Ti-Catalyzed Homolytic Opening of Ozonides: A Sustainable C–C Bond-Forming Reaction

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Ⓢ *Supporting Information*

ABSTRACT: The unprecedented homolytic opening of ozonides promoted and catalyzed by titanocene(III) is reported. This novel reaction proceeds at room temperature under neutral, mild conditions compatible with many

functional groups and provides carbon radicals suitable to form C–C bonds via both homocoupling and cross-coupling processes. The procedure has been advantageously exploited for the straightforward synthesis of the natural product brittonin A.
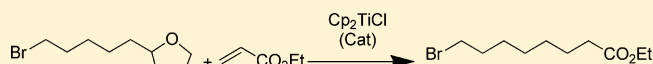
Titanium is one of the most abundant safe transition metals on Earth.[1] Among titanium catalysts, Cp$_2$TiCl (Nugent's reagent) has emerged as a powerful tool in organic synthesis.[2–5] In fact, this single-electron-transfer (SET) reagent has been shown to be capable of promoting and/or catalyzing transformations as useful as the radical opening of epoxides,[6,7] radical cascade cyclizations,[8,9] Barbier-type allylations and propargylations,[10,11] Michael-type additions of aldehydes to conjugated enals,[12] Reformatsky-type reactions,[13] pinacol couplings,[14] H-atom transfers from water to alkenes,[15] alkynes,[15] ketones,[16,17] and free radicals,[18–20] THF-ring formation reactions,[21] and regiodivergent epoxide opening (REO) processes.[22] In this paper, we present a novel reaction, the homolytic opening of ozonides, which can be promoted and catalyzed by Cp$_2$TiCl. This process opens a new way for the selective formation of C–C bonds at room temperature under mild conditions compatible with several functional groups including esters, ethers, silanes, alkyl bromides, and fluorinated derivatives.

Ozonides (1,2,4-trioxolanes) are often simply considered as reactive intermediates that have to be reduced in situ to ozonolysis products.[23] Nevertheless, although some of them are explosive, many others are more stable than is commonly perceived and can be stored and handled without decomposition.[24,25] Moreover, they can be easily prepared under environmentally friendly conditions, for example, by simply bubbling up an ozone flow into an alkene solution. Free-radical chemistry of ozonides, however, is still poorly understood, and in fact, it is generally believed that ozonides are inert under radical conditions.[25] Nevertheless, the presumably weak O–O bond of ozonides offers an attractive starting point to initiate reagent-controlled free-radical processes under mild conditions.[26] With this idea in mind, we deemed that the homolytic opening of ozonides by oxophilic Cp$_2$TiCl might generate two oxygenated radicals which, via two alternative decarbonylation pathways, could eventually converge to a carbon radical suitable for the formation of new C–C bonds (Scheme 1).

**Scheme 1. Hypothetical Generation of Carbon Radicals from Ozonides Promoted by Cp$_2$TiCl**
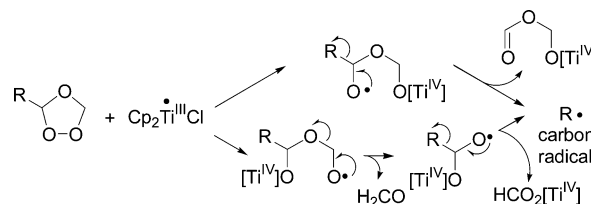
To check our hypothesis, we prepared ozonides **1–6** (Figure 1) and treated them with (over)stoichiometric quantities of Cp$_2$TiCl. Thus, we gratifyingly obtained homocoupling products **9–14**, together with minor amounts of reduction products **19–24** (Table 1, SC column). Moreover, reactions of ozonides **4** and **6** with olefin **8**, promoted by stoichiometric proportions of Cp$_2$TiCl, provided Michael-type addition products **16** and **17**, respectively (Table 1, SC column). Despite the moderate yields obtained, these preliminary results showed that this Ti-based method can be used not only for homocoupling reactions but also for cross-coupling processes.

