Published in final edited form as:

Synthesis (Stuttg). 2015 October ; 47(19): 3020–3026. doi:10.1055/s-0034-1379934.

Acetoxy-Substituted Cyclopropane Dicarboxyls as Stable Donor-Acceptor-Acceptor Cyclopropanes

Yahaira Reyes and Keith T. Mead*

Department of Chemistry, Mississippi State University, Mississippi State, MS 39762, USA

Abstract

A study of cyclopropanations of oxy-substituted ethenes with ethyl α -diazoaroyl acetates is described. Whereas trimethylsilyl vinyl ether and ethyl vinyl ether gave dihydrofuran products, stable cyclopropanes were isolated when vinyl acetate was used. Yields ranged from 0–87%, depending on the nature and position of the aryl ring substituent.

Graphical abstract

Keywords

Cyclopropanations; Donor-acceptor-acceptor Rhodium catalyzed; Beta-lactones; Dihydrofurans

Donor-acceptor cyclopropanes (DACs) have found increasing use in the synthesis of a range of cyclic structures in recent years, largely due to their ability to give rise to reactive 1,3-dipole intermediates on Lewis acid activation.¹ For simplicity, cyclopropanes that take part in these reactions can be subdivided into monoactivated (I) and diactivated (II) structures. Predictably, diactivated, or donor-acceptor-acceptor, cyclopropanes yield the corresponding 1,3-dipole intermediates with relative ease owing to their increased anion stabilization (eq 1). Moreover, when generated in the presence of suitable dipolarophiles, formal [3 + 2],² [3 + 3],³ and [4 + 3]⁴ cycloadditions are possible, leading to the formation of complex ring structures.

Fax: +1-662-325-1618. mead@chemistry.msstate.edu.

Supporting Information for this article is available online at <http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000084>.

Monoactivated cyclopropanes (I), in general, are more sluggish to similar reactivity. However, the exception to this is observed when the donor is an alkoxy group. This subset of DACs is particularly useful, as these structures provide simultaneous formation of both enolate and activated carbonyl equivalents upon ring opening (eq 2). Moreover, despite their acid-lability, they are sufficiently stable to allow purification on silica gel. These derivatives, too, have served as substrates for the synthesis of a variety of cyclic structures, via formal [3 + 2] strategies.⁵

Equation 2

When one considers the related oxy-substituted cyclopropane dicarbonyl substrates, a different picture emerges. The literature shows that when the oxy-substituent is alkoxy in nature, or even acetoxy in certain cases, the initial product can rearrange to a dihydrofuran ring⁶ (Scheme 1). In fact, exceptions to this rule are rare.⁷ This is understandable, given the presence of the additional acceptor group. France and coworkers initially reported the formation of alkoxy-substituted cyclopropane dicarbonyls from reactions of β -heteroarylketone- α -diazoesters with alkoxy alkenes,⁸ but later reassigned the correct structures to be dihydrofurans.⁹

Intuitively, the use of vinyl acetate (Scheme 1, $R' = \text{Ac}$) should suppress the rearrangement step by weakening the donor capacity. However, literature examples documenting the use of this strategy are limited and have produced mixed results, with the formation of both cyclopropane and dihydrofuran products being reported.¹⁰ Given the lack of information in this area, we decided to study cyclopropanations of ethyl α -diazoaryl acetates with both simple alkoxy and acetoxy alkenes. Ethyl α -diazoaryl acetates **2** used for this study were prepared from commercially available aryl aldehydes **1** using the method of Erhunmwunse and Steel¹¹ (Table 1).

Initial studies began with ethyl α -diazobenzoyl acetate **2a** (Table 2). Cyclopropanations of **2a** with trimethylsilyl vinyl ether (entry 1) and ethyl vinyl ether (entry 2) in pentane using Rh_2esp_2 as catalyst gave moderate yields of the expected dihydrofuran products **3a** and **3b**, respectively, as sole products. By complete contrast, when vinyl acetate was used (entry 3), only the diastereomeric mixture of cyclopropanes **4a** were isolated by column chromatography. Subsequent attempts to increase the yield of cyclopropane products were unsuccessful, including slow addition of **2a** to the catalyst-alkene mixture (entry 4), change of solvent (entries 5 and 6), increasing the alkene equivalents (entry 7), and using different catalysts (entries 8–10).

It is noteworthy that even though dihydrofuran formation was not observed when vinyl acetate was used, two other products *were* isolated. These were dimerization product **5**, a known side product generated during cyclopropanations,¹² and β -lactone **6** (Figure 1). In order to maximize the yield of the cyclopropane, and minimize β -lactone formation, the diazo component was used in excess.¹³ For compound **4a**, this was achieved using 1.4 eq. of **2a**. However, for other derivatives as much as a 3-fold excess of the diazo reagent was required for optimal results (Table 3).

As Table 3 shows, the yield of the acetoxy-substituted cyclopropane product is highly influenced by substituent effects, although we can offer no explanation for the trends observed. The most striking change is found in the progression of *p*-methyl (**2g**) to *p*-ethyl (**2h**) to *p*-isopropyl (**2b**), providing yields of 16%, 40%, and 73%, respectively. Halogenated structures, in general, gave higher yields than their alkylated counterparts, with *meta*-substitution giving superior results relative to *para*. Overall, yields ranged from 0–87%. In all cases, the cyclopropane diastereomers were inseparable. In those mixtures showing sufficient peak separation by ¹H NMR, a 6:1 diastereomeric ratio could be estimated, although the major isomer could not be identified.

