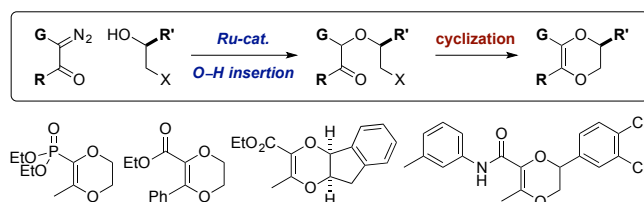# Synthesis of Substituted 1,4-Dioxenes through O–H Insertion and Cyclization Using Keto-Diazo Compounds

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ABSTRACT: 1,4-Dioxenes present interesting potential as synthetic intermediates, and as unusual motifs for incorporation into biologically active compounds. Here, an efficient synthesis of functionalized 1,4-dioxenes is achieved in two steps. Using keto-diazo compounds, a ruthenium catalyzed O–H insertion with β-halohydrins followed by treatment with base results in cyclization with excellent selectivity, through O–alkylation of the keto-enolate. A variety of halohydrins and anion-stabilizing groups in the diazo-component are tolerated, affording novel functionalized dioxenes. Enantioenriched β-bromohydrins provide enantioenriched 1,4-dioxenes.

In early stage drug discovery there is considerable interest in the incorporation of novel motifs, and more sp[3] rich, less planar structures to aid in the exploration of novel chemical and intellectual property (IP) space.[1,2] 1,4-Dioxenes are partially saturated oxygen heterocycles that may present interesting potential in this context, but which remain relatively unexplored. Most commonly these heterocycles have been used as synthetic intermediates in the preparation of dioxanes through reaction of the olefin. Reactions of dioxenes include cyclopropanation with diazo compounds,[3] Paternò-Büchi reactions,[4] and other reactions.[5] Fluorinated derivatives have been used in materials science as monomers for polymerization with applications in the production of films and coatings.[6] Within

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agrochemistry, 1,4-dioxene-containing compounds have been shown to act as bioisosteres for 1,4-oxathenes exhibiting fungicidal properties; dioxincarboxamide showed increased fungicidal activity compared with systemic fungicide Carboxin (Figure 1).[7,8] To date their uses as motifs in medicinal chemistry has been limited to tool compounds as allosteric receptors of mAChRs for investigating Alzheimer's disease and schizophrenia.[9] There are examples in patents describing activity towards targets including inhibitors of the HIV virus,[10] Nrf2 inhibitors,[11] and antibacterial activity.[12]

Carboxin X = S, Y = H
Dioxincarboxamide X = O, Y = Me
fungicidal activity against bean rust   M4 positive allosteric modulator

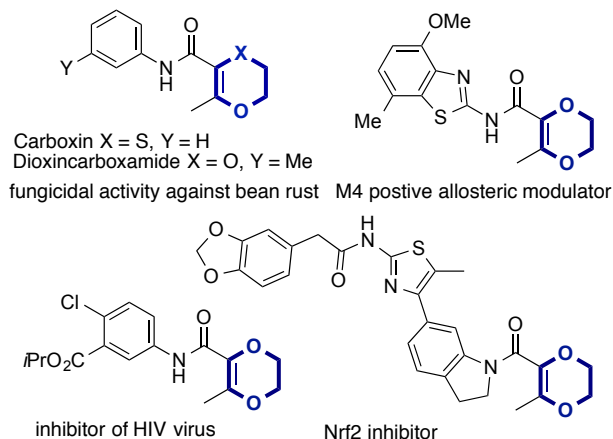inhibitor of HIV virus   Nrf2 inhibitor

Figure 1. Examples of 1,4-dioxenes in biologically active compounds

Dioxenes have been prepared by the alkylation of ethylene glycol,[7,13] displacement of 1,2-dihaloethanes with symmetrical benzoin derivatives,[14] or direct functionalization of unsubstituted 1,4-dioxene.[15,5a] However, these approaches do not allow facile incorporation of substituents at the sp^3 hybridized 5- and 6-positions, and there remain few methods to generate functionalized dioxene derivatives. In 1999, Zercher and co-workers reported a procedure to form 2,3,5,6-substituted dioxenes involving a Rh(II)-catalyzed O–H insertion with symmetrical 1,2-diols followed by hemi-acetal formation and acid catalyzed dehydration (Scheme 1a).[16] More recently, Lacour and co-workers described the synthesis of tri- and tetrasubstituted 1,4-dioxenes through a Ru-catalyzed ring expansion of epoxides with retention of stereochemistry, along with a minor deoxygenation product (Scheme 1b).[17]