Formation of products **9–14** and **19–24** strongly supports the idea that the reaction mechanism proceeds via carbon radical intermediates which could dimerize to homocoupling products **9–14** or be trapped by a second Cp$_2$TiCl species to give an organometallic alkyl-Ti^{IV} derivative. This organometallic intermediate could in turn be hydrolyzed to reduction products **19–24** by the final aqueous quenching. In fact, when we treated ozonide **4** with Cp$_2$TiCl and after 1 h reaction, when all starting material was consumed, we added D$_2$O and a mixture of **12**, and deuterium-labeled product **25** was formed (Scheme 2), thus supporting the hypothetical mechanism via formation and
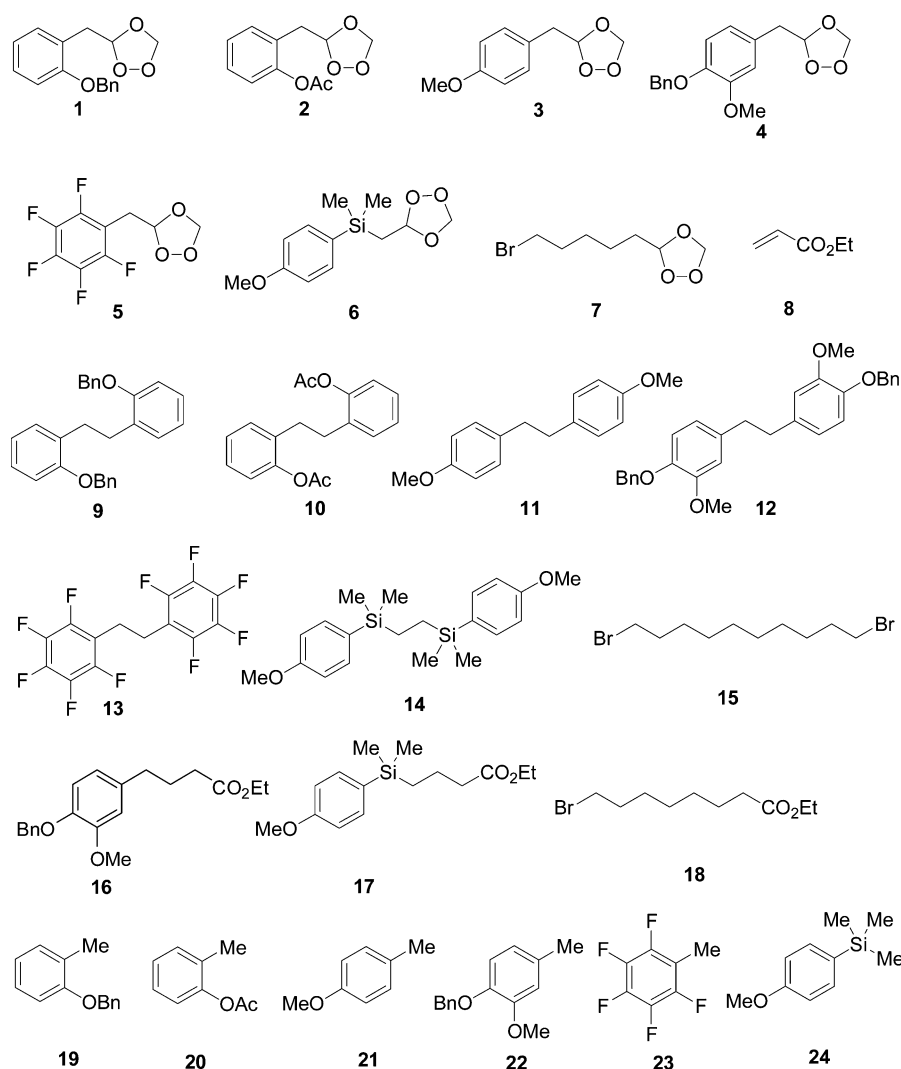
Figure 1. Chemical structure of ozonides **1**−**7**, olefin **8**, homocoupling products **9**−**15**, cross-coupling products **16**−**18**, and reduction products **19**−**24**.

Table 1. Homocoupling and Cross-Coupling Reactions of Ozonides 1−7 Promoted (SC Column) and Catalyzed (CC Column) by Cp$_2$TiCl

substrate	products (yield, %) SC[a]	products (yield, %) CC[b]
1	**9** (61) + **19** (37)	**9** (99)
2	**10** (60) + **20** (30)	**10** (97)
3	**11** (72) + **21** (25)	**11** (98)
4	**12** (61) + **22** (37)	**12** (99)
5	**13** (80) + **23** (18)	**13** (99)
6	**14** (79) + **24** (18)	**14** (98)
7		**15** (90)
4 + 8	**16** (16) + **12** (32) + **22** (42)	**16** (38) + **12** (38) + **22** (6)
6 + 8	**17** (14) + **14** (31) + **24** (40)	**17** (30) + **14** (37)
7 + 8		**15** (25) + **18** (60)

[a]SC: Stoichiometric conditions. [b]CC: Catalytic conditions.

subsequent hydrolysis of an organometallic alkyl-Ti^{IV} intermediate.