Given the surprising absence of dihydrofuran products in these reactions, we decided to see if we could induce rearrangement of cyclopropanes **4** into dihydrofurans by treatment with Lewis acids. Not only did we not observe this with a variety of Lewis acids (SnCl₄, BF₃OEt₂, In(OTf)₃), but when TiCl₄ was employed, we were able to isolate 1-naphthol product **8** in good yield (Scheme 2). In this case, ring closure from the presumed intermediate **7** is favored, although reversible formation of a dihydropyran is likely.¹⁴ This reaction is currently under further investigation.

All reactions were performed using oven-dried glassware under inert atmosphere (Ar or N₂). Reactions were monitored on silica gel TLC plates (UV 254). Column chromatography was performed on silica gel using various combinations of hexane, EtOAc, DCM, and petroleum ether as the eluting solvents. Anhydrous solvent DMSO, ethyldiazoacetate (EDA), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was purchased from Sigma Aldrich in a SureSeal™ bottle and used without further purification. Other solvents and reagents such as pentane and DCM were dried over calcium hydride and distilled before use. Alkenes such as ethyl vinyl ether and vinyl acetate were distilled prior to use. IBX used in the reactions was synthesized using the standard procedure developed by Dess and Martin.¹⁵ Ethyl α -diazoaroyl acetates **2** used for this study were prepared utilizing the method of Erhunmwunse and Steel¹¹ using commercially available aldehydes. Compounds were purified using column chromatography or the Biotage Isolera™ One flash chromatography system. All of the ¹H, ¹³C, MS spectra for compounds **2b–k**, **3a**, **3b**, and **4a–k** can be found in the supporting Information.

General procedure for ethyl α -diazoaroyl acetates **2**

Following reported procedure¹¹: to a solution of EDA (2–3 eq) in DMSO, DBU (0.1 eq) and **1** were sequentially added and stirred. A solution of IBX (2.5 eq) in DMSO was added to the reaction and was stirred overnight. Reaction was quenched by slow addition of 5 % NaHCO₃ then filtered through cotton. Compound was extracted with DCM, washed with

sat. NaHCO₃, and dried with Na₂SO₄. Solvents were removed under reduced pressure and compound was purified using flash chromatography.

Ethyl- α -diazobenzoyl acetate (2a)¹¹

EDA (0.06 mL, 0.57055 mmol, 3 eq), DBU (2.90 μ L, 0.0196 mmol, 0.1 eq), benzaldehyde (0.02 mL, 0.1959 mmol, 1 eq). 48.2 mg; Isolated yield: 82 %; yellow oil. ¹H NMR (600 MHz, CDCl₃): 7.60 (d, *J* = 7.0, 2H), 7.48 (t, *J* = 7.4, 1H), 7.38 (t, *J* = 7.8, 2H), 4.21 (q, *J* = 7.3, 2H), 1.21 (t, *J* = 7.3, 3H); R_f: 0.43 (Hex: EtOAc; 3:1).

We have shown that stable acyloxy-substituted donor-acceptor-acceptor cyclopropanes can be prepared and isolated when α -diazo- β -ketoesters are reacted with vinyl acetate under rhodium catalysis. Further scrutiny of this relatively under-investigated class of compounds is on-going, and is expected to yield new synthetic methods.

Ethyl-2-diazo-3-(4-isopropylphenyl)-3-oxopropanoate (2b)

4-isopropylbenzaldehyde (0.15 mL, 0.9605 mmol, 1 eq), EDA (0.32 mL, 2.8815 mmol, 3 eq), DBU (0.01 mL, 0.0668 mmol, 0.1 eq), IBX (539.8 mg, 1.9277 mmol, 2 eq); 200.6 mg; Isolated yield: 80% yellow oil; ¹H NMR (300 MHz, CDCl₃): 7.60 (d, *J* = 8.3, 2H), 7.28 (d, *J* = 8.2, 2H), 4.26 (q, *J* = 7.1, 2H), 3.02-2.88 (m, 1H), 1.28-1.23 (m, 9H); ¹³C (CDCl₃): 186.3, 161.1, 153.7, 134.5, 128.6, 125.8, 61.4, 34.1, 23.6, 14.1; HRMS (ESI-TOF): Calculated for C₁₄H₁₆N₂NaO₃ (283.1059) [M + Na]⁺, Found: 283.1006; R_f: 0.64 (Hex: EtOAc; 4:1).

Ethyl-2-diazo-3-(3-bromophenyl)-3-oxopropanoate (2c)

3-bromobenzaldehyde (0.09 mL, 0.8414 mmol, 1 eq), EDA (0.28 mL, 2.5242 mmol, 3.0 eq), DBU (0.01 mL, 0.0668 mmol, 0.1 eq), IBX (473.6 mg, 1.6913 mmol, 2.0 eq); 222.7 mg; Isolated yield: 89%; yellow oil; ¹H NMR (600 MHz, CDCl₃): 7.75 (s, 1H), 7.65 (d, *J* = 7.9, 1H), 7.54 (d, *J* = 7.7, 1H), 7.29 (t, *J* = 7.9, 1H), 4.25 (q, *J* = 7.1, 2H), 1.25 (t, *J* = 7.1, 3H); ¹³C (CDCl₃): 185.4, 160.6, 138.8, 134.9, 131.2, 129.2, 126.8, 121.8, 61.7, 14.1; HRMS (ESI-TOF): Calculated for C₁₁H₉⁷⁹BrN₂NaO₃ (318.9694) [M + Na]⁺, Found: 318.9646; R_f: 0.51 (Hex: Et₂O; 2:1).