As part of our interest in the synthesis of new functionalized heterocycles as fragments and lead-like compounds for drug discovery, we recently reported an efficient synthesis of oxetanes by a 2-step O–H insertion/C–C bond forming cyclization strategy (Scheme 1c).[18,19] A variety of functionalized diazo-compounds could be employed, to form oxetane products in high yield.[18b] Following this work, we were interested in alternative diazo compounds where cyclization to form 4- or 6-membered rings may compete, and consequently investigated diazo compounds derived from β-ketoesters toward the synthesis of dioxenes. In this *Note* we report the preparation of functionalized di-, tri- and tetra-substituted 1,4-dioxenes by a 2-step ruthenium catalyzed O–H insertion/anionic C–O bond forming cyclization using functionalized bromohydrins and keto-diazo compounds (Scheme 1d).
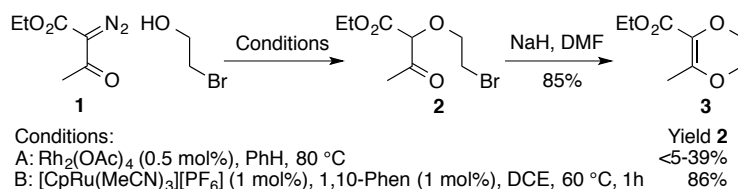
Scheme 1. Synthetic strategies for the preparation of 1,4-dioxenes and oxetanes using diazo-compounds
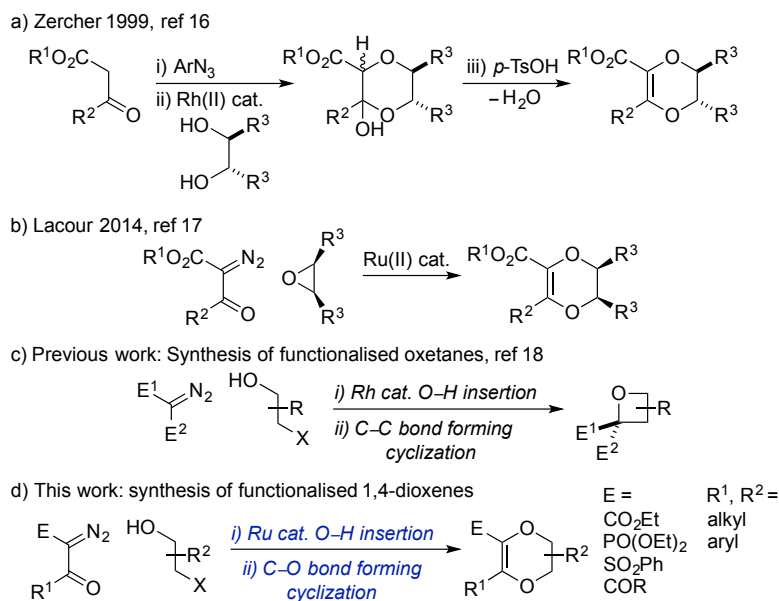
Our initial investigations targeted 3-methyl-1,4-dioxene-2-carboxylate **3**, reacting α-diazo-β-ketoester **1** with bromoethanol (Scheme 2). Using previously successful conditions for O–H insertion (conditions A) with catalytic [Rh$_2$(OAc)$_4$] did afford the desired ether product **2** but with variable yields and formation of an unexpected and inseparable side-product (2-bromoethyl ethyl carbonate).

Investigations into the cyclization at this stage showed promising results. Varied conditions, changing solvent and base combinations gave successful cyclization to generate dioxenes, in all cases occurring selectively through the oxygen atom to give the dioxene products without formation of the possible oxetane.

