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Tandem Cyclization−Michael Reaction by Combination of Metal- and Organocatalysis

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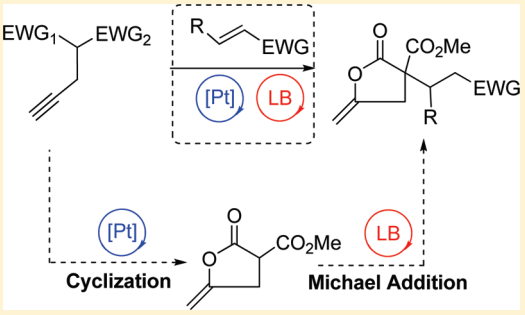
Supporting Information

ABSTRACT: The use of a catalytic amount of platinum complexes (1 mol %) was found to be compatible with different organocatalysts (DABCO or the Jørgensen−Hayashi catalyst) that were used in the functionalization of various activated methylenes. By this method, a series of lactones with C-3 quaternary centers and substitution at C-5 were prepared.



Lactones are present in a large number of natural products. Recently, a variety of lactones with quaternary centers at C-3 and substitution at C-5 have been isolated.[1] Examples of complex structures which incorporate this moiety include spirovibsanin (**A**),[1a,b] *trans*-dehydrocrotonin (**B**),[1c] and biologically active tetranoditerpenoids (**C**)[1d] (Figure 1), along with teucrin A,[1e] neoclerodane diterpenes,[1f] and sesquiterpenes of *Collybia maculate* (not shown).[1g] Less complex examples include some β3-adrenergic receptor agonists (**D**)[2a] and serine protease inhibitors (**E**).[2b] Various methodologies have been developed for the synthesis of furanones with this substitution pattern (**F**).[2c,d]

In the past decade, organocatalysis[3] has opened a new window for carrying out organic transformations. One of its primary advantages is the avoidance of expensive metal reagents or catalysts. However, more recent attention has been focused on the combination of metal[4] and organocatalysis[3] to provide a complementary method for obtaining new complex structures or for enhancing the reactivity of the metal.[5] Dixon,[6a] Jørgensen,[6b] and Córdova[6c] have each reported catalytic systems involving initial activation using a Lewis base followed by π-alkyne trapping with a metal catalyst (eq 1, Scheme 1).

In this context, one of the most useful starting materials in organocatalysis is a methylene activated by two electron-withdrawing groups (EWG-CHR-EWG). However, a large difference in reactivity is observed between acyclic and cyclic substrates,[7] with better reactivities generally observed in the latter case due to increased acidity (see the Bordwell pK_a table).[8] Given our group's experience working with π-acid activated alkynes using platinum catalysis[9] and organocatalysis[10] although in the opposite mode as described above (i.e., first platinum catalysis, then the Lewis base), we hypothesized that propargyl malonate derivatives **1** could be cyclized using platinum to afford intermediate **3**.

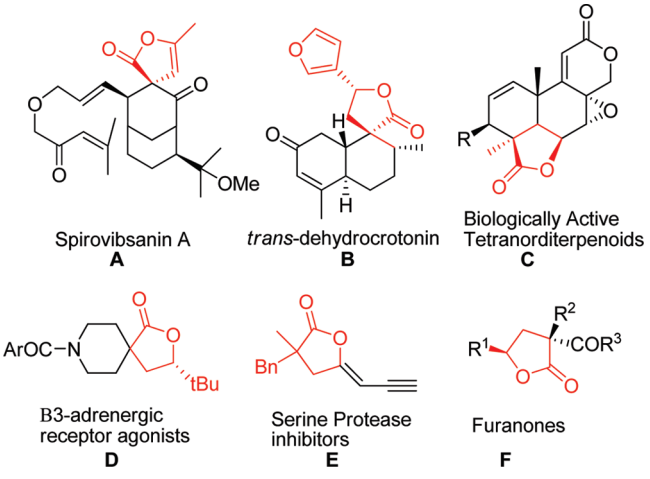


Figure 1. Lactones present in different natural products.

Subsequently, lactone **3**, with its highly acidic α-proton, would be a prime target for an organocatalytic addition to activated alkenes (eq 2, Scheme 1) to afford compounds **4**. In this work, we present our efforts toward developing this tandem procedure for the synthesis of γ-lactones with a C-3 quaternary center.

We began by screening platinum catalysts (**5a**−**f**)[9] in toluene at room temperature while using 20 mol % of DABCO as the organocatalyst to deprotonate the acidic position. As shown in Table 1, the best catalyst was **5c**,[11] which gave compound **4a** with a conversion of 96% (entry 3, Table 1). Other similar catalysts,

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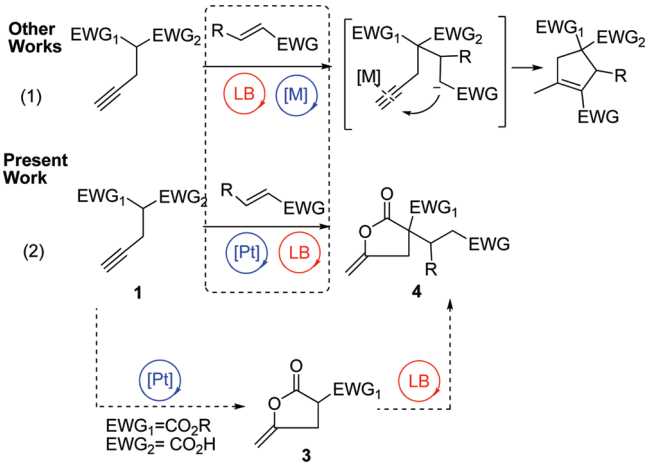
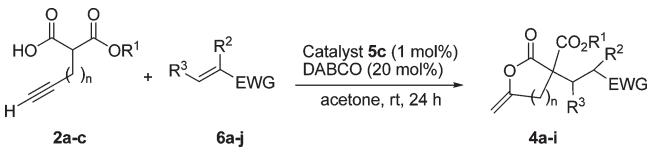
such as **5a**, **5b**, or the iodo derivative **5f** (entries 1, 2, and 6), gave only moderate conversion, and Pt(IV) complexes were even less successful (entries 4 and 5). No reaction of any kind was observed in the absence of platinum catalysts (entry 7), indicating that the cyclization was necessary to achieve deprotonation. Next, we tested different solvents (entries 8–10) and found that acetone, xylene, and toluene provided the best results.[12] However, reaction times were slightly better in acetone than in the nonpolar solvents. With these conditions in hand, we were prepared to investigate the scope of the reaction (Table 2).