This observation suggested that a decrease of the Cp$_2$TiCl concentration might slow the formation rate of the organometallic alkyl-Ti^{IV} derivative, thus contributing to an increase the yields of radical-coupling products **9**−**15**. To investigate

Scheme 2. Reaction between Ozonide 4 and Cp$_2$TiCl, Followed by Addition of D$_2$O
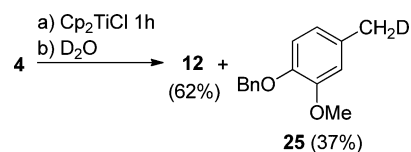
this idea, we treated ozonides **1**−**7** with substoichiometric quantities of Cp$_2$TiCl using the combination of 2,4,6-collidine and Me$_3$SiCl developed in our laboratory as titanocene-regenerating agent.[27] Thus, to our delight, this Ti-catalyzed reaction provided coupling products **9**−**15** in virtually quantitative yields (Table 1, CC column). Moreover, Ti-catalyzed cross-couplings between olefin **8** and ozonides **4**, **6**, and **7** (Table 1, CC column) gave Michel-type addition products **16**, **17**, and **18** in yields substantially higher than those obtained using stoichiometric proportions of Cp$_2$TiCl.[28] It should be noted that all these reactions took place at room temperature under neutral, mild conditions compatible with different functional groups, including esters, ethers, silanes, alkyl bromides, and perfluorinated phenyl groups. Finally, a
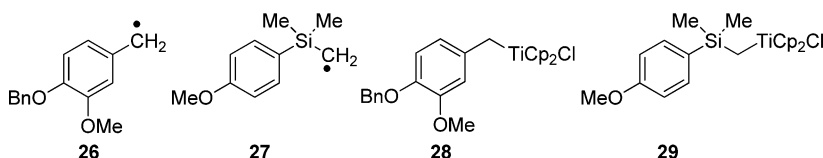
Figure 2. Chemical structure of potential intermediates **26**−**29**.

control experiment in the absence of titanium did not provide any coupling product.

The high yields of radical-coupling product **13** obtained in both Ti-promoted and Ti-catalyzed transformations of pentafluorinated ozonide **5** (80% and 99%, respectively) suggest that the presence of five strongly electronegative fluorine atoms on the benzene ring does not seriously compromise the stability of the pentafluorophenyl radical which, in fact, can achieve radical couplings before decomposition. Fluorinated aromatic derivatives are appreciated as agrochemicals, pharmaceuticals, and electronic devices.[29] In this way, it seems that the Ti-catalyzed radical opening of ozonides might be used in the synthesis of pentafluorophenyl derivatives under mild and environmentally friendly conditions.

Ti-catalyzed reaction between ozonide **7** and olefin **8** gave an acceptable 60% yield of Michael-type addition product **18**. This is noteworthy because Michael addition reactions are generally accomplished using nucleophilic reagents which are not compatible with primary alkyl bromides.

The low yield of reduction product **22** (only 6%) obtained from the Ti-catalyzed reaction between ozonide **4** and Michael acceptor compound **8**, together with the lack of reduction product **24** in the corresponding reaction between **6** and **8** (Table 1, CC column), indicate that, under these conditions with low Cp_2TiCl concentration, intermediate radicals **26** and **27** largely predominate over organometallic species **28** and **29** (Figure 2). Intriguingly, however, yields of Michael-type addition products **16** and **17** were substantially higher than those obtained when stoichiometric proportions of Cp_2TiCl were used, conditions under which the concentration of alkyl-Ti(IV) species **28** and **29** is considerable (42% and 40% yields of reduction products **22** and **24**). These results suggest that radicals **26** and **27** are even more reactive toward **8** (more nucleophilic) than organometallic derivatives **28** and **29**, respectively.

The mechanism of the above Ti-catalyzed processes possibly proceeds via the catalytic cycle depicted in Scheme 3.