Ethyl-2-diazo-3-(3-chlorophenyl)-3-oxopropanoate (2d)

3-chlorobenzaldehyde (0.11 mL, 0.9895 mmol, 1 eq), EDA (0.33 mL, 2.9685 mmol, 3.0 eq), DBU (0.01 mL, 0.0668 mmol, 0.1 eq), IBX (555.2 mg, 1.9827 mmol, 2.0 eq); 225.6 mg; Isolated yield: 90 %; yellow oil; ¹H NMR (600 MHz, CDCl₃): 7.59 (s, 1H), 7.50-7.47 (m, 2H), 7.34 (t, *J* = 7.9, 1H), 4.24 (q, *J* = 7.1, 2H), 1.24 (t, *J* = 7.1, 3H); ¹³C (CDCl₃): 185.4, 160.5, 138.5, 133.7, 131.9, 128.9, 128.2, 126.3, 61.6, 14.0; HRMS (ESI-TOF): Calculated for C₁₁H₉ClN₂NaO₃ (275.0199) [M + Na]⁺, Found: 275.0161; R_f: 0.51 (Hex: Et₂O; 2:1).

Ethyl-2-diazo-3-(3-methylphenyl)-3-oxopropanoate (2e)

m-tolualdehyde (0.08 mL, 0.7142 mmol, 1 eq), EDA (0.24 mL, 2.1426 mmol, 3.0 eq), DBU (0.01 mL, 0.0668 mmol, 0.1 eq), IBX (406.3 mg, 1.4509 mmol, 2.0 eq); 126.7 mg; Isolated

yield: 76 %; yellow oil; ^1H NMR (300 MHz, CDCl_3): 7.42-7.40 (m, 2H), 7.32-7.29 (m, 2H), 4.23 (q, $J=7.1$, 2H), 2.39 (s, 3H), 1.25 (t, $J=7.1$, 3H); ^{13}C (CDCl_3): 187.0, 161.0, 137.7, 137.0, 132.9, 128.6, 127.6, 125.4, 61.5, 21.2, 14.1; HRMS (ESI-TOF): Calculated for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{NaO}_3$ (255.0746) $[\text{M} + \text{Na}]^+$, Found: 255.0727; R_f : 0.25 (Hex: EtOAc; 8:1).

Ethyl-2-diazo-3-(2-methylphenyl)-3-oxopropanoate (2f)

α -tolualdehyde (0.12 mL, 1.037 mmol, 1 eq), EDA (0.36 mL, 3.211 mmol, 3.0 eq), DBU (0.02 mL, 0.1337 mmol, 0.1 eq), IBX (601.5 mg, 2.1482 mmol, 2.0 eq); 141.4 mg; Isolated yield: 59 %; yellow oil; ^1H NMR (600 MHz, CDCl_3): 7.35-7.32 (m, 1H), 7.23-7.22 (m, 3H), 4.17 (q, $J=6.6$, 2H), 2.35 (s, 3H), 1.17 (t, $J=6.6$, 3H); ^{13}C (CDCl_3): 188.8, 160.5, 137.9, 135.0, 130.4, 130.2, 126.5, 125.2, 61.5, 19.1, 14.0; HRMS (ESI-TOF): Calculated for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{NaO}_3$ (255.0746) $[\text{M} + \text{Na}]^+$, Found: 255.0743; R_f : 0.14 (Pet: EtOAc; 10:1).

Ethyl-2-diazo-3-(4-methylphenyl)-3-oxopropanoate (2g)

p-tolualdehyde (0.20 mL, 1.6962 mmol, 1 eq), EDA (0.57 mL, 5.0855 mmol, 3.0 eq), DBU (0.03 mL, 0.1696 mmol, 0.1 eq), IBX (925.3 mg, 3.3046 mmol, 2.0 eq); 321.3 mg; Isolated yield: 82 %; yellow oil; ^1H NMR (600 MHz, CDCl_3): 7.54 (d, $J=7.5$, 2H), 7.21 (d, $J=7.5$, 2H), 4.26 (q, $J=6.9$, 2H), 2.40 (s, 3H), 1.27 (t, $J=6.9$, 3H); ^{13}C (CDCl_3): 186.5, 161.1, 143.0, 134.2, 128.55, 128.50, 61.5, 21.6, 14.2; HR MS (ESI-TOF): Calculated for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{NaO}_3$ (255.0746) $[\text{M} + \text{Na}]^+$, Found: 255.0862; R_f : 0.20 (Hex: EtOAc; 8:1).

Ethyl-2-diazo-3-(4-ethylphenyl)-3-oxopropanoate (2h)

4-ethylbenzaldehyde (0.11 mL, 0.8035 mmol, 1 eq), EDA (0.27 mL, 2.4105 mmol, 3.0 eq), DBU (12.0 μL , 0.0802 mmol, 0.1 eq), IBX (477.4 mg, 1.7050 mmol, 2.0 eq); 142.7 mg; Isolated yield: 72 %; yellow oil; ^1H NMR (300 MHz, CDCl_3): 7.56 (d, $J=8.3$, 2H), 7.22 (d, $J=8.2$, 2H), 4.23 (q, $J=7.1$, 2H), 2.67 (q, $J=7.6$, 2H), 1.28-1.22 (m, 6H); ^{13}C (600 MHz, CDCl_3): 186.3, 161.0, 149.1, 134.4, 128.5, 127.2, 61.4, 28.8, 15.0, 14.1; HRMS (ESI-TOF): Calculated for $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_3$ (247.1083) $[\text{M} + \text{H}]^+$, Found: 247.1074; R_f : 0.17 (Hex: Et₂O; 8:1).