Scheme 1. Strategy for the Synthesis of Substituted Lactones (LB = Lewis Base)



The ethyl-substituted malonate derivative **2b** gave the corresponding lactone (**4b**) in worse yield than **2a** (see entries 1 and 2, Table 2). Adding an extra methylene linker before the alkyne

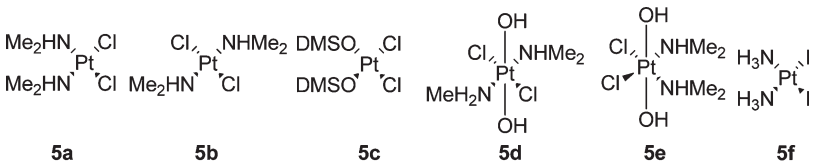
Table 2. Scope of the Reaction with Different Alkenes[a]

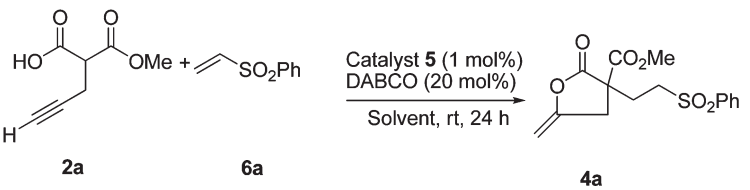


entry	R^1 (n)	EWG/R^2/R^3	R^3	yield[b] (%)
1	Me (1), **2a**	SO_2Ph/H/H, **6a**	H	69, **4a**
2	Et (1), **2b**	SO_2Ph/H/H, **6a**	H	46, **4b**
3[c]	Et (2), **2c**	SO_2Ph/H/H, **6a**	H	22, **4c**
4	Me (1), **2a**	CN/H/H, **6b**	H	70, **4d**
5	Me (1), **2a**	COMe/H/H, **6c**	H	71, **4e**
6	Me (1), **2a**	CO_2Et/H/H, **6d**	H	66, **4f**
7	Me (1), **2a**	CN/H/Me, **6e**	Me	nr[d]
8	Me (1), **2a**	CN/H/Ph, **6f**	Ph	nr[d]
9	Me (1), **2a**	CO_2Et/H/Me, **6g**	Me	nr[d]
10[c]	Me (1), **2a**	CO_2Et/CO_2Et/Me, **6h**	Me	53, **4g**/**4g'**[e]
11[c]	Me (1), **2a**	NO_2/H/Et, **6i**	Et	30, **4h**/**4h'**[e]
12	Me (1), **2a**	NO_2/H/Ph, **6j**	Ph	72, **4i**/**4i'**[e]

[a] All reactions were performed with 0.30 mmol of **2a**–**c**, 0.45 mmol of **6a**–**j**, 1 mol % of catalyst **5c**, 20 mol % of DABCO in 0.2 mL of acetone, and 50 μL of H_2O over 24 h. [b] Isolated yield after flash chromatography. [c] This reaction was stopped after 48 h. [d] No reaction. [e] A diastereomeric ratio of 3:1 was obtained.

Table 1. Screening Platinum Catalysts for the Tandem Reaction of 2-(Methoxycarbonyl)pent-4-ynoic Acid 2a in the Presence of Catalytic DABCO[a]





entry	solvent	catalyst	conversion[b] (%)
1	Tol	**5a**	41
2	Tol	**5b**	57
3	Tol	**5c**	96
4	Tol	**5d**	0
5	Tol	**5e**	22
6	Tol	**5f**	29
7	Tol		nr[c]
8	xylene	**5c**	96
9	CH_2Cl_2	**5c**	73
10	acetone	**5c**	>98

[a] All reactions were performed on a 0.1 mmol scale in 0.1 mL of solvent and stopped after 24 h. [b] Conversion was determined by ^{1}H NMR. [c] No reaction.

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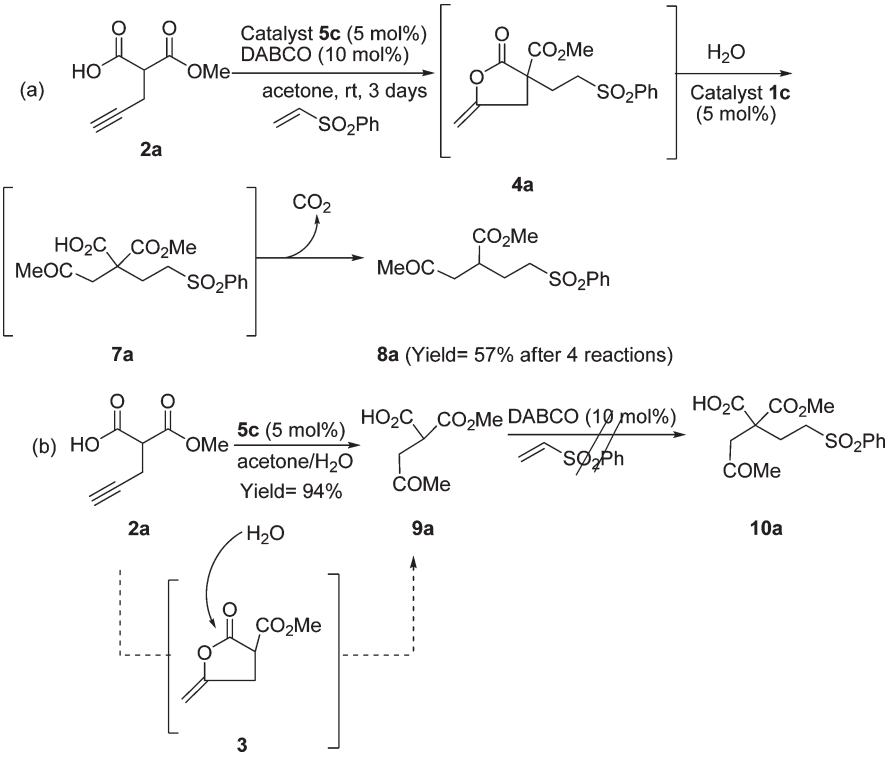
Scheme 2. Decarboxylation Process and Opening Lactone with Water Molecule