Scheme 2. Synthesis of 1,4-dioxene **3** by O–H insertion and cyclization

Conditions:
A: $Rh_2(OAc)_4$ (0.5 mol%), PhH, 80 °C   <5-39%
B: $[CpRu(MeCN)_3][PF_6]$ (1 mol%), 1,10-Phen (1 mol%), DCE, 60 °C, 1h   86%
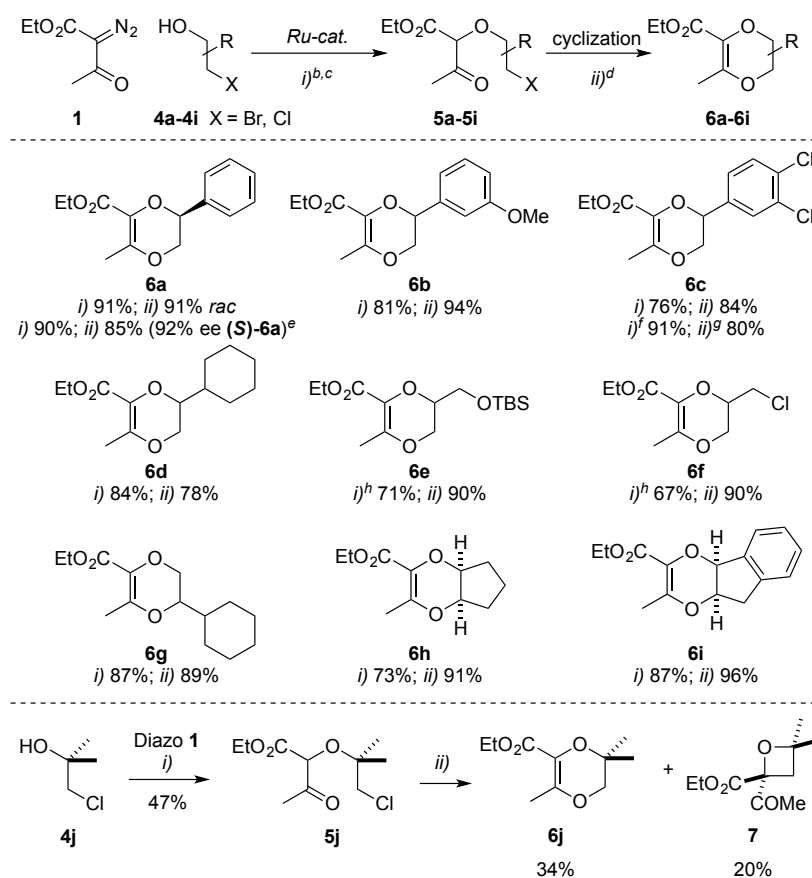
Yield **2**

The encouraging cyclization attempts prompted us to explore alternative catalytic systems to improve the efficiency of the O–H insertion step. Lacour reported a Ru-catalyst for the O–H insertion of keto-ester diazo compounds in the alcohol as solvent ($[CpRu(MeCN)_3][PF_6]$ (2.5 mol%), 1,10-phenanthroline (2.5 mol%)).[20] Pleasingly, using this catalyst with excess bromoethanol (3 equiv) in DCE at 60 °C afforded ether **2** in 53% yield without formation of the side product.[21] On further optimization, the excess of bromoethanol was decreased without affecting the yield by increasing reaction concentration and reducing the catalyst loading to 1 mol%, strictly maintaining a 1:1 Ru:phen ratio.[21] By using a small excess of diazo compound **1** (1.2 equiv), an 86% isolated yield of bromide **2** was obtained (Scheme 2; Conditions B).

An excellent yield of 1,4-dioxene **3** was then obtained on treating **2** with NaH in DMF at 0 °C for 1 h. The 6-membered dioxene ring was formed exclusively with no evidence for formation of the oxetane keto-ester that would occur through C-alkylation, which we had observed exclusively in previous work. The reaction sequence was similarly successful using a tosylate leaving group. Performing the O–H insertion on 2-tosyloxyethanol to afford **2a** (not shown) and cyclisation under the same conditions gave yields of 92% and 88% respectively.[22]

With these optimized conditions, the introduction of substituents onto 2-bromoethanol was examined to form chiral 2,3,6-trisubstituted 1,4-dioxenes. Both aryl and alkyl substituents were