Ethyl-2-diazo-3-(4-fluorophenyl)-3-oxopropanoate (2i)

4-fluorobenzaldehyde (0.09 mL, 0.8055 mmol, 1 eq), EDA (0.27 mL, 2.4165 mmol, 3.0 eq), DBU (0.01 mL, 0.0668 mmol, 0.1 eq), IBX (451.1 mg, 1.6110 mmol, 2.0 eq); 142.8 mg; Isolated yield: 75 %; yellow oil; ^1H NMR (600 MHz, CDCl_3): 7.68-7.66 (m, 2H), 7.10 (t, $J=8.6$, 2H), 4.25 (q, $J=7.1$, 2H), 1.27 (t, $J=7.1$, 2H); ^{13}C (CDCl_3): 185.4, 165.9 (d, $J=253.6$), 160.9, 133.1 (d, $J=3.1$), 131.1 (d, $J=9.2$), 115.0 (d, $J=22.0$), 61.6, 14.2; HRMS (ESI-TOF): Calculated for $\text{C}_{11}\text{H}_9\text{FN}_2\text{NaO}_3$ (259.0495) $[\text{M} + \text{Na}]^+$, Found: 259.0457; R_f : 0.10 (Pet: EtOAc; 12:1).

Ethyl-2-diazo-3-(4-bromophenyl)-3-oxopropanoate (2j)

Reaction was performed over two steps as described in the literature procedure:¹¹ 4-bromobenzaldehyde (170.1 mg, 0.9193 mmol, 1 eq), EDA (0.30 mL, 2.6976 mmol, 3.0 eq),

DBU (0.01 mL, 0.0668 mmol, 0.1 eq), IBX (507.1 mg, 1.8109 mmol, 2.0 eq); 210.6 mg; Isolated yield: 77 %; yellow oil; ^1H NMR (300 MHz, CDCl_3): 7.55 (d, J = 8.6, 2H), 7.48 (d, J = 8.6, 2H), 4.23 (q, J = 7.1, 2H), 1.27 (t, J = 7.1, 3H); ^{13}C (CDCl_3): 185.8, 160.7, 135.7, 131.0, 130.0, 127.0, 61.7, 14.1; HRMS (ESI-TOF): Calculated for $\text{C}_{11}\text{H}_9^{79}\text{BrN}_2\text{NaO}_3$ (318.9694) $[\text{M} + \text{Na}]^+$, Found: 318.9516; R_f : 0.12 (Pet: EtOAc; 17:1).

Ethyl-2-diazo-3-(4-chlorophenyl)-3-oxopropanoate (2k)

4-chlorobenzaldehyde (111.9 mg, 0.7960 mmol, 1 eq), EDA (0.27 mL, 2.4105 mmol, 3.0 eq), DBU (0.01 mL, 0.0668 mmol, 0.1 eq), IBX (450.5 mg, 1.609 mmol, 2.0 eq); 133.9 mg; Isolated yield: 67 %; yellow oil; ^1H NMR (300 MHz, CDCl_3): 7.59 (d, J = 8.6, 2H), 7.38 (d, J = 8.6, 2H), 4.24 (q, J = 7.1, 2H), 1.27 (t, J = 7.1, 3H); ^{13}C (CDCl_3): 185.7, 160.7, 138.5, 135.2, 129.9, 128.1, 61.6, 14.2; HRMS (ESI-TOF): Calculated for $\text{C}_{11}\text{H}_9\text{ClN}_2\text{NaO}_3$ (275.0199) $[\text{M} + \text{Na}]^+$, Found: 275.0198; R_f : 0.13 (Pet: EtOAc; 12:1).

General cyclopropanation procedure

To a 15 mL round bottom flask, $\text{Rh}_2(\text{esp})_2$ (0.1 mol %) was added and purged under argon. Pentane (0.2 M solution of alkene) followed by styrene (alkene) was added and reaction temperature was dropped to 0°C . After 10 min, a solution of ethyl- α -diazobenzoyl acetate (1.4 eq., 0.2 M in pentane) was added in one shot. After 15 minutes, ice bath was removed and mixture was stirred for 16 hrs. Mixture was then concentrated under reduced pressure and was purified using flash chromatography. *** Note: all of the acetoxycyclopropanes were purified using column chromatography (6:1 DCM: Hex) and in some cases, 2–3 eq of diazo was added to increase the cyclopropane yield versus β -lactones.

Ethyl-2-phenyl-5-(trimethylsilyloxy)-4,5-dihydrofuran-3-carboxylate (3a)

Trimethylvinylloxysilane (0.08 mL, 0.5185 mmol, 1 eq), ethyl- α -diazobenzoylacetate **2a** (158.4 mg, 0.7259 mmol, 1.4 eq), Rh_2esp_2 (0.4 mg, 0.0005 mmol, 0.001 eq); 49.8 mg; Isolated yield: 31 %; clear oil; ^1H NMR (600 MHz, CDCl_3): 7.81 (d, 2H), 7.40–7.38 (m, 3H), 5.95 (dd, J = 2.5, J = 7.0), 4.17–4.10 (m, 2H), 3.27 (dd, J = 7.0, J = 16.3, 1H), 2.94 (dd, J = 2.5, J = 16.3, 1H), 1.21 (t, J = 7.1, 3H), 0.21 (s, 9H); ^{13}C (CDCl_3): 165.0, 162.6, 130.1, 129.9, 129.2, 127.5, 101.7, 98.9, 59.7, 40.8, 14.2, 0.17; HRMS (ESI-TOF): Calculated for $\text{C}_{16}\text{H}_{22}\text{NaO}_4\text{Si}$ (329.1185) $[\text{M} + \text{Na}]^+$, Found: 329.1181; R_f : 0.44 (Pet: EtOAc; 6:1).