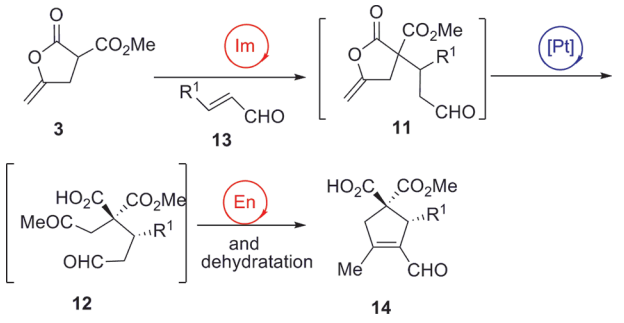
moiety was tolerated (e.g., **2c**), but the yield was substantially decreased (entry 3).

Nitriles (**6b**), ketones (**6c**), and esters (**6d**) underwent the reaction in this catalytic system with malonate **2b**, providing complete conversion and yields ranging from 66 to 71% (entries 4−6). Unfortunately, β-substituted double bonds **6e**−**g** did not react under these conditions, indicating that a greater electronic activation was needed to overcome the added steric hindrance (entries 7−9). Thus, we attempted the reaction with trisubstituted alkene **6h**, which provided the final product **4g**/**4g**′ as a 3:1 mixture of diastereomers (entry 10). Interestingly, a nitro group was also reactive enough with the β-substituted double bonds **6i** and **6j** to achieve the final compounds **4h** and **4i** in moderate to good yields (entries 11 and 12).[13]

To know if we could increase the number of the steps in which the catalyst is involved and to make the catalytic cycle more complex, we increased the catalytic loading of the platinum complex **5c** to 5 mol % and lengthened the reaction time (eq a, Scheme 2). Under these conditions, the reaction gave known intermediate **4a** (observed by TLC), which was then opened by attack of a water molecule to the ester moiety catalyzed by **5c** that could act as a Lewis acid, enhancing this ring-opening process.[14] Thus, intermediate ketone **7a** was obtained and was subsequently decarboxylated by the basic conditions of the reaction media (DABCO) to give the final sulfone **8a** (eq a, Scheme 2).

Next, we performed an experiment to test the dependence of the Michael addition on the existence of a cyclic lactone intermediate (eq b, Scheme 2). We synthesized ketone **9a** by formation of lactone **3** followed by opening with a water molecule catalyzed by platinum. Then, we tried to deprotonate it with 10 mol % of DABCO under the same reaction conditions, and only starting material **9a** was recovered, even after 5 days, indicating that only the cyclic subtrates can react under these reaction conditions.[15]

Scheme 3. Tandem Process Iminium-Metal-Catalyzed and Enamine Reaction



Given the known reactivity of enol lactones,[16] and having determined that the cyclic intermediate was required for the Michael addition, we became interested in performing iminium activation of α,β-unsaturated aldehydes using diarylprolinol ethers.[17] Following the reaction outlined in Scheme 3, lactone **3** would react under iminium catalysis to give the aldehyde **11**, followed by opening with a water molecule catalyzed by platinum to give intermediate **12**. Finally, aldehyde **12** would cyclize via enamine chemistry with the prolinol ether catalyst, and dehydration of the obtained aldol would give the final compound **14**.

With this premise in mind, we started the reaction with crotonaldehyde **13a**, lactone **3**, the silylprolinol ether **15** (20 mol %)[18] and 1 mol % of platinum catalyst **5c** (eq 1, Scheme 4). Gratifyingly, the reaction gave the desired acid product as a mixture of

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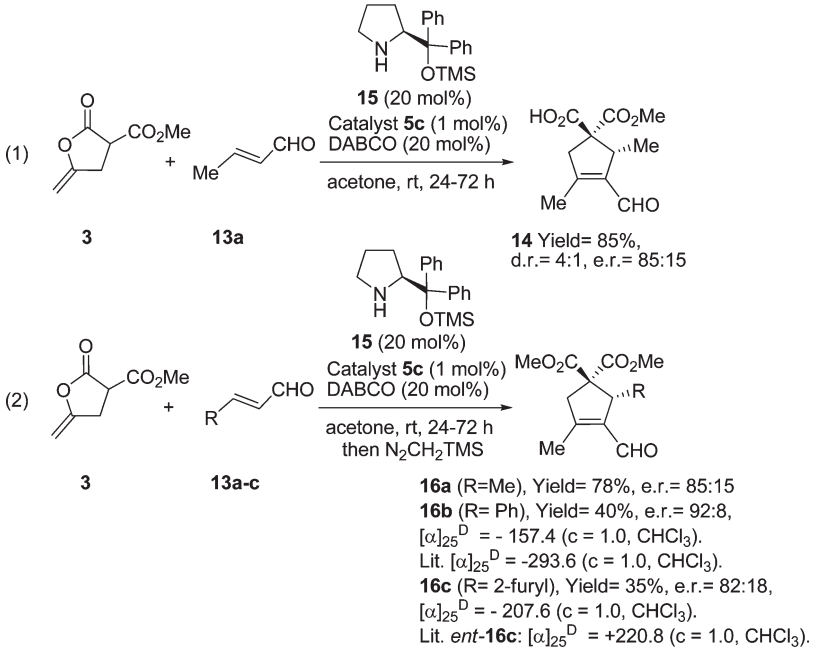
Scheme 4. Reaction of Lactone 3 with Different α,β-Unsaturated Aldehydes 13



diastereoisomers (4:1) with a moderate enantiomeric ratio (er = 85.15) and good yield. The relative configuration was confirmed by NOESY experiments (see the Supporting Information). This reaction allows the synthesis of these chiral acids via an iminium ion/platinum/enamine ion catalysis cascade.

