6, 131.5, 129.0, 128.9, 127.9, 61.4, 48.5, 39.9, 23.6, 23.2; IR (film) ν 3420, 3025, 2930, 1725, 1600, 1495, 1455, 1365, 1150, 1060, 845, 750, 700; EIHRMS calcd for $C_{20}H_{26}O_2Na$ 321.1825, found 321.1824.

*4.2.4. 3,4-Bis(4-bromophenyl)-3,4-dimethylhexane-1,6-diol (**7**)*

(CH–EA 10:90) GP3: (153 mg, 0.34 mmol, 67%); GP4 (169 mg, 0.37 mmol, 74%), colorless solid; mp 199 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.35 (d, J=6.5 Hz, 2H), 7.33 (d, J=6.5 Hz, 2H), 6.95 (d, J=8.2 Hz, 2H), 6.90 (d, J=8.2 Hz, 2H), 3.40–3.28 (m, 2H), 3.15–3.06 (m, 2H), 2.38 (ddd, J=13.8, 9.7, 4.2 Hz, 1H), 2.17 (ddd, J=13.8, 9.7, 4.2 Hz, 1H), 1.96–1.76 (m, 2H), 1.28 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=144.2, 133.4, 133.2, 131.9, 131.9, 122.0, 122.0, 61.0, 60.9, 48.4, 48.3, 39.9, 39.6, 23.2, 22.8; IR (film) ν 3445, 3025, 2965, 2875, 1605, 1495, 1450, 1375, 1255, 1065, 960, 855, 750, 700; EIHRMS calcd for $C_{20}H_{24}O_2Br_2Na$ 479.0016, found 479.0025; elemental analysis calcd (%) for $C_{20}H_{24}O_2Br_2$: C 52.65, H 5.30; found: C 52.67, H 5.51.

*4.2.5. 2,2′-(1,1′,2,2′,3,3′,4,4′-Octahydro-1,1′-binaphthyl-1,1′-diyl)diethanol (**8**)*

(CH–EA 50:50) GP3: (63 mg, 18 mmol, 36%); GP4: (82 mg, 0.235 mmol, 47%), colorless solid; mp 184 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ=7.02–7.33 (m, 5H), 4.21 (dd, J=5.1, 5.1 Hz, 2H), 3.14–3.27 (m, 4H), 2.73–2.86 (m, 4H), 2.55–2.66 (m, 8H), 2.01–2.33 (m, 2H), 2.63–2.83 (m, 8H), 0.92–1.27 (m, 8H); ^{13}C NMR (75 MHz, DMSO-d_6) δ=141.8, 139.4, 130.0, 128.9, 125.8, 125.1, 59.0, 48.5, 42.5, 40.8, 34.6, 31.9, 23.8; IR (film) ν=3340, 2925, 2880, 1485, 1445, 1035, 745, 655; EIHRMS calcd for $C_{24}H_{30}O_2Na$ 373.2138, found 373.2130.

*4.2.6. Diphenylpropan-1-ol (**11**)*

(CH–EA 80:20) GP3: (190 mg, 0.9 mmol, 90%); GP4: (97 mg, 0.46 mmol, 46%).

*4.2.7. 3,3-Diphenylprop-2-en-1-ol (**12**)*[37]

(CH–EA 85:15) GP4 (99 mg, 0.47 mmol, 47%).

*4.2.8. 3,3-Bis-(4-chlorophenyl)propan-1-ol (**13**)*

(CH–EA 90:10) GP4: (262 mg, mmol, 93%); GP4: (118 mg, mmol, 42%), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J=8.5 Hz, 4H), 7.14 (d, J=8.5 Hz, 4H), 4.12 (t, J=7.0 Hz, 1H), 3.58 (t, J=7.0 Hz, 2H), 2.24 (q, J=6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.82 (C), 132.61 (C), 129.48 (CH), 129.10 (CH), 60.86 (CH_2), 46.20 (CH), 38.25 (CH_2); IR (film) ν=3445, 3025, 2965, 2875, 1605, 1495, 1450, 1375, 1255, 1065, 960, 855, 750, 700; EIHRMS calcd for $C_{15}H_{14}OCl_2$ 280.0422, found 280.0426.

*4.2.9. 3,3-Bis-(4-chlorophenyl)prop-2-en-1-ol (**14**)*[38]

(CH–EA 90:10) GP4: (135 mg, 0.48 mmol, 48%).