Ethyl-5-ethoxy-2-phenyl-4,5-dihydrofuran-3-carboxylate (3b)

Ethyl vinyl ether (0.04 mL, 0.4182 mmol, 1 eq), ethyl- α -diazobenzoylacetate **2a** (134.9 mg, 0.6182 mmol, 1.4 eq), Rh_2esp_2 (1.2 mg, 0.0002 mmol, 0.003 eq); 48.1 mg; Isolated yield: 46 %; light yellow oil; ^1H NMR (600 MHz, CDCl_3): 7.81 (d, J = 7.57, 2H), 7.41–7.37 (m, 3H), 5.64 (dd, J = 2.7, J = 7.4, 1H), 4.16–4.09 (m, 2H), 3.95–3.93 (m, 1H), 3.67–3.64 (m, 1H), 3.27 (dd, J = 7.4, J = 16.5, 1H), 2.98 (dd, J = 2.68, J = 16.5, 1H), 1.26 (t, J = 7.1, 3H), 1.20 (t, J = 7.1, 3H); ^{13}C (CDCl_3): 164.8, 162.9, 130.2, 130.0, 129.3, 127.5, 104.1, 102.0, 64.2, 59.7, 38.3, 15.1, 14.2; HRMS (ESI-TOF): Calculated for $\text{C}_{15}\text{H}_{17}\text{O}_4$ (261.1121) $[\text{M} - \text{H}]^+$, Found: 261.1145; R_f : 0.34 (Pet: EtOAc; 8:1).

Ethyl 2-acetoxy-1-benzoylcyclopropanecarboxylate (4a)

Vinyl acetate (0.20 mL, 2.1820 mmol, 1 eq), ethyl- α -diazobenzoylacetate **2a** (670.3 mg, 3.0718 mmol, 1.4 eq), Rh₂esp₂ (2.0 mg, 0.0003 mmol, 0.001 eq); 305.8 mg; Yield of diastereomers: 51 %; yellow oil; 142.8 mg of β -lactone; ¹H NMR (600 MHz, CDCl₃): 7.89 (d, *J* = 7.3, 2H), 7.55 (t, *J* = 7.3, 1H), 7.45 (t, *J* = 7.3, 2H), 4.81 (dd, *J* = 5.2, *J* = 6.9, 1H), 4.01 (q, *J* = 7.1, 2H), 2.17-2.14 (m, 1H), 2.09 (s, 3H), 1.83-1.76 (m, 1H), 0.93 (t, *J* = 7.1, 3H); ¹³C (CDCl₃): 193.1, 170.6, 167.2, 136.7, 132.9, 128.5, 128.4, 128.3, 128.1, 61.6, 56.6, 38.8, 20.5, 20.3, 13.6; HRMS(ESI-TOF): Calculated for C₁₅H₁₆NaO₅ (299.0895) [M + Na]⁺, Found: 299.0912; R_f: 0.17 (DCM: Hex; 6:1).

Ethyl-2-acetoxy-1-(4-isopropylbenzoyl)cyclopropanecarboxylate (4b)

Vinyl acetate (23.5 μ L, 0.2549 mmol, 1 eq), ethyl-2-diazo-3-(4-isopropylphenyl)-3-oxopropanoate **2b** (200.6 mg, 0.7707 mmol, 3 eq), Rh₂esp₂ (0.2 mg, 0.0002 mmol, 0.001 eq); 59.3 mg; Yield of diastereomers: 73 %; yellow oil; 61.4 mg of β -lactone; ¹H NMR (600 MHz, CDCl₃): 7.86 (d, *J* = 8.1, 2H), 7.30 (d, *J* = 8.1, 2H), 4.81-4.79 (m, 1H), 4.07 (q, *J* = 7.0, 2H), 2.98-2.93 (m, 1H), 2.14-2.12 (m, 1H), 2.09 (s, 3H), 1.78-1.75 (m, 1H), 0.95 (t, *J* = 7.0, 3H); 192.5, 170.7, 167.3, 154.6, 134.3, 128.8, 128.5, 126.5, 126.4, 61.5, 56.5, 38.7, 34.2, 23.6, 23.5, 20.5, 20.1, 13.6; HRMS (ESI-TOF): Calculated for C₁₈H₂₂NaO₅ (341.1365) [M + Na]⁺, Found: 341.1306; R_f: 0.22 (DCM: Hex; 6:1).

Ethyl-2-acetoxy-1-(3-bromobenzoyl)cyclopropanecarboxylate (4c)

Vinyl acetate (0.05 mL, 0.5424 mmol, 1 eq), ethyl-2-diazo-3-(3-bromophenyl)-3-oxopropanoate **2c** (286.6 mg, 0.9646 mmol, 1.7 eq), Rh₂esp₂ (0.2 mg, 0.0003 mmol, 0.0005 eq); 165.2 mg; Yield of diastereomers: 86 %; yellow oil; 36.7 mg of β -lactone; ¹H NMR (600 MHz, CDCl₃): 8.04 (s, 1H), 7.86 (d, *J* = 7.5, 1H), 7.68 (d, *J* = 7.6, 1H), 7.33 (t, *J* = 7.7, 1H), 4.77-4.75 (m, 1H), 4.07 (q, *J* = 7.1, 2H), 2.16-2.14 (m, 1H), 2.10 (s, 3H), 1.87-1.85 (m, 1H), 0.98 (t, *J* = 7.1, 3H); ¹³C (CDCl₃): 191.9, 170.5, 166.8, 138.5, 135.6, 131.0, 129.9, 126.6, 122.6, 61.6, 56.7, 38.6, 20.4, 20.3, 13.6; HRMS (ESI-TOF): Calculated for C₁₅H₁₅⁷⁹BrNaO₅ (377.0001) [M + Na]⁺, Found: 376.9923; R_f: 0.20 (DCM: Hex; 6:1).