To obtain the absolute configuration by chemical correlation, we repeated the reaction but treated the crude mixture with N_2CH_2-TMS (eq 2, Scheme 4). Thus, acid **14** was converted into diester **16a** in a one-pot manner in good yield (eq 2, Scheme 4). Aldehydes **13b** (R = Ph) and **13c** (R = 2-furyl) underwent the same reaction to give diesters **16b** and **16c** with moderate yields and moderate to good enantiomeric ratios. The absolute configuration of compounds **16b**[6c] and **16c**[19] was obtained by correlation with known compounds in the literature, obtaining similar optical rotations and indicating *R* configuration for the chiral center.

In conclusion, we have found that the use of catalytic amounts of platinum complexes (1 mol %) is compatible with different organocatalysts (DABCO or the Jørgensen−Hayashi catalyst),[16] allowing the functionalization of various acylic malonates and allowing the synthesis of lactones with a quaternary center at C-3 and substitution at C-5 in a facile manner.

EXPERIMENTAL SECTION

General Methods. NMR spectra were acquired on a 300 MHz spectrometer, running at 300 and 75 MHz for ^1H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, 7.26 ppm for ^1H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR). ^{13}C NMR spectra were acquired on a broad band decoupled mode. Analytical thin-layer chromatography (TLC) was performed using precoated aluminum-backed plates and visualized by ultraviolet irradiation or $KMnO_4$ dip. Purification of reaction products was carried out by flash chromatography (FC) using silica gel. Melting points were measured using an open capillary tubes and are uncorrected. The optical rotations were measured at room temperature (20−23 °C) using a polarimeter (concentration in g/100 mL). Alkenes **6a**−**j**, esters **1a**,**b**, catalyst **15**, and aldehydes **13** were purchased from commercial available sources. Platinum complexes were synthetized according to the procedures described in the literature.[8] The ee's were determined by HPLC employing chiral HPLC columns.

*Diethyl 2-(But-3-ynyl)malonate (**1c**).* Under an argon inert atmosphere, NaH (5.5 mmol, 1.1 equiv) was added portionwise at 0 °C to a solution of the corresponding malonate (5.0 mmol) in anhydrous THF (10 mL). The mixture was allowed to warm to room temperature and the corresponding propargyl bromide was added (5.5 mmol, 1.1 equiv). After the completion of the reaction (which is followed by TLC), the reaction was quenched with water and extracted with EtOAc (3 × 15 mL). The organic phase was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The product was directly obtained as colorless oil (40% yield) and purified using flash column chromatography, elution with EtOAc/hexane (1:3): ^1H NMR (300 MHz, $CDCl_3$) δ 4.19 (q, J = 7.5 Hz, 4H), 3.54 (t, J = 7.4 Hz, 1H), 2.28 (td, J = 7.1, 2.6 Hz, 2H), 2.10 (q, J = 7.1 Hz, 2H), 1.99 (t, J = 2.6 Hz, 1H.), 1.26 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9 (C), 82.4 (C), 70.0 (CH), 61.4 (CH_2), 50.5 (CH), 27.3 (CH_2), 16.3 (CH_2), 14.0 (CH_3); (MS-ESI$^+$) $[M]^+$ calcd for $C_{11}H_{16}O_4$ 213.1126, found 213.1124.

Procedure for the Monohydrolysis of the Substituted Malonates 2a and 2c. To a solution of substrate (2.2 mmol) in methanol (**2a**) or ethanol (**2c**) (5 mL) was added NaOH (2.4 mmol, 1.1 equiv). The mixture was stirred at room temperature for 18 h. Then, 10 mL of aqueous saturated sodium bicarbonate were added, and the mixture was extracted with EtOAc (3 × 10 mL). The aqueous phase was acidified to pH = 1 with concentrated HCl and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure, obtaining pure acid compounds.

*2-(Methoxycarbonyl)pent-4-ynoic Acid (**2a**).* The product was directly obtained following the standard procedure from commercial available **1a** as white solid (91% yield) without further purification: mp = 94.9−95.3 °C; ^1H NMR (300 MHz, $CDCl_3$) δ7.82 (bs, 1H), 3.74

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(s, 3H), 3.59 (t, J = 7.5 Hz, 1H), 2.74 (dd, J = 7.4, 1.6 Hz, 2H), 1.99 (t, J = 2.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$)δ 172.8 (C), 168.2 (C), 79.5 (C), 70.8 (CH), 53.1 (CH_3), 50.8 (CH), 18.4 (CH_2); (electrospray$^+$) $[M + Na]^+$ calcd for $C_7H_8O_4Na$ 179.0322, found 179.0314.

*2-(Ethoxycarbonyl)hex-5-ynoic Acid (**2c**).* The product was directly obtained following the standard procedure starting from **1c** as colorless oil (87% yield) without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.93 (bs, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.65 (t, J = 7.3 Hz, 1H), 2.34 (td, J = 6.8, 2.5 Hz, 2H), 2.15 (q, J = 7.1 Hz, 2H), 2.04 (t, J = 2.6 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4 (C), 168.8 (C), 82.1 (C), 70.0 (CH), 61.9 (CH_2), 50.3 (CH), 27.3 (CH_2), 16.3 (CH_2), 13.9 (CH_3); (MS-ESI$^+$) $[M + Na]^+$ calcd for $C_9H_{12}O_4Na$ 207.0627, found 207.0627.

Procedure for the Synthesis of Acid 2b by Transesterification. To a solution of compound **2a** (2.2 mmol) in ethanol (5 mL) was added NaOH (2.4 mmol, 1.1 equiv). The mixture was stirred at room temperature for 18 h. Then, 10 mL of aqueous saturated sodium bicarbonate were added, and the mixture was extracted with EtOAc (3 × 10 mL). The aqueous phase was acidified to pH = 1 with concentrated HCl and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure, obtaining pure the acid compound **2b**.