Scheme 3. Catalytic Cycle Proposed for Titanocene(III)-Catalyzed Homolytic Opening of Ozonides
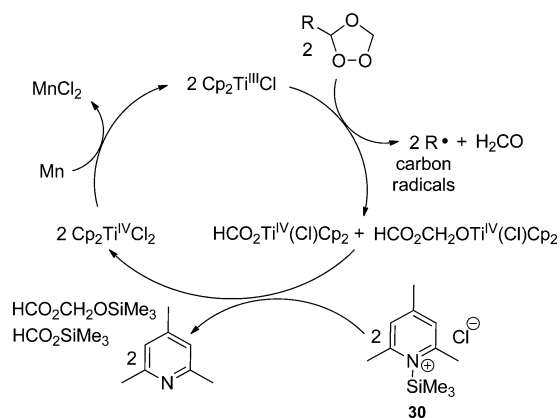
$Cp_2Ti^{III}Cl$ would react with ozonides providing the desired carbon radicals, formaldehyde, $HCO_2Ti^{IV}(Cl)Cp_2$, and $HCO_2CH_2OTi^{IV}(Cl)Cp_2$ (via the mechanism proposed in Scheme 1). $Cp_2Ti^{IV}Cl_2$ would be subsequently regenerated from $HCO_2Ti^{IV}(Cl)Cp_2$ and $HCO_2CH_2OTi^{IV}(Cl)Cp_2$ by the collidinium salt **30**, derived from the combination of 2,4,6-collidine and Me_3SiCl used as titanocene-regenerating agent.[27,30] Finally, Mn would reduce $Cp_2Ti^{IV}Cl_2$ to the active single-electron-transfer reagent $Cp_2Ti^{III}Cl$, thus closing the catalytic cycle.

Synthesis of natural products constitutes one of the most demanding tests of the utility of a new method in organic chemistry. Therefore, we decided to try out the Ti-catalyzed opening of ozonides by synthesizing brittonin A (**31**), a natural dimer isolated from the Japanese liverwort *Frullana brittoniae*.[31] The synthesis was performed from commercially available alkene **32** (Scheme 4), in a sustainable two-step synthetic sequence which provided an excellent 72% overall yield, substantially improving previously reported procedures.[32]

In summary, here we describe for the first time the homolytic opening of ozonides promoted and catalyzed by titanocene-(III), thus showing that ozonides are not inert under radical conditions. This unprecedented reaction provides carbon radicals useful for the formation of C−C bonds at room temperature under neutral, mild conditions compatible with several functional groups including esters, ethers, silanes, alkyl halides and perfluorinated aromatic derivatives. The reaction allows both homocoupling and cross-coupling processes. Moreover, the procedure has been advantageously exploited for the straightforward synthesis of the natural product brittonin A.

■ EXPERIMENTAL SECTION

General Methods. General details have been described elsewhere.[20] Silica gel was used as solid support for flash chromatography. Compounds **12**[33] and **31**[34] are known, and products **10**, **11**, **13**, **15**, and **19**−**24** are commercially available. Their NMR spectra matched those previously reported and/or those of commercial samples.

General Procedure for Ozonide Preparation. Ozonized oxygen (1.3 w/w O_3 in O_2, 10 L/h) was bubbled through a solution of the starting alkene (5 mmol) in CH_2Cl_2 (35 mL) at −78 °C (10−20 min). Reaction progress was monitored by TLC. O_2 was subsequently bubbled through the solution to displace any free ozone. Solvent was then removed in vacuo, and the residue was purified by flash chromatography (hexane/Et_2O mixtures).

Ozonide 1. This ozonide was obtained (73% yield) from commercial 2-allylphenyl benzyl ether as a colorless oil: IR (film) ν_{max} 1244, 1453, 1591, 1602, 1723, 2928, 3033 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52−7.38 (m, 5H), 7.35−7.26 (m, 2H), 7.04 (d, J = 8.1 Hz, 1H), 6.98 (d, J = 8.9 Hz, 1H), 5.55 (t, J = 5.2 Hz, 1H), 5.17−5.15 (m, 4H), 3.15 (dd, J = 14.0, 5.2 Hz, 1H), 3.22 (dd, J = 13.7, 4.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 156.6 (C), 137.0 (C), 131.6 (CH), 128.6 (CH), 128.4 (CH), 127.9 (CH), 127.1 (CH), 123.5 (C), 120.9 (CH), 111.7 (CH), 102.7 (CH); 94.0 (CH_2), 70.0 (CH_2), 33.2 (CH_2); HRMS (EI) m/z calcd for $C_{16}H_{16}O_4$ [M]$^+$ 272.1049, found 272.1053.