Ethyl-2-acetoxy-1-(3-chlorobenzoyl)cyclopropanecarboxylate (4d)

Vinyl acetate (0.05 mL, 0.5424 mmol, 1 eq), ethyl-2-diazo-3-(3-chlorophenyl)-3-oxopropanoate **2d** (309.7 mg, 1.2258 mmol, 2.3 eq), Rh₂esp₂ (0.4 mg, 0.0005 mmol, 0.001 eq); 146.3 mg; Yield of diastereomers: 87 %; yellow oil; 60.3 mg of β -lactone; ¹H NMR (600 MHz, CDCl₃): 7.89 (s, 1H), 7.81 (d, *J* = 7.7, 1H), 7.53 (d, *J* = 7.2, 1H), 7.39 (t, *J* = 7.8, 1H), 4.7-4.75 (m, 1H), 4.07 (q, *J* = 7.1, 2H), 2.16-2.14 (m, 1H), 2.10 (s, 3H), 1.87-1.85 (m, 1H), 0.98 (t, *J* = 7.1, 3H); ¹³C (CDCl₃): 192.0, 170.6, 166.8, 138.3, 134.6, 132.7, 129.6, 128.1, 126.2, 61.6, 56.7, 38.6, 20.4, 20.3, 13.6; HRMS (ESI-TOF): Calculated for C₁₅H₁₅ClNaO₅ (333.0506) [M + Na]⁺, Found: 333.0435; R_f: 0.30 (DCM: Hex; 6:1).

Ethyl-2-acetoxy-1-(3-methylbenzoyl)cyclopropanecarboxylate (4e)

Vinyl acetate (36.0 μ L, 0.3905 mmol, 1 eq), ethyl-2-diazo-3-(3-methylphenyl)-3-oxopropanoate **2e** (126.7 mg, 0.5455 mmol, 1.4 eq), Rh₂esp₂ (0.4 mg, 0.0005 mmol, 0.001 eq); 30.6 mg; Yield of diastereomers: 27 %; clear oil; 26.0 mg of β -lactone; ¹H NMR (600 MHz, CDCl₃): 7.71-7.69 (m, 2H), 7.36-7.35 (m, 1H), 7.34-7.31 (m, 1H), 4.85-4.83 (m, 1H), 4.04 (q, *J* = 7.1, 2H), 2.16 (s, 3H), 2.17-2.15 (m, 1H), 2.09 (s, 3H), 1.79-1.77 (m, 1H), 0.95 (t, *J* = 7.1, 3H); ¹³C (CDCl₃): 193.3, 170.6, 167.2, 138.3, 136.7, 133.7, 128.6, 128.3, 125.4, 61.6, 56.6, 38.9, 21.2, 20.5, 20.4, 13.6; HRMS (ESI-TOF): Calculated for C₁₆H₁₈NaO₅ (313.1052) [M + Na]⁺, Found: 313.1010; R_f: 0.25 (DCM: Hex; 6:1).

Ethyl-2-acetoxy-1-(4-methylbenzoyl)cyclopropanecarboxylate (4g)

Vinyl acetate (30.0 μ L, 0.3254 mmol, 1 eq), ethyl-2-diazo-3-(4-methylphenyl)-3-oxopropanoate **2g** (102.7 mg, 0.4421 mmol, 1.4 eq), Rh₂esp₂ (0.3 mg, 0.0004 mmol, 0.001 eq); 15.4 mg; Yield of diastereomers: 16 %; clear oil; 18.5 mg of β -lactone; ¹H NMR (600 MHz, CDCl₃): 7.81 (d, *J* = 7.5, 2H), 7.24 (d, *J* = 7.8, 2H), 4.82-4.80 (m, 1H), 4.06-4.05 (m, 2H), 2.40 (s, 3H), 2.15-2.13 (m, 1H), 2.09 (s, 3H), 1.77-1.75 (m, 1H), 0.98 (t, *J* = 7.1, 3H); ¹³C (CDCl₃): 192.5, 170.7, 167.4, 143.9, 133.9, 129.1, 129.0, 128.8, 128.4, 61.6, 56.4, 38.7, 21.6, 20.5, 20.2, 13.7; HRMS (ESI-TOF): calculated for C₁₆H₁₈NaO₅ (313.1052) [M + Na]⁺, Found: 313.1120; R_f: 0.19 (DCM: Hex; 6:1).

Ethyl-2-acetoxy-1-(4-ethylbenzoyl)cyclopropanecarboxylate (4h)

Vinyl acetate (24.0 μ L, 0.2603 mmol, 1 eq), ethyl-2-diazo-3-(4-ethylphenyl)-3-oxopropanoate **2h** (191.3 mg, 0.7768 mmol, 3 eq), Rh₂esp₂ (0.2 mg, 0.0003 mmol, 0.001 eq); 31.4 mg; Yield of diastereomers: 40 %; clear oil; 47.8 mg of β -lactone; ¹H NMR (300 MHz, CDCl₃): 7.83 (d, *J* = 8.0, 2H), 7.25 (d, *J* = 8.0, 2H), 4.81 (dd, *J* = 5.3, *J* = 6.7, 1H), 4.05 (q, *J* = 7.0, 2H), 2.68 (q, *J* = 7.6, 2H), 2.15-2.12 (m, 1H), 2.09 (s, 3H), 1.78-1.75 (m, 1H), 1.24 (t, *J* = 7.6, 3H), 0.99 (t, *J* = 7.0, 3H); ¹³C (CDCl₃): 192.5, 170.6, 167.3, 150.1, 134.1, 128.5, 127.9, 61.6, 56.4, 38.7, 28.9, 20.5, 20.1, 15.1, 13.6; HRMS: Calculated for C₁₇H₂₀NaO₅ (327.1208) [M + Na]⁺, Found: 327.0902; R_f: 0.23 (DCM: Hex; 6:1).