*2-(Ethoxycarbonyl)pent-4-ynoic Acid (**2b**).* The product was directly obtained following the procedure as a colorless oil (83% yield) without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.26 (bs, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.56 (t, J = 7.6 Hz, 1H), 2.72 (ddd, J = 7.6, 2.5, 1.0 Hz, 2H), 1.99 (t, J = 2.6 Hz, 1H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1 (C), 167.8 (C), 79.6 (C), 70.7 (CH), 62.2 (CH_2), 51.0 (CH), 18.3 (CH_2), 13.9 (CH_3); (MS-ESI$^+$) $[M + H]^+$ calcd for $C_8H_{11}O_4$ 171.0657, found 171.0656.

General Procedure for Addition Reaction (Tables 1 and 2, Scheme 2). To a solution of the corresponding acid **2a**−**c** (0.3 mmol) in acetone (0.3 mL) were added the platinum complex **5c** (0.003 mmol, 1 mol %), DABCO (0.06 mmol, 20 mol %), the corresponding $\alpha\beta$-unsaturated compound **6a**−**j** (0.3 mmol, 1.5 equiv), and 50 μL of water. After completion of the reaction (which is followed by TLC), the mixture was concentrated to give a crude, which was purified using flash column chromatography. Elution with EtOAc/hexane (1:3) afforded the pure compounds.

*Methyl 5-Methylene-2-oxo-3-(2-(phenylsulfonyl)ethyl)tetrahydrofuran-3-carboxylate (**4a**).* The product was directly obtained following the standard procedure as a white solid (69% yield): mp = 105.2−105.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93−7.89 (m, 2H), 7.71−7.66 (m, 1H), 7.62−7.56 (m, 2H), 4.84 (dt, J = 2.9, 2.0 Hz, 1H), 4.42 (dt, J = 3.2, 1.6 Hz, 1H), 3.75 (s, 3H), 3.42 (ddd, J = 13.9, 10.3, 6.3 Hz, 1H), 3.30 (dt, J = 16.6, 1.8 Hz, 1H), 3.19 (ddd, J = 13.9, 10.4, 6.1 Hz, 1H), 2.82 (dt, J = 16.6, 2.0 Hz, 1H), 2.33 (ddd, J = 17.7, 14.0, 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4 (C), 168.6 (C), 151.6 (C), 138.4 (C), 134.1 (CH), 129.5 (CH), 128.1 (CH), 90.8 (CH_2), 53.7 (CH_3), 53.4 (C), 51.6 (CH_2), 36.6 (CH_2), 27.1 (CH_2); (MS-ESI$^+$) $[M + Na]^+$ calcd for $C_{15}H_{16}O_6SNa$ 347.0565, found 347.0565.

*Ethyl 5-Methylene-2-oxo-3-(2-(phenylsulfonyl)ethyl)tetrahydrofuran-3-carboxylate (**4b**).* The product was directly obtained following the standard procedure as white solid (46% yield): mp = 101.4−102.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 7.1 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.4 Hz, 2H), 4.76 (dt, J = 2.9, 1.9 Hz, 1H), 4.35 (dt, J = 2.9, 1.5 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.37 (ddd, J = 13.9, 10.4, 6.2 Hz, 1H), 3.22 (dt, J = 16.5, 1.6 Hz, 1H), 3.13 (ddd, J = 13.9, 10.5, 6.1 Hz, 1H), 2.75 (dt, J = 16.5, 1.9 Hz, 1H), 2.25 (ddd, J = 17.4, 14.0, 6.0 Hz, 2H), 1.17 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4 (C), 168.1 (C), 151.6 (C), 138.6 (C), 134.1 (CH), 129.5 (CH), 128.1 (CH), 90.6 (CH_2), 63.0 (CH_2), 53.4 (C), 51.7 (CH_2), 36.7 (CH_2), 27.1 (CH_2), 13.9 (CH_3); (MS-ESI$^+$) $[M + H]^+$ calcd for $C_{16}H_{19}O_6S$ 339.0896; found 339.0902.

*Ethyl 6-Methylene-2-oxo-3-(2-(phenylsulfonyl)ethyl)tetrahydro-2H-pyran-3-carboxylate (**4c**).* The product was directly obtained following the standard procedure as a colorless oil (22% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 7.2 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.5 Hz, 2H), 4.64 (s, 1H), 4.29 (s, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.43 (ddd, J = 13.7, 9.1, 7.1 Hz, 1H), 3.08 (ddd, J = 13.7, 10.9, 6.4 Hz, 1H), 2.56−2.46 (m, 2H), 2.30−2.16 (m, 2H), 1.69 (ddd, J = 13.6, 9.7, 7.3 Hz, 2H), 1.17 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4 (C), 166.6 (C), 153.4 (C), 138.7 (C), 134.0 (CH), 129.4 (CH), 128.1 (CH), 96.0 (CH_2), 62.8 (CH_2), 53.1 (C), 52.0 (CH_2), 28.7 (CH_2), 28.1 (CH_2), 24.0 (CH_2), 14.0 (CH_3); (MS-ESI$^+$) $[M + H]^+$ calcd for $C_{17}H_{21}O_6S$ 353.1053, found 353.1054.

*Methyl 3-(2-Cyanoethyl)-5-methylene-2-oxotetrahydrofuran-3-carboxylate (**4d**).* The product was directly obtained following the standard procedure as yellow oil (70% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80 (s, 1H), 4.40 (s, 1H), 3.75 (s, 3H), 3.31 (d, J = 16.6 Hz, 1H), 2.86 (d, J = 16.6 Hz, 1H), 2.66−2.45 (m, 2H), 2.34−2.32 (m 2H); ^{13}C NMR (75 MHz, $CDCl_3$)δ171.3 (C), 168.5 (C), 151.6 (C), 118.4 (C), 90.8 (CH_2), 53.8 (C), 53.7 (CH_3), 36.3 (CH_2), 29.8 (CH_2), 13.1 (CH_3); (MS-ESI$^+$) $[M + Na]^+$ calcd for $C_{10}H_{11}NO_4Na$ 232.0580, found 232.0574.