Scheme 4. Straightforward Synthesis of Brittonin A
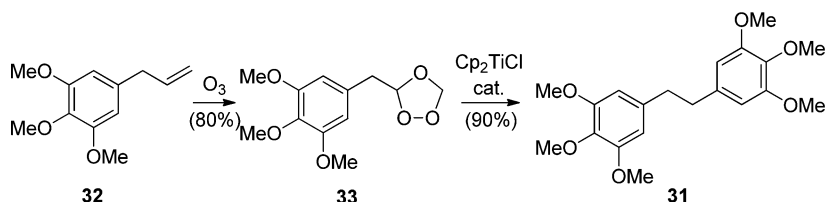
Ozonide 2. Ozonide **2** was obtained (68% yield) from commercial 2-allylphenyl acetate as a colorless oil: IR (film) ν_{max} 1211, 1370, 1492, 1766, 2894 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.35 (dd, J = 7.7, 1.2 Hz, 1H), 7.31 (dt, J = 8.1, 2.0 Hz, 1H), 7.22 (dt, J = 7.7, 1.2 Hz, 1H); 7.12 (dd, J = 8.1, 1.2 Hz, 1H), 5.39 (t, J = 4.5 Hz, 1H), 5.09 (br s, 1H), 5.04 (br s, 1H), 3.05 (dd, J = 14.0, 4.1 Hz, 1H), 2.98 (dd, J = 14.0, 4.0 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$, DEPT) δ 169.2 (C), 149.3 (C), 131.7 (CH), 128.3 (CH), 126.7 (C), 126.0 (CH), 122.6 (CH), 102.5 (CH), 94.0 (CH$_2$), 32.9 (CH$_2$), 20.8 (CH$_3$); HRMS (EI) m/z calcd for C$_{11}$H$_{12}$O$_5$ [M]$^+$ 224.0685, found 224.0714.

Ozonide 3. Commercial 1-allyl-4-methoxybenzene was ozonized to **3** (80%): colorless oil; IR (film) ν_{max} 1033, 1100, 1253, 1514, 1612, 2904 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.23 (d, J = 8.5 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 5.35 (t, J = 4.8 Hz, 1H), 5.18 (br s, 1H), 5.08 (br s, 1H), 3.82 (s, 3H), 3.02 (d, J = 4.8 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$, DEPT) δ 158.7 (C), 130.7 (CH), 126.5 (C), 113.9 (CH), 103.7 (CH), 94.1 (CH$_2$), 55.1 (CH$_3$), 37.3 (CH$_2$); HRMS (EI) m/z calcd for C$_{10}$H$_{12}$O$_4$ [M]$^+$ 196.0736, found 196.0734.

Ozonide 4. Commercial 4-allyl-1-(benzyloxy)-2-methoxybenzene (benzyl eugenol) was ozonized to **4** (78%): colorless oil; IR (film) ν_{max} 1514, 1608, 1746, 1770, 2955 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.48−7.30 (m, 5H), 6.88 (d, J = 8.5 Hz, 1H); 6.86 (d, J = 2.0 Hz, 1H), 6.78 (dd; J = 8.1, 2.0 Hz, 1H), 5.36 (t, J = 4.8 Hz, 1H), 5.18 (s, 1H), 5.17 (s, 2H), 5.09 (s, 1H), 3.92, (s, 3H), 3.0 (d, J = 4.9 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$, DEPT) δ 149.6 (C), 147.3 (C), 137.2 (C), 128.5 (CH), 127.8 (CH), 127.6 (C), 127.3 (CH), 121.7 (CH), 114.0 (CH), 113.4 (CH), 103.6 (CH); 94.1 (CH$_2$), 71.0 (CH$_2$), 55.9 (CH$_3$), 31.6 (CH$_2$); HRMS (EI) m/z calcd for C$_{17}$H$_{18}$O$_5$ [M]$^+$ 302.1154, found 302.1166.

Ozonide 5. Commercial allylpentafluorobenzene was ozonized to **5** (65%): colorless oil; IR (film) ν_{max} 1429, 1524, 2850, 2919, 2965 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.48 (m, 1H), 5.14 (s, 1H), 5.07 (s, 1H), 3.12 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$, DEPT) δ 101.5 (CH), 94.2 (CH$_2$), 25.8 (CH$_2$), (aromatic carbon signals could not be observed, possibly due to the lack of NOE together with the splitting derived from the coupling to fluorine atoms); HRMS (EI) m/z calcd for C$_9$H$_5$F$_5$O$_3$ [M]$^+$ 256.0159, found 256.0187.