Ethyl-2-acetoxy-1-(4-fluorobenzoyl)cyclopropanecarboxylate (4i)

Vinyl acetate (30.5 μ L, 0.3308 mmol, 1 eq), Ethyl-2-diazo-3-(4-fluorophenyl)-3-oxopropanoate **2i** (232.8 mg, 0.9856 mmol, 3 eq), Rh₂esp₂ (0.3 mg, 0.0004 mmol, 0.001 eq); 39.3 mg; Yield of diastereomers: 41 %; clear oil; 104.0 mg of β -lactone; ¹H NMR (600 MHz, CDCl₃): 7.97-7.95 (m, 2H), 7.11 (t, *J* = 8.5, 2H), 4.75-4.73 (m, 1H), 4.07-4.03 (m, 2H), 2.13-2.11 (m, 1H), 2.10 (s, 3H), 1.84-1.82 (m, 1H), 0.98 (t, *J* = 7.1, 3H); ¹³C (CDCl₃): 191.5, 170.8, 167.2, 166.5 (d, *J* = 255.1), 133.05 (d, *J* = 3.1), 131.0 (d, *J* = 9.3), 115.7 (d, *J* = 22.0), 61.7, 56.6, 38.6, 20.5, 20.0, 13.7; HRMS (ESI-TOF): Calculated for C₁₅H₁₅FN₂O₅ (317.0801) [M + Na]⁺, Found: 317.0604; R_f: 0.22 (DCM: Hex; 6:1).

Ethyl-2-acetoxy-1-(4-bromobenzoyl)cyclopropanecarboxylate (4j)

Vinyl acetate (22.0 μ L, 0.2386 mmol, 1 eq), ethyl-2-diazo-3-(4-bromophenyl)-3-oxopropanoate **2j** (211.1 mg, 0.7105 mmol, 3 eq), Rh₂esp₂ (0.2 mg, 0.0003 mmol, 0.001 eq); 45.1 mg; yield of diastereomers: 53 %; clear oil; 100.7 mg of β -lactone. ¹H NMR (600 MHz, CDCl₃): 7.79 (d, *J* = 8.5, 2H), 7.58 (d, *J* = 8.5, 2H), 4.73 (dd, *J* = 5.3, *J* = 6.8, 1H), 4.06-4.03 (m, 2H), 2.13-2.10 (m, 1H), 2.09 (s, 3H), 1.84-1.82 (m, 1H), 0.97 (t, *J* = 7.1, 3H); ¹³C (CDCl₃): 192.2, 170.7, 167.1, 135.5, 131.7, 131.7, 130.1, 129.8, 128.1, 61.8, 56.7, 38.6, 20.5, 20.2, 13.7; HRMS (ESI-TOF): Calculated for C₁₅H₁₅⁷⁹BrNaO₅ (377.0001) [M + Na]⁺, Found: 376.9995; R_f: 0.27 (DCM: Hex; 6:1).

Ethyl-2-acetoxy-1-(4-chlorobenzoyl)cyclopropanecarboxylate (4k)

Vinyl acetate (23.5 μ L, 0.2549 mmol, 1 eq), ethyl-2-diazo-3-(4-chlorophenyl)-3-oxopropanoate **2k** (195.2 mg, 0.7726 mmol, 3 eq), Rh₂esp₂ (0.2 mg, 0.0003 mmol, 0.001 eq); 37.4 mg; Yield of diastereomers: 47 %; clear oil; 58.7 mg of β -lactone. ¹H NMR (600 MHz, CDCl₃): 7.87 (d, *J* = 8.1, 2H), 7.42 (d, *J* = 8.1, 2H), 4.74-4.72 (m, 1H), 4.06-4.02 (m, 2H), 2.13-2.11 (m, 1H), 2.09 (s, 3H), 1.84-1.82 (m, 1H), 0.97 (t, *J* = 7.0, 3H); ¹³C (CDCl₃): 191.9, 170.7, 167.1, 139.4, 135.0, 130.0, 129.7, 128.7, 128.7, 61.7, 56.7, 38.6, 20.5, 20.1, 13.7; HRMS (ESI-TOF): Calculated for C₁₅H₁₅ClNaO₅ (333.0506) [M + Na]⁺, Found: 333.0462; R_f: 0.30 (DCM: Hex; 6:1).

Ethyl 1-hydroxy-2-naphthoate (8)¹⁶

To a solution of ethyl 2-acetoxy-1-benzoylcyclopropanecarboxylate **4a** (200.4 mg, 0.7253 mmol, 1 eq) at 0 °C, TiCl₄ (1.50 mL, 1.4507 mmol, 2 eq) was added dropwise. Reaction was left at 0 °C to slowly warm up over a period of 16hrs. Reaction was quenched with water and extracted with DCM. Solvent was then removed and compound was purified using flash chromatography. 105.7 mg; Isolated yield: 67 %; white solid; ¹H NMR (600 MHz, CDCl₃): 12.0 (s, 1H), 8.38 (d, *J* = 8.3, 1H), 7.72 (d, *J* = 8.8, 1H), 7.70 (d, *J* = 8.3, 1H), 7.56 (t, *J* = 7.0, 1H), 7.47 (t, *J* = 7.0, 1H), 7.21 (d, *J* = 8.8, 1H), 4.41 (q, *J* = 7.3, 2H), 1.40 (t, *J* = 7.3, 3H); R_f: 0.53 (Hex: EtOAc; 10:1).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Institutes of Health Grant R15 GM088840-01, for financial support of this research. The NMR data were made possible through NSF CRIF Award 0840220, which supported the acquisition of the 600 MHz NMR.