*Methyl 5-Methylene-2-oxo-3-(3-oxobutyl)tetrahydrofuran-3-carboxylate (**4e**).* The product was directly obtained following the standard procedure as a yellow oil (71% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (s, 1H), 4.33 (s, 1H), 3.72 (s, 3H), 3.26 (dt, J = 16.5, 1.5 Hz, 1H), 2.74 (dt, J = 16.5, 1.5 Hz, 1H), 2.70−2.43 (m, 2H), 2.16 (t, J = 7.6 Hz, 2H), 2.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.5 (C), 172.1 (C), 169.4 (C), 152.2 (C), 90.0 (CH_2), 54.0 (C), 53.3 (CH_3), 38.4 (CH_2), 36.6 (CH_2), 29.9 (CH_3), 27.9 (CH_2); (MS-ESI$^+$) $[M + Na]^+$ calcd for $C_{11}H_{14}O_5Na$ 249.0733, found 249.0741.

*Methyl 3-(3-Ethoxy-3-oxopropyl)-5-methylene-2-oxotetrahydrofuran-3-carboxylate (**4f**).* The product was directly obtained following the standard procedure as a colorless oil (66% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.84 (s, 1H), 4.43 (s, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 3.38 (d, J = 16.5 Hz, 1H), 2.86 (d, J = 16.5 Hz, 1H), 2.61−2.50 (m, 1H), 2.46−2.24 (m, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0 (C), 171.9 (C), 169.2 (C), 152.2 (C), 90.0 (CH_2), 60.8 (CH_2), 54.2 (C), 53.4 (CH_3), 36.0 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 14.1 (CH_3); (MS-ESI$^+$) $[M + Na]^+$ calcd for $C_{12}H_{16}O_6Na$ 279.0839; found 279.0837.

*Diethyl 2-(1-(3-(Methoxycarbonyl)-5-methylene-2-oxotetrahydrofuran-3-yl)ethyl)malonate (**4g**/**4g**′).* The product was directly obtained following the standard procedure as a colorless oil (53% yield). Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80−4.77 (m, 1H), 4.40−4.38 (m, 1H), 4.25−4.12 (m, 4H), 3.78 (s, 3H), 3.57 (d, J = 5.7 Hz, 1H), 3.44−3.31 (m, 2H), 3.02 (dt, J = 17.0, 2.1 Hz, 1H), 1.30−1.23 (m, 6H), 1.10 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5 (C), 168.6 (C), 168.4 (C), 168.1 (C), 152.9 (C), 89.6 (CH_2), 62.0 (CH_2), 61.7 (CH_2), 59.4 (C), 53.7 (CH_3), 53.4 (CH), 36.3 (CH), 31.8 (CH_2), 14.2 (CH_3), 14.1 (CH_3), 13.1 (CH_3). Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80−4.77 (m, 1H), 4.40−4.38 (m, 1H), 4.25−4.12 (m, 4H), 3.79 (s, 3H), 3.55 (d, J = 5.7 Hz, 1H), 3.44−3.31 (m, 2H), 3.00 (dt, J = 16.8, 2.3 Hz, 1H), 1.30−1.23 (m, 6H), 1.10 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 (C), 168.5 (C), 168.4 (C), 168.2 (C), 152.8 (C), 89.6 (CH_2), 62.1 (CH_2), 61.8 (CH_2), 59.7 (C), 53.9 (CH_3), 53.1 (CH), 36.1 (CH), 32.0 (CH_2), 14.0 (CH_3), 13.9 (CH_3), 13.8 (CH_3); (MS-ESI$^+$) $[M + Na]^+$ calcd for $C_{16}H_{22}O_8Na$ 343.1393, found 343.1390.

*Methyl 5-Methylene-3-(1-nitrobutan-2-yl)-2-oxo-tetrahydrofuran-3-carboxylate (**4h**/**4h**′).* The product was directly obtained following the standard procedure as a white solid (30% yield), mp = 114.9−116.1 °C. Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80−4.77 (m, 1H), 4.63 (dd, J = 14.0, 4.2 Hz, 1H), 4.43 (dd, J = 14.0, 6.4 Hz, 1H), 4.38−4.34 (m, 1H), 3.74 (s, 3H), 3.25 (dt, J = 17.0, 2.0 Hz, 1H), 3.00−2.90 (m, 1H),

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2.90 (dt, J = 17.0, 2.0 Hz, 1H), 1.66 (ddq, J = 14.7, 7.4, 3.5 Hz, 1H), 1.46−1.27 (m, 1H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9 (C), 168.9 (C), 151.6 (C), 90.4 (CH_2), 76.0 (CH_2), 57.7 (C), 53.7 (CH_3), 41.9 (CH), 34.6 (CH_2), 22.2 (CH_2), 11.4 (CH_3). Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80−4.68 (m, 2H), 4.48−4.35 (m, 2H), 3.76 (s, 3H), 3.39 (dt, J = 16.8, 1.7 Hz, 1H), 3.00−2.87 (m, 1H), 2.79 (dt, J = 16.8, 1.8 Hz, 1H), 1.46−1.27 (m, 2H), 0.97 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9 (C), 168.9 (C), 151.9 (C), 90.2 (CH_2), 75.3 (CH_2), 58.2 (C), 53.7 (CH_3), 42.4 (CH), 32.7 (CH_2), 22.7 (CH_2), 11.9 (CH_3); (MS-ESI$^+$) $[M + H]^+$ calcd for $C_{11}H_{16}NO_6$ 258.0972, found 258.0976.

*Methyl 5-Methylene-3-(2-nitro-1-phenylethyl)-2-oxotetrahydrofuran-3-carboxylate (**4i**).* The product was directly obtained following the standard procedure as a white solid (72% yield). The minor diastereoisomer could not be isolated: mp = 114.9−116.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.31 (m, 3H), 7.26−7.22 (m, 2H), 5.25 (dd, = 13.7, 10.9 Hz, 1H), 4.98 (dd, J = 13.7, 3.5 Hz, 1H), 4.58 (q, J = 2,4 Hz, 1H), 4.27 (dd, J = 10.8, 3.5 Hz, 1H), 4.10 (td, J = 3.2, 1.6 Hz, 1H), 3.85 (s, 3H), 3.09 (dt, J = 16.9, 1.6 Hz, 1H), 2.86 (dt, J = 16.9, 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5 (C), 169.2 (C), 151.5 (C), 133.8 (C), 129.5 (CH), 129.2 (CH), 129.0 (CH), 90.1 (CH_2), 76.6 (CH_2), 57.8 (C), 54.0 (CH_3), 46.6 (CH), 35.6 (CH_2); (MS-ESI$^+$) $[M + Na]^+$ calcd for $C_{15}H_{15}NO_6Na$ 328.0797, found 328.0784.