*4.2.10. 3-Methyl-5-phenylpentan-1-ol (**20**)*

(CH–EA 80:20) GP3: (90 mg, 0.50 mmol, 50%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.14–7.23 (md, J=6.7 Hz, 2H), 7.06–7.14 (md, J=7.0 Hz, 3H), 3.58 (dd, J=7.8, 7.5 Hz, 2H), 2.46–2.65 (m, 2H), 1.30–1.66 (m, 5H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=142.9, 128.4, 128.4, 128.4, 125.7, 61.1, 39.9, 39.0, 33.4, 29.3, 19.6; IR (film) ν 3375, 3025, 2930, 1600, 1495, 1455, 1055, 895, 745, 700; EIHRMS calcd for $C_{12}H_{18}O$ [M^+] 178.1358, found 178.1357.

*4.2.11. 1-Phenethylbut-1-ene-4-ol (**21**)*

(CH–EA 80:20) GP3: (26 mg, 0.15 mmol, 15%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.17–7.24 (md, J=7.5 Hz, 2H), 7.08–7.14 (md, J=6.2 Hz, 3H), 4.84 (d, J=1.4 Hz, 1H), 4.79 (d, J=0.8 Hz, 1H), 3.65 (t, J=6.4 Hz, 2H), 2.70 (dd, J=9.8, 8.5 Hz, 2H), 2.28 (t, J=8.9 Hz, 2H), 2.26 (t, J=6.3 Hz, 2H), 1.34 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=145.5, 141.9, 128.5, 128.4, 128.4, 125.9, 112.0, 60.4, 39.4,

37.6, 34.3; IR (film) ν 3375, 3025, 2930, 1600, 1495, 1455, 1055, 895, 745, 700; EIHRMS calcd for $C_{12}H_{16}O$ [M^+] 176.1201, found 176.1200.

4.2.12. 2-(4-tert-Butylcyclohex-1-enyl)ethanol (**22**)[36]

(CH–EA 94:6) GP4: (131 mg, 0.71 mmol, 71%).

4.3. Experimental procedure for the opening of 18 in the presence of *tert*-butyl acrylate

4.3.1. GP5

Strictly deoxygenated THF (15 mL) was added to a mixture of Cp_2TiCl_2 (50 mg, 0.2 mmol) and Mn dust (440 mg, 8.0 mmol) under Ar atmosphere and the suspension was stirred at rt until it turned green (about 15 min). Then, a solution of 2,4,6-collidine (925 μl, 7.0 mmol) and Me_3SiCl (510 μl, 4.0 mmol) in THF (4 mL) was added and the mixture was stirred for 5 min. Then, a solution of oxetane (176 mg, 1 mmol) and *tert*-butyl acrylate (1.50 mL, 10 mmol) in THF (5 mL) was added and the mixture was stirred at 60 °C overnight. Then, a solution of 2 N of HCl was added and the mixture was extracted with AcOEt. The organic layer was dried over $MgSO_4$ and the solvent removed. The residue was purified by flash chromatography (mixtures of CH–EA).

4.3.2. GP6

Strictly deoxygenated THF (15 mL) was added to a mixture of Cp_2TiCl_2 (50 mg, 0.2 mmol), Mn dust (440 mg, 8.0 mmol), and collidine hydrochloride (396 mg, 2.5 mmol) under Ar atmosphere and the suspension was stirred at rt until it turned green (about 15 min). Then, a solution of oxetane (177 mg, 1.0 mmol) and *tert*-butyl acrylate (1.50 mL, 10 mmol) in THF (5 mL) was added and the mixture was stirred at 60 °C overnight. Then, a solution of 2 N of HCl was added and the mixture was extracted with AcOEt. The organic layer was dried over $MgSO_4$ and the solvent removed. The residue was purified by flash chromatography (mixtures of CH–EA).

4.3.3. tert-Butyl-6-hydroxy-4-methyl-4-phenethyl-hexanoate (**23**)

(CH–EA 80:20) GP5: (155 mg, 0.50 mmol, 50%); GP6 (182 mg, 0.60 mmol, 60%); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.22–7.15 (m, 2H), 7.12–7.04 (m, 3H), 3.65 (t, J=7.6 Hz, 2H), 2.52–2.44 (m, 2H), 2.17–2.11 (m, 2H), 1.58–1.50 (m, 4H), 1.47–1.40 (m, 2H), 1.37 (s, 9H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=173.6, 142.9, 128.4, 128.4, 128.3, 125.7, 80.3, 59.3, 41.9, 41.7, 34.6, 34.4, 30.4, 30.2, 28.1, 24.9; IR (film) ν 3435, 2935, 1725, 1455, 1370, 1250, 1150, 1030, 845, 745, 700; EIHRMS calcd for $C_{15}H_{20}O_2$ [$M^+-C_4H_{10}O$] 232.1463, found 232.1197.

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