References

1. (a) Reissig H-U, Zimmer R. Chem. Rev. 2003; 103:1151–1196. [PubMed: 12683780] (b) Yu M, Pagenkopf BL. Tetrahedron. 2005; 61:321–347.
2. (a) de Nanteuil F, Waser J. Angew. Chem. Int. Ed. 2011; 50:12075–12079. (b) Fang J, Ren J, Wang Z. Tetrahedron Lett. 2008; 49:6659–6662. (c) Benfatti F, de Nanteuil F, Waser J. Org. Lett. 2012;

- 14:386–389. [PubMed: 22188445] (d) Pohlhaus PD, Johnson JS. J. Am. Chem. Soc. 2005; 127:16014–16015. [PubMed: 16287274] (e) Korotkov VS, Larionov OV, Hofmeister A, Magull J, de Meijere A. J. Org. Chem. 2007; 72:7504–7510. [PubMed: 17824644] (f) Carson CA, Kerr MA. J. Org. Chem. 2005; 70:8242–8244. [PubMed: 16277360]
3. (a) Gorbacheva EO, Tabolin AA, Novikov RA, Khomutova YA, Nelyubina YV, Tomilov YV, Loffe SL. Org. Lett. 2013; 15:350–353. [PubMed: 23293920] (b) Young IS, Kerr MA. Angew. Chem. Int. Ed. 2003; 42:3023–3026. (c) Young IS, Kerr MA. Org. Lett. 2004; 6:139–141. [PubMed: 14703370] (d) Sapeta K, Kerr MA. J. Org. Chem. 2007; 72:8597–8599. [PubMed: 17919002] (e) Kang Y-B, Sun X-L, Tang Y. Angew. Chem. Int. Ed. 2007; 46:3918–3921. (f) Perreault C, Goudreau SR, Zimmer LE, Charette AB. Org. Lett. 2008; 10:689–692. [PubMed: 18257580]
4. Ivanova OA, Budynina EM, Grishin YK, Trushkov IV, Verteletskii PV. Angew. Chem. Int. Ed. 2008; 47:1107–1110.
5. (a) Abd Rabo Moustafa MM, Pagenkopf BL. Org. Lett. 2010; 12:3168–3171. [PubMed: 20550103] (b) Bajtos B, Pagenkopf BL. Org. Lett. 2009; 11:2780–2783. [PubMed: 19507849] (c) Qi X, Ready JM. Angew. Chem. Int. Ed. 2008; 47:7068–7070.
6. Verhé R, De Kimpe N, De Buyck L, Courtheyn D, van Caenegem L, Schamp N. Bull. Soc. Chim. Belges. 1983; 92:371–396.
7. Wenkert E, Alonso ME, Buckwalter BL, Chou KJ. J. Am. Chem. Soc. 1977; 99:4778–4782.
8. Phun LH, Patil DV, Cavitt MA, France S. Org. Lett. 2011; 13:1952–1955. [PubMed: 21417304]
9. Phun LH, Patil DV, Cavitt MA, France S. Org. Lett. 2012; 14:6379–6380.
10. (a) Doyle MP, Davies SB, Hu W. Org. Lett. 2000; 2:1145–1147. [PubMed: 10804575] (b) Wenkert E, Ananthanarayan TP, Ferreira VF, Hoffmann MG, Kim HS. J. Org. Chem. 1990; 55:4975–4976.
11. Erhunmwunse MO, Steel PG. J. Org. Chem. 2008; 73:8675–8677. [PubMed: 18839995]
12. Davies HML, Antoulinakis EG. Organic Reactions. 2004
13. Marcoux D, Goudreau SR, Charette AB. J. Org. Chem. 2009; 74:8939–8955. [PubMed: 19894700]
- 14.
- For related reactions, see reference 8 and: Phun LH, Aponte-Guzman J, France S. Angew. Chem. Int. Ed. 2012; 51:3198–3202.
15. Dess DB, Martin JC. J. Am. Chem. Soc. 1991; 113:7277–7287.
16. Youn SW, Kim BS, Jagdale AR. J. Am. Chem. Soc. 2012; 134:11308–11311. [PubMed: 22721172]

5 **6**

Figure 1.
Side products generated during cyclopropanation of **2a** with vinyl acetate

Scheme 1.

Scheme 2.

Table 1

Synthesis of Diazo Compounds for Study

Entry	R ¹	R ²	R ³	% Yield ^a
a	H	H	H	82
b	H	H	iPr	80
c	H	Br	H	89
d	H	Cl	H	90
e	H	Me	H	76
f	Me	H	H	59
g	H	H	Me	82
h	H	H	Et	72
i	H	H	F	75
j	H	H	Br	77
k	H	H	Cl	67

^a Isolated yields.

Table 2

Cyclopropanation reactions of **2a** with alkoxy alkenes^a

Entry	R ^a	Catalyst	Solvent	Product	% Yield ^b
1	TMS	Rh ₂ esp ₂	Pentane	3a	31
2	Et	Rh ₂ esp ₂	Pentane	3b	46
3	Ac	Rh ₂ esp ₂	Pentane	4a	51 ^c
4	Ac	Rh ₂ esp ₂	Pentane	4a	33 ^d
5	Ac	Rh ₂ esp ₂	Et ₂ O	-	0
6	Ac	Rh ₂ esp ₂	DCM	4a	5
7	Ac	Rh ₂ esp ₂	Pentane	4a	39 ^e
8	Ac	Rh ₂ (Oct) ₄	Pentane	4a	39
9	Ac	Rh ₂ (OAc) ₄	Pentane	4a	33
10	Ac	Cu(OTf) ₂	Pentane	-	0

^a 0.2M solution of alkene in solvent;^b isolated yields;^c Isolated yield of diastereomers;^d Slow syringe pump addition of **2a** over 16 h;^e 5 equivalents of vinyl acetate used.

Table 3

Isolated yields of acetoxy-substituted cyclopropanes^a

^a Quoted yields are for isolated mixtures of diastereomers; 0.2M solutions of **2a-k** in pentane, (1.4–3eq) were added to 0.2M solutions of vinyl acetate in pentane (1 eq).