*Methyl 4-Oxo-2-(2-(phenylsulfonyl)ethyl)pentanoate (**8a**).* To a solution of acid **2a** (0.3 mmol) in acetone (0.3 mL) were added platinum complex **5c** (0.003 mmol, 5 mol %), DABCO (0.06 mmol, 20 mol %), the phenyl vinyl sulfone (0.3 mmol, 1.5 equiv), and 250 μL of water. The reaction was stirred at room temperature during 72 h. Then the mixture was concentrated and purified using flash column chromatography. Elution with EtOAc/hexane (1:1) gave the pure compound **8a** as a yellow oil (57% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (dt, J = 7.1, 1.7 Hz, 2H), 7.60 (tt, J = 7.4, 1.7 Hz, 1H), 7.51 (tt, J = 7.4, 1.4 Hz, 2H), 3.81 (t, J = 7.0 Hz, 1H), 3.57 (s, 3H), 3.16−2.99 (m, 2H), 2.91−2.77 (m, 2H), 2.52−2.41 (m, 1H), 2.06 (s, 3H), 1.96−179 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (C), 174.0 (C), 138.8 (C), 133.9 (CH), 129.4 (CH), 128.0 (CH), 53.9 (CH_2), 52.1 (CH_3), 44.7 (CH_2), 38.5 (CH), 29.9 (CH_3), 24.4 (CH_2); (electrospray$^+$) $[M + Na]^+$ calcd for $C_{14}H_{18}O_5SNa$ 321.0773, found 321.0755.

*2-(Methoxycarbonyl)-4-oxopentanoic Acid (**9a**).* To a solution of acid **2a** (0.3 mmol) in acetone (0.3 mL) were added platinum complex **5c** (0.015 mmol, 5 mol %) and 250 μL of water. The mixture was stirred at room temperature for 72 h. Then 3 mL of aqueous saturated sodium bicarbonate was added, and the mixture was extracted with EtOAc (3 × 3 mL). The aqueous phase was acidified to pH = 1 with concentrated HCl and then extracted with EtOAc (3 × 3 mL). The organic solvent was dried over $MgSO_4$, filtered, and concentrated under reduced pressure, obtaining pure acid compound **9a**. The product was directly obtained following the procedure as yellow oil (94% yield) without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (bs, 1H), 3.81 (t, J = 7.0 Hz, 1H), 3.69 (s, 3H), 3.03 (d, J = 7.0 Hz, 2H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (C), 172.5 (C), 169.4 (C), 53.0 (CH_3), 46.5 (CH), 41.9 (CH_2), 29.6 (CH_3); (MS-ESI$^+$) $[M + Na]^+$ calcd for $C_7H_{10}O_5Na$ 197.0420, found 197.0422.

*Methyl 5-Methylene-2-oxotetrahydrofuran-3-carboxylate (**3**).* To a solution of acid **2a** (0.3 mmol) in acetone (0.3 mL) were added platinum complex **5c** (0.003 mmol, 1 mol %) and 250 μL of water. The mixture was stirred at room temperature during 6 h. Then the reaction mixture was extracted with EtOAc (3 × 3 mL); the organic solvent was dried over $MgSO_4$, filtered and concentrated under reduced pressure, obtaining pure compound **3**. The product was directly obtained as a yellow oil (yield 91%) without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (q, J = 2.3 Hz, 1H), 4.35 (dt, J = 2.7, 1.8 Hz, 1H), 3.76 (s, 3H), 3.71 (dd, J = 10.4, 7.6 Hz, 1H), 3.24 (ddt, J = 16.7, 7.6, 2.1 Hz, 1H), 3.02 (ddt, J = 16.7, 10.4, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7 (C), 167.4 (C), 153.2 (C), 89.8 (CH_2), 53.4 (CH), 46.2 (CH_3), 29.3 (CH_2); (MS-TOF MS EI$^+$) $[M]^+$ calcd for $C_7H_8O_4$ 156.0423, found 156.0425.

Procedure for the Synthesis of the Cyclic Acid 14 (Scheme 4). *(1S,2R)-3-Formyl-1-(methoxycarbonyl)-2,4-dimethylcyclopent-3-enecarboxylic Acid (**14**).* To a solution of lactone **3** (0.3 mmol) in acetone (0.3 mL) were added DABCO (0.06 mmol, 20 mol %), $PtCl_2(DMSO)_2$ (0.003 mmol, 1 mol %), **15** (0.06 mmol, 20 mol %), the corresponding α,β-unsaturated aldehyde (0.45 mmol, 1.5 equiv), and 50 μL of water. The reaction was stirred at room temperature for 24−72 h. Then 3 mL of aqueous saturated sodium bicarbonate was added, and the mixture was extracted with EtOAc (3 × 3 mL). The aqueous phase was acidified to pH = 1 with concentrated HCl and then extracted with EtOAc (3 × 3 mL). The organic solvent was dried over $MgSO_4$, filtered, and concentrated under reduced pressure, obtaining pure acid compounds **14a**−**c**. The product **14a** was directly obtained following the procedure as yellow oil (yield 85%) without further purification. The relative configuration was confirmed by NOESY experiment (see SI-38, Supporting Information). Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.87 (s, 1H), 8.06 (bs, 1H), 3.82 (q, J = 7.4 Hz, 1H), 3.75 (s, 3H), 3.55 (dquint, J = 19.4, 1.4 Hz, 1H), 2.94 (d, J = 19.4 Hz, 1H), 2.12 (d, J = 1.4 Hz, 3H), 1.05 (d, J = 7,1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.4 (CH), 176.0 (C), 169.8 (C), 157.9 (C), 139.8 (C), 62.1 (C), 52.8 (CH_3), 45.5 (CH_2), 43.6 (CH), 14.6 (CH_3), 14.0 (CH_3) Minor diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.87 (s, 1H), 8.06 (bs, 1H), 3.89−3.42 (m, 1H), 3.74 (s, 3H), 3.51−3.42 (m, 1H), 2.90 (d, J = 19.4 Hz, 1H), 2,08 (s, 3H), 1.11 (d, J = 7,1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.4 (CH), 176.0 (C), 169.8 (C), 157.9 (C), 139.8 (C), 62.1 (C), 53.0 (CH_3), 45.3 (CH_2), 43.8 (CH), 14.6 (CH_3), 14.0 (CH_3); (MS-ESI$^+$) $[M + H]^+$ calcd for $C_{11}H_{15}O_5$ 227.0914, found 227.0920.