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examined using readily available β-halohydrins (**4**, Scheme 3). With the substituted β-halohydrins, the O–H insertion required a longer reaction time (15 h) to achieve high yields presumably due to increased steric demands. Similarly, cyclization required warming to 25 °C for 30 min to obtain the 1,4-dioxenes, such as **6a**, in an excellent yield. Using the corresponding enantioenriched β-bromohydrin (93% *ee*, (*S*)-**4a**), gave the enantioenriched 1,4-dioxene ((*S*)-**6a**) with retention of ee (92% *ee*).[23]

Scheme 3. Synthesis of 2,3,6- and 2,3,5-trisubstituted dioxenes, and 2,3,5,6-tetrasubstituted dioxenes[a]

[a]Yields quoted for separate steps *i)* and *ii)*. [b]Conditions *i* for O–H insertion: β-halohydrin **4** (1.0 mmol), **1** (1.2 equiv), [CpRu(MeCN)₃][PF₆] (1.0 mol%), 1,10-phenanthroline (1.0 mol%), 1,2-dichloroethane, 0.5 M, 60 °C, 15 h. [c]Bromohydrin used (X = Br) unless stated. [d]Conditions *ii* for cyclization: **5** (0.5 mmol), NaH (1.2 equiv), DMF, 0.025 M, 0 °C, 60 min; then 25 °C, 30 min. [e]Using enantioenriched β-

bromohydrin (93% *ee*). [f]Reaction on 8.0 mmol scale. [g]Reaction on 5.0 mmol scale. [h]Used chlorohydrin; X = Cl.

Both electron-rich and electron-poor aromatic substituents gave similar high yields for both steps (**6b** and **6c**). To demonstrate the scalability of the procedure, dichlorophenyl derivative **6c** was prepared on a larger scale, affording >1 g of the dioxene. Alkyl substituents could be incorporated at the 6-position of the 1,4-dioxenes using the same conditions employed for the aryl substituents (**6d-f**). Pleasingly, the cyclization was effective when chlorides were utilized as the leaving group (**6e-f**). When using the secondary alcohol derivatives, this procedure gives access to 2,3,6-trisubstituted dioxenes as complementary regioisomers to those accessed by Lacour.[17] Alternatively, the 2,3,5-trisubstituted dioxene **6g** was formed from 2-bromo-2-cyclohexylethan-1-ol, also with excellent yield, with cyclization at the secondary bromide. The scope was then expanded to include fused ring tetrasubstituted dioxene derivatives (**6h-i**), from *trans*-2-bromocyclopentan-1-ol, and *trans*-2-bromo-1-indanol in excellent yields over the two steps for both examples. When using tertiary alcohol, 1-chloro-2-methyl-propanol **4j**, a reduced yield (47%) was obtained for the O–H insertion (**5j**). Interestingly, when subjected to the standard cyclization conditions, while the desired 2,3,6,6-tetrasubstituted 1,4-dioxene **6j** was formed as the major product (34%), the 2,2,4,4-tetrasubstituted oxetane **7** was also formed. This may be due a favorable conformation for cyclization to the 4-membered ring being enforced by the *gem*-dimethyl group.

Next, we examined the functional groups on the diazo compound in order to generate functionalized 1,4-dioxenes (Table 1). Diazo compounds **8a,b** (R = *i*Pr and Ph respectively) were examined to probe for the effect of the ketone substituent. Both were well tolerated through the O–H insertion and cyclization steps to form dioxenes **10a,b**, with a reaction time of 15 h providing high conversions. Pleasingly, the use of different anion stabilizing groups on the diazo component was also successful, allowing for the synthesis of novel 2-sulfonyl (**10c**) and 2-phosphonyl 1,4-dioxenes (**10d**) with good yields. The same conditions were used in each case, with the exception of diazo **8c**, which

gave a low yield for the OH insertion using the Ru catalyst (33% yield). Here, in the absence of an ester group, the use of [Rh$_2$(OAc)$_4$] with **8c** gave a much improved 84% yield.