Ozonide 6. Commercial allyl(4-methoxyphenyl)dimethylsilane was ozonized to **6** (70% yield): colorless oil; IR (film) ν_{max} 826, 1112, 1248, 1503, 1595, 2896, 2956 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.57 (d, J = 8.5 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 5.28 (t, J = 6.1 Hz, 1H); 5.25 (s, 1H), 5.07 (s, 1H), 3.87 (s, 3H), 1.40 (d, J = 6.1 Hz, 2H), 0.48 (s, 3H), 0.47 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$, DEPT) δ 160.7 (C), 135.0 (CH), 128.4 (C), 113.7 (CH), 103.1 (CH), 94.1 (CH$_2$), 54.9 (CH$_3$), 18.6 (CH$_2$), −2.0 (CH$_3$), −2.2 (CH$_3$); HRMS (EI) m/z calcd for C$_{12}$H$_{18}$O$_4$Si [M]$^+$ 254.0974, found 254.1003.

Ozonide 7. Commercial 7-bromo-1-heptene was ozonized to **7** (68% yield): colorless oil; IR (film) ν_{max} 1059, 1111, 1453, 1461, 2889, 2936 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.18 (s, 1H), 5.14 (t, J = 4.9 Hz, 1H), 5.03 (s, 1H), 3.40 (t, J = 6.7 Hz, 2H), 1.91−1.83 (m, 2H), 1.77−1.72 (m, 2H), 1.51−1.45 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$, DEPT) δ 103.5 (C), 94.0 (CH$_2$), 33.4 (CH$_2$), 32.4 (CH$_2$), 30.9 (CH$_2$), 27.8 (CH$_2$), 22.9 (CH$_2$); HRMS (EI) m/z calcd for C$_7$H$_{14}$O$_3$Br [M + H]$^+$ 225.0126, found 225.0150.

General Procedure for Ti-Promoted Opening of Ozonides. Deoxygenated THF (20 mL) was added to a mixture of Cp$_2$TiCl$_2$ (743 mg, 3 mmol) and Mn dust (439 mg, 8 mmol) under an Ar atmosphere, and the suspension was stirred at rt until it turned lime green (after about 15 min). A solution of the corresponding ozonide (1-6) (1 mmol) in THF (2 mL) was then added and the mixture was stirred for 30 min. Et$_2$O (20 mL) was added and the solution washed with 2 N HCl and brine. The organic layer was dried over anhyd Na$_2$SO$_4$ and the solvent removed. Flash chromatography (hexane/t-BuOMe mixtures) of the residue furnished products **9**−**14** and **19**−**24** in yields summarized in Table 1 (SC column).

Dimer 9. Colorless oil: IR (film) ν_{max} 750, 1029, 1446, 1497, 1599, 2897, 3434; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.60−6.80 (m, 18H), 5.08 (s, 4H), 3.07 (s, 4H); ^{13}C NMR (75 MHz, CDCl$_3$, DEPT) δ 156.6 (C), 137.6 (C), 131.1 (CH), 130.2 (CH), 128.4 (CH), 127.6 (CH), 127.1 (CH), 126.9 (CH), 120.6 (CH), 111.6 (CH), 69.7 (CH$_2$); 30.9 (CH$_2$); HRMS (EI) m/z calcd for C$_{28}$H$_{26}$O$_2$ [M]$^+$ 394.1933, found 394.1943.

Dimer 14. Colorless oil: IR (film) ν_{max} 809, 1130, 1278, 1503, 1593, 2955, 3435 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ; 7.43 (d, J = 8.5 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H), 3.84 (s, 3H), 0.65 (s, 2H), 0.24 (s, 6H), ^{13}C NMR (75 MHz, CDCl$_3$, DEPT) δ 160.2 (C), 135.1 (CH), 130.2 (C), 113.4 (CH), 55.0 (CH$_3$), 8.0 (CH$_2$), −3.4 (CH$_3$); HRMS (EI) m/z calcd for C$_{20}$H$_{30}$O$_2$Si$_2$ [M]$^+$ 358.1784, found 358.1797.