General Procedure for the Synthesis of Diesters 16a−c (Scheme 4). To a solution of lactone **3** (0.3 mmol) in acetone (0.3 mL) were added DABCO (0.06 mmol, 20 mol %), $PtCl_2(DMSO)_2$ (0.003 mmol, 1 mol %), **15** (0.06 mmol, 20 mol %), the corresponding $\alpha\beta$-unsaturated aldehyde (0.45 mmol, 1.5 equiv), and 50 μL of water. Then, 3 mL of aqueous saturated sodium bicarbonate was added, and the mixture was extracted with EtOAc (3 × 3 mL). The aqueous phase was acidified to pH = 1 with concentrated HCl and then extracted with EtOAc (3 × 3 mL). The organic solvent was dried over $MgSO_4$, filtered, and concentrated under reduced pressure, obtaining pure acid compounds **14a**−**c**. To a solution of these acid compounds **14a**−**c** (0.2 mmol) in MeOH (0.2 mL) was added dropwise (diazomethyl)trimethylsilane (0.6 mmol, 3 equiv), and the mixture was further stirred for 4 h in darkness. After completion of the reaction (which is followed by TLC), 50 μL of glacial acetic was added, and stirring was continued for 30 min. Then the reaction mixture was extracted with CH_2Cl_2 (3 × 3 mL), and the organic layer was washed three times with 3 mL of aqueous saturated sodium bicarbonate, dried over Na_2SO_4, filtered, and concentrated under reduced pressure, obtaining the crude compounds which were purified using flash column chromatography. Elution with EtOAc/hexane (1:3) affords the pure compounds.

*(R)-Dimethyl 3-Formyl-2,4-dimethylcyclopent-3-ene-1,1-dicarboxylate (**16a**).* The product was directly obtained following the standard procedure as yellow oil (yield 78%): $[\alpha]^{25}_D$ = −108.9 (c = 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (s, 1H), 3.83 (q, J = 7.1 Hz, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.48 (d, J = 19.3 Hz, 1H), 2.81 (d, J = 19.3 Hz, 1H), 2.05 (s, 3H), 0.95 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.0 (CH), 171.8 (C), 170.0 (C), 156.9 (C), 140.0 (C), 62.2 (C), 53.0 (CH_3), 52.6 (CH_3), 45.6 (CH_2), 43.6 (CH), 14.7 (CH_3), 14.0 (CH_3); (MS-ESI$^+$) $[M + H]^+$ calcd for $C_{12}H_{17}O_5$ 241.1070, found 241.1072. The enantiomeric excess was determined by HPLC using a Chiralcel IC column [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 39.2 min, τ_{minor} = 34.7 min (er = 85:15).

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*(R)-Dimethyl 3-Formyl-4-methyl-2-phenylcyclopent-3-ene-1,1-dicarboxylate (**16b**)*[6c]. The product was directly obtained following the standard procedure as a yellow oil (40% yield): $[\alpha]^{25}_D$ = −157.4 (*c* = 1.0, $CHCl_3$) (lit.[6c] $[\alpha]^{25}_D$ = −293.6 (*c* = 1.0, $CHCl_3$)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.15−7.10 (m, 3H), 7.02−6.99 (m, 2H), 5.03 (s, 1H), 3.72 (d, *J* = 19.1 Hz, 1H), 3.70 (s, 3H), 3.08 (s, 3H), 2.88 (d, *J* = 19.6 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.9 (CH), 171.0 (C), 168.4 (C), 157.2 (C), 137.5 (C), 137.3 (C), 127.8 (CH), 127.4 (CH), 126.7 (CH), 62.9 (C), 54.7 (CH), 52.5 (CH_3), 51.5 (CH_3), 45.9 (CH_2), 13.5 (CH_3). The enantiomeric excess was determined by HPLC using a Chiralcel IC column [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 18.8 min, τ_{minor} = 34.2 min (er = 92:8).

*(R)-Dimethyl 3-Formyl-2-(furan-2-yl)-4-methylcyclopent-3-ene-1,1-dicarboxylate (**16c**)*[16]. The product was directly obtained following the standard procedure as a yellow oil (35% yield): $[\alpha]^{25}_D$ = −207.6 (*c* = 1.0, $CHCl_3$) (lit. enantiomer: *ent*-**16c**:[16] $[\alpha]^{25}_D$ = +220.8 (*c* = 1.0, $CHCl_3$)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.16 (dd, *J* = 1.8, 0.8 Hz, 1 H), 6.18 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.02 (dd, *J* = 3.2, 0.3 Hz, 1H), 5.10 (s, 1H), 3.74−3.70 (m, 1H), 3.69 (s, 3H), 3.38 (s, 3H), 2.92 (d, *J* = 19.4 Hz, 1H), 2.22 (q, *J* = 1.0 Hz, 3H). The enantiomeric excess was determined by HPLC using a Chiralcel IC column [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 18.8 min, τ_{minor} = 34.2 min (er = 82:18).

■ ASSOCIATED CONTENT

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

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(11) The presence of water is completely necessary to obtain reactivity toward the corresponding aqua complex (see ref 9).

(12) All these reactions were performed in the presence of 50 μL of H_2O. Dried solvents inhibit the cyclization reaction.

(13) Different trials with cinchona and thiourea−cinchona alkaloid catalysts have been attempted, obtaining in all the cases moderate enantioselectivies.

(14) Lower catalytic loading of complex **5c** (1−2 mol%) did not afford the final compound **8a**, and only the intermediate lactone **4a** was observed. Lactone **3** exclusively in the presence of water did not react after 48 h, indicating that the platinum complex is necessary to obtain the opened products.

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