**Table 1.** Synthesis of functionalized 2,3-disubstituted dioxenes.[a]
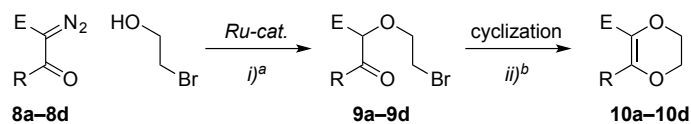
entry	R	E		Yield **9** (%)	Yield **10** (%)
1	iPr	CO$_2$Et	**a**	84	89
2	Ph	CO$_2$Et	**b**	85	80
3	Me	SO$_2$Ph	**c**	84[c]	79
4	Me	PO(OEt)$_2$	**d**	61	90

[a]O–H insertion conditions: 2-bromoethanol (1.0 mmol), **8** (1.2 equiv.), [CpRu(MeCN)$_3$][PF$_6$] (1.0 mol%), 1,10-phenanthroline (1.0 mol%), 1,2-dichloroethane, 0.5 M, 60 °C, 15 h. [b]Cyclization conditions: **9** (0.3–0.4 mmol), NaH (1.2 equiv.), DMF, 0.025 M, 0 °C for 60 min; then 25 °C, 30 min. [c]O–H insertion conditions for **8c**: 2-bromoethanol (0.5 mmol), **8** (1.1 equiv.), [Rh$_2$(OAc)$_4$] (0.5 mol %), PhH, 0.1 M, 80 °C, 90 min.

An unusual result was observed when diketone diazo **8e** was employed, targeting bicyclic 1,4-dioxene **10e**, whereby cyclization occurred directly under the O–H insertion reaction conditions (Scheme 4). Dioxene **10e** was formed in low yield (21%), with ether **9e** only observed in ca 1% yield.[24] Following O–H insertion the enol tautomer is likely to form readily, due to the relatively increased acidity of the methine proton, at the same time positioning the oxygen atom suitably to react.

Scheme 4. Formation of bicyclic dioxene **10e** with in situ cyclization, and intramolecular C–H insertion from diazo **8f**.
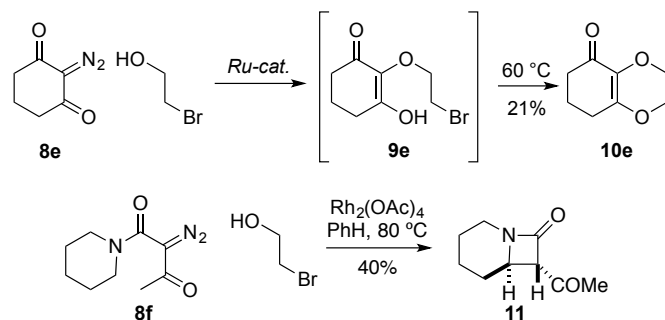
Attempts to form dioxenes from piperidine amide keto diazo compound **8f** were unsuccessful; using the Ru catalyst gave no reaction, presumably due to the Lewis basicity of the bulky amide. Interestingly, using Rh$_2$(OAc)$_4$ an intramolecular C–H insertion reaction occurred with a 40% yield, forming β-lactam **11** as a single diasteroisomer (Scheme 4).[25,26] As an alternative route to amide derivatives, the ester of dioxene **6c** was readily hydrolyzed with 1 M NaOH in EtOH to generate carboxylate sodium salt **12** (Scheme 5). This salt successfully underwent amide coupling with pyrrolidine, using HATU, yielding amide **13**. Similar amide coupling with *m*-toluidine, generated a 6-substituted derivative of dioxincarboxamide **14** (Figure 1). Alternatively, reduction of the ester with DIBAL formed the alcohol product **15** in high yield. Many of these derivatives present interesting shape and physicochemical properties as lead-like compounds.