General Procedure for Ti-Promoted Cross-Coupling of Ozonides with Olefin 8. Deoxygenated THF (20 mL) was added to a mixture of Cp$_2$TiCl$_2$ (743 mg, 3 mmol) and Mn dust (439 mg, 8 mmol) under an Ar atmosphere, and the suspension was stirred at rt until it turned lime green. Olefin **8** (2.7 mL, 30 mmol) was poured into the green suspension, and then a solution of the corresponding ozonide (**4** or **6**) (2 mmol) in THF (2 mL) was slowly added during 60 min. The mixture was stirred during 4 h, Et$_2$O (20 mL) was added, and the solution was washed with 2 N HCl and brine. The organic layer was dried over anhydrous Na$_2$SO$_4$, and the solvent removed. Flash chromatography (hexane/t-BuOMe mixtures) of the residue gave products **12**, **16**, and **22** or **14**, **17**, and **24** in yields indicated in Table 1(SC column).

Cross-Coupling product 16. Colorless oil: ^{1}H NMR (500 MHz, CDCl$_3$) δ; 7.43 (d, J = 7.5 Hz, 2H), 7.36 (t, J = 7.5 Hz, 2H), 7.29 (d, J = 7.5 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 6.73 (br s, 1H), 6.65 (d, J = 8.1 Hz, 1H), 5.12 (s, 2 H), 4.12 (q, J = 7.2 Hz, 2H), 3.88 (s, 3H), 2.58 (t, J = 7.6 Hz, 2H), 2.31 (t, J = 7.4 Hz, 2H), 1.92 (quintuplet, 2H), 1.25 (t, J= 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$, DEPT) δ 173.5 (C), 149.6 (C), 146.5 (C), 137.4 (C), 134.8 (C), 128.4 (CH), 127.7 (CH), 127.2 (CH), 120.4 (CH), 114.4 (CH), 112.5 (CH), 71.3 (CH$_2$), 60.2 (CH$_2$), 56.0 (CH$_3$), 34.7 (CH$_2$), 33.6 (CH$_2$), 26.6 (CH$_2$), 14.2 (CH$_3$); HRMS (EI): m/z calcd for C$_{20}$H$_{24}$O$_4$Na [M + Na]$^+$ 351.1572, found 351.1582.

Cross-Coupling Product 17. Colorless oil: 1H NMR (500 MHz, CDCl$_3$) δ 7.42 (d, J = 8.5 Hz, 2H), 6.91 (d, J = 8.5 Hz, 2H), 4.11 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 2.30 (t, J = 7.4 Hz, 2H), 1.72−1.58 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 0.84−0.62 (m, 2H), 0.25 (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$, DEPT) δ 173.5 (C), 160.3 (C), 134.9 (CH), 129.8 (C), 113.5 (CH), 60.1 (CH$_2$), 55.0 (CH$_3$), 37.9 (CH$_2$), 19.7 (CH$_2$), 15.7 (CH$_2$), 14.2 (CH$_3$), −2.3 (CH$_3$); HRMS (EI) m/z calcd for C$_{15}$H$_{24}$O$_3$NaSi [M + Na]$^+$ 303.1392, found 303.1398.

General Procedure for Ti-Catalyzed Opening of Ozonides. Deoxygenated THF (20 mL) was added to a mixture of Cp$_2$TiCl$_2$ (50 mg, 0.2 mmol) and Mn dust (439 mg, 8 mmol) under an Ar atmosphere, and the suspension was stirred at rt until it turned lime green (after about 15 min). A solution of 2,4,6-collidine (848 mg, 7 mmol) and Me$_3$SiCl (434 mg, 4 mmol) in THF (2 mL) was poured into the green suspension, and then the corresponding ozonide (1−7) (1 mmol) in THF (2 mL) was added and the mixture stirred for 3 h. Et$_2$O (20 mL) was added and the solution washed with 2 N HCl and

brine. The organic layer was dried over anhyd Na_2SO_4 and the solvent removed, leaving a residue constituted of a pure dimer (**9−15**) (NMR analysis) in virtually quantitative yield.

General Procedure for Ti-Catalyzed Cross-Coupling of Ozonides with Olefin 8. Deoxygenated THF (20 mL) was added to a mixture of Cp_2TiCl_2 (50 mg, 0.2 mmol) and Mn dust (439 mg, 8 mmol) under an Ar atmosphere, and the suspension was stirred at rt until it turned lime green. Then, a solution of 2,4,6-collidine (848 mg, 7 mmol) and Me_3SiCl (434 mg, 4 mmol) in THF (2 mL) and olefin **8** (0.18 mL, 2 mmol) were added. Subsequently, a solution of the corresponding ozonide (**4**, **6**, or **7**) (1 mmol) in THF (2 mL) was slowly added during 60 min. The mixture was stirred during 6 h, Et_2O (20 mL) was added, and the solution was washed with 2 N HCl and brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent removed. Flash chromatography (hexane/t-BuOMe mixtures) of the residue provided products **12**, **16**, and **22**, **14** and **17**, or **15** and **18** in yields summarized in Table 1 (CC column).