Scheme 5. Derivatization of 1,4-dioxene **6c**.
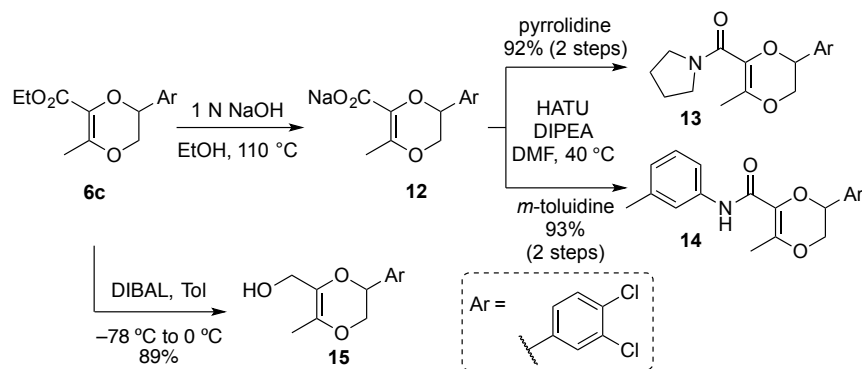
In summary, we have described an efficient 2-step strategy for the preparation of diversely functionalized 1,4-dioxenes through a Ru-catalyzed O–H insertion and cyclization. Choice of substituents on the bromohydrin affords control of substitution pattern on the dioxene products. A variety of anion stabilizing functional groups were tolerated in both O–H insertion and C–O cyclization steps, affording functionalized dioxenes. A diverse range of functional groups could be incorporated at the 2-, 3-, 5- and 6- positions of the dioxene ring, allowing for exploration of novel chemical space.

EXPERIMENTAL SECTION

General Experimental Considerations. All nonaqueous reactions were run under an inert atmosphere (argon) with flame-dried glassware and anhydrous solvents using standard techniques. Anhydrous solvents were obtained by filtration through drying columns (THF, CH_2Cl_2) or used as supplied (DMF, 1,2-dichloroethane). Flash column chromatography was performed using 230-400 mesh silica with the indicated solvent system. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm), aqueous potassium permanganate stain, PMA (phosphomolybdic acid), ninhydrin or vanillin. Infrared spectra (ν_{max}, FTIR ATR) were recorded in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance spectra were recorded on either 400 MHz or 500 MHz spectrometers. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform: δ = 7.27 ppm, DMSO: δ = 2.50 ppm). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, quin = quintet, sep = septet, m = multiplet and br = broad), coupling constant in Hz, integration, assignment]. ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard (^{13}CDCl$_3$: 77.0 ppm, (^{13}CD$_3$)$_2$SO: 39.5 ppm). ^{31}P NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million referenced to the standard 85% phosphoric acid: 0 ppm. *J* values

are reported in Hz. Assignments of ^{1}H/^{13}C spectra were made by the analysis of δ/*J* values, and COSY, DEPT-135, HSQC, and HMBC experiments as appropriate. Melting points are uncorrected. **Reagents:** Commercial reagents were used as supplied or purified by standard techniques where necessary. Diazo transfer reagents (tosyl azide and *p*-ABSA) were prepared by reported procedures.[27] Diazo compounds **1**,[28] **8b**,[29] **8c**,[30] **8d**,[31] **8e**,[32] and **8f**,[33] were prepared according to the referenced literature procedures. For all diazo compounds synthesized, the resonance for the fully substituted C=N=N carbon in the ^{13}C NMR could not be seen due to quadrupole coupling to ^{14}N, therefore the carbon resonance is not reported. Although we have not experienced any problems in the handling of azides or diazo reagents, extreme care should be taken when manipulating them due to their potentially explosive nature. Substituted β-bromhydrins were prepared by reported procedures.[18]

Synthesis of 1,4-Dioxene 3

(±)-Ethyl 2-(2-bromoethoxy)-3-oxobutanoate (2) A microwave vial (0.5–2.0 mL volume) was charged with 2-bromoethanol (125 mg, 1.0 mmol), 1,10-phenanthroline (1.7 mg, 0.01 mmol) and tris(acetonitrile)cyclopentadienylruthenium (II) hexafluorophosphate (4.3 mg, 0.01 mmol). The reaction vessel was flushed with argon and sealed with a cap. Diazo **1** (188 mg, 1.2 mmol) in 1,2-dichloroethane (2.0 mL) was added to the sealed vial. The reaction mixture was heated in an oil bath at 60 °C for 1 h, then allowed to cool to rt. The reaction mixture was diluted with CH$_2$Cl$_2$ (10 mL) and concentrated *in vacuo*. A mixture of Et$_2$O/pentane (1:1, 80 mL) was added to the residue to precipitate out metal salts, and filtered through a pad of celite. The filtrate was concentrated *in vacuo*. Purification by flash chromatography (15% to 20% Et$_2$O in pentane) afforded bromide **2** as a pale yellow oil (217 mg, 86%); R_f = 0.14 (15% Et$_2$O in pentane); IR (film) / cm^{-1} 2982, 1747 (C=O), 1725 (C=O), 1412, 1357, 1339, 1258, 1183, 1130, 1063, 1014, 863, 807, 678, 620, 571; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.44 (s, 1 H, C*H*(CO$_2$Et)(COMe)), 4.32–4.25 (m, 2 H, CO$_2$C*H$_2$*CH$_3$), 4.04 (dt, *J* = 10.6, 5.7 Hz, 1 H, OC*H*H), 3.80 (dt, *J* = 10.6, 6.4 Hz, 1 H, OCH*H*), 3.57–3.52 (m, 2 H, CH$_2$Br), 2.32 (s, 3 H, COCH$_3$), 1.31 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H$_3$*); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 201.4 (C=O ketone), 166.7

(C=O ester), 85.5 (*C*H(CO$_2$Et)(COMe)), 70.9 (O*C*H$_2$), 62.1 (CO$_2$*C*H$_2$CH$_3$), 29.5 (*C*H$_2$Br), 26.5 (CO*C*H$_3$), 14.1 (CO$_2$CH$_2$*C*H$_3$); HRMS (ESI-TOF) *m/z* Calcd for C$_8$H$_{13}$BrO$_4$Na$^+$ [M+Na]$^+$: 274.9895, Found: 274.9900.

(±)-Ethyl 3-oxo-2-(2-(tosyloxy)ethoxy)butanoate (2a) A microwave vial (0.5–2.0 mL volume) was charged with 2-hydroxyethyl 4-methylbenzenesulfonate (216 mg, 1.0 mmol), 1,10-phenanthroline (1.7 mg, 0.01 mmol) and tris(acetonitrile)cyclopentadienylruthenium (II) hexafluorophosphate (4.3 mg, 0.01 mmol). The reaction vessel was flushed with argon and sealed with a cap. Diazo 1 (188 mg, 1.2 mmol) in 1,2-dichloroethane (2.0 mL) was added to the sealed vial. The reaction mixture was heated in an oil bath at 60 °C for 15 h, then allowed to cool to rt. The reaction mixture was diluted with CH$_2$Cl$_2$ (10 mL) and concentrated *in vacuo*. A mixture of Et$_2$O/pentane (1:1, 80 mL) was added to the residue to precipitate out metal salts, and filtered through a pad of celite. The filtrate was concentrated *in vacuo*. Purification by flash chromatography (50% Et$_2$O in pentane) afforded tosylate **2a** as a pale yellow oil (315 mg, 92%); R$_f$ = 0.13 (50% Et$_2$O in pentane); IR (film) / cm^{-1} 2985, 1748, 1726, 1356, 1189, 1174, 1143, 1096, 1017, 919, 816, 771, 662; *Keto tautomer*: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.85–7.72 (m, 2 H, 2 × Ar-H), 7.41–7.30 (m, 2 H, 2 × Ar-H), 4.37 (s, 1 H, C*H*(CO$_2$Et)(COMe)), 4.29–4.17 (m, 4 H, CO$_2$C*H$_2$*CH$_3$ and OCH$_2$), 3.92–3.84 (m, 1 H, C*H*HOTs), 3.80 (ddd, *J* = 11.5, 6.5, 3.6 Hz, 1 H, CH*H*OTs), 2.44 (s, 3 H, Ar-CH$_3$), 2.21 (s, 3 H, COCH$_3$), 1.29 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H$_3$*); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 201.1 (C=O ketone), 166.5 (C=O ester), 145.0 (Ar-C$_q$-Me), 132.7 (Ar-C$_q$-SO$_2$), 129.9 (2 × Ar-CH), 127.9 (2 × Ar-CH), 85.5 (*C*H(CO$_2$Et)(COMe)), 68.7 (O*C*H$_2$), 68.4 (*C*H$_2$OTs), 62.1 (CO$_2$*C*H$_2$CH$_3$), 26.4 (CO*C*H$_3$), 21.6 (Ar-*C*H$_3$), 14.1 (CO$_2$CH$_2$*C*H$_3$); *Enol tautomer*: ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.0 (s, 1 H, OH), 7.85–7.72 (m, 2 H, 2 × Ar-H), 7.41–7.30 (m, 2 H, 2 × Ar-H), 4.29–4.17 (m, 4 H, CO$_2$C*H$_2$*CH$_3$ and OCH$_2$), 3.92–3.84 (m, 2 H, CH$_2$OTs), 2.44 (s, 3 H, Ar-CH$_3$), 1.99 (s, 3 H, COCH$_3$), 1.30 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H$_3$*); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 167.0 (*C*OH), 166.5 (C=O ester), 145.0 (Ar-C$_q$-Me), 132.7 (Ar-C$_q$-SO$_2$), 129.8 (2 × Ar-CH), 127.9 (2 × Ar-CH), 124.3 (*C$_q$*(CO$_2$Et)(COH(Me))), 71.1 (O*C*H$_2$), 68.6 (*C*H$_2$OTs), 60.9 (CO$_2$*C*H$_2$CH$_3$), 21.6 (Ar-

CH$_3$), 16.0 (COCH_3), 14.2 (CO$_2$CH$_2$$CH_3$). FTMS (+p NSI) *m/z* Calcd for C$_{15}$H$_{21}$O$_7$S$^+$ [M+H]$^+$: 345.1003, Found: 345.0999.

Ethyl 3-methyl-5,6-dihydro-1,4-dioxine-2-carboxylate (3) DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 25 mg, 0.6 mmol) which had been cooled to 0 °C. Bromide **2** (127 mg, 0.5 mmol) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 8 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH$_4$Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (4 × 20 mL). The organic extracts were combined, dried (Na$_2$SO$_4$) and concentrated *in vacuo*. Purification by flash chromatography (25% Et$_2$O in pentane) afforded dioxene **3** as a white crystalline solid (73 mg, 85%); R$_f$ = 0.22 (25% Et$_2$O in pentane); mp = 54–56 °C; IR (film) / cm^{-1} 2989, 2945, 2906, 1708 (C=O), 1631 (C=C), 1468, 1454, 1381, 1369, 1312, 1283, 1260, 1244, 1163, 1099, 1026, 941, 922, 886, 766, 671; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.26 (q, *J* = 7.1 Hz, 2 H, CO$_2$CH_2CH$_3$), 4.16–4.12 (m, 2 H, OCH_2CH$_2$O), 4.10–4.06 (m, 2 H, OCH$_2$CH_2O), 2.23 (s, 3 H, CH$_3$), 1.33 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$CH_3); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 163.9 (CO$_2$), 147.4 ((Me)C_q=C), 125.1 ((EtO$_2$C)C_q=C), 65.1 (OCH$_2$CH$_2$O), 63.2 (OCH$_2$$CH_2$O), 60.5 (CO$_2$$CH_2CH_3$), 17.8 (CH$_3$), 14.4 (CO$_2CH_2$$CH_3$); HRMS (ESI-TOF) *m/z* Calcd for C$_8$H$_{13}$O$_4$$^+$ [M+H]$^+$: 173.0814, Found: 173.0813.

*Synthesis of Trisubstituted 1,4-Dioxenes **6a**–**6j** and oxetane **7***

General Procedure A: Ru-Catalyzed O–H Insertion with β-Halohydrins

A microwave vial (0.5–2.0 mL volume) was charged with the requisite β-halohydrin **4** (1.0 mmol, 1.0 equiv), 1,10-phenanthroline (1.8 mg, 0.01 mmol, 1.0 mol%) and tris(acetonitrile)-cyclopentadienylruthenium (II) hexafluorophosphate (4.3 mg, 0.01 mmol, 1.0 mol%). The reaction vessel was flushed with argon and sealed with a cap. The requisite diazo (1.2 mmol, 1.2 equiv) in 1,2-dichloroethane (2.0 mL) was added to the sealed vial. The reaction mixture was heated in an oil bath at 60 °C for 15 h, then allowed