Cross-Coupling Product 18. Colorless oil: IR (film) ν_{max} 1180, 1461, 1734, 2856, 2930 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.14 (q, J = 7.1 Hz, 2H), 3.41 (t, J = 6.8 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 1.90−1.83 (m, 2H), 1.64 (m, 2H), 1.45 (m, 2H), 1.37−1.32 (m, 4H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$, DEPT) δ 173.7 (C), 60.1 (CH$_2$), 34.2 (CH$_2$), 33.8 (CH$_2$), 32.7 (CH$_2$), 28.9 (CH$_2$), 28.3 (CH$_2$), 27.9 (CH$_2$), 24.8 (CH$_2$), 14.2 (CH$_3$); HRMS (EI): m/z calcd for $C_{10}H_{19}O_2Br$ [M]$^+$ 250.0568, found 250.0595.

Formation of Deuterium-Labeled Derivative 25. Deoxygenated THF (12 mL) was added to a mixture of Cp_2TiCl_2 (420 mg, 1.68 mmol) and Mn dust (246 mg, 4.48 mmol) under an Ar atmosphere, and the suspension was stirred until it turned lime green. A solution of ozonide **4** (170 mg, 0.56 mmol) in THF (1.2 mL) was added, and the mixture was stirred until all staring material was consumed (30 min, TLC analysis). Then, D_2O (0.3 mL, 16.8 mmol) was added and the mixture stirred for 5 h. Et_2O (20 mL) was added and the solution washed with 2 N HCl and brine. The organic layer was dried over anhyd Na_2SO_4 and the solvent removed. Flash chromatography (hexane/t-BuOMe, 9:1) of the residue furnished compounds **12** (78 mg, 62%) and **25** (48 mg, 37%, 45% deuterium incorporation).

Deuterium-Labeled Derivative 25. Only distinctive signals with respect to **22**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.30 (t, J = 2.4 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$, DEPT) δ 20.7 (t, J = 20.1 Hz, CH$_2$); HRMS (EI) m/z calcd for $C_{15}H_{15}DO_2$ [M]$^+$ 229.1213, found 229.1218.

Synthesis of Brittonin A (31). Deoxygenated THF (3 mL) was added to a mixture of Cp_2TiCl_2 (6 mg, 0.023 mmol) and Mn dust (51 mg, 0.93 mmol) under an Ar atmosphere, and the suspension was stirred at room temperature until it turned lime green. Then, a solution of 2,4,6-collidine (0.1 mL, 0.82 mmol) and Me_3SiCl (0.06 mL, 0.46 mmol) in THF (0.4 mL) was added. Subsequently, a solution of ozonide **33** (30 mg, 0.12 mmol) in THF (0.5 mL) was added, and the solution was stirred for 3 h. The reaction was then quenched with 2 N HCl and extracted with Et_2O. The organic layer was washed with brine and dried (anhydrous Na_2SO_4) and the solvent removed. Flash chromatography (hexane/AcOEt, 85:15) of the residue afforded brittonin A (**31**) (19 mg, 90% yield). NMR data of brittonin A matched those previously reported.[45]

Ozonide 33. Commercial 5-allyl-1,2,3-trimethoxybenzene (**32**) was ozonized to **33** (80% yield): colorless oil; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.47 (s, 2H), 5.34 (t, J = 5.0 Hz, 1H), 5.18 (s, 1H), 5.10 (s, 1H), 3.85 (s, 6H), 3.83 (s, 3H), 2.97 (d, J = 5 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$, DEPT) δ = 153.2 (C), 137.0 (C), 130.1 (C), 106.7 (CH), 103.5 (CH), 94.1 (CH$_2$), 60.8 (CH$_3$), 56.1 (CH$_3$), 38.6 (CH$_2$); HRMS (EI) m/z calcd for $C_{12}H_{16}O_6Na$ [M + Na]$^+$ 279.0845, found 279.0846.

ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C spectra of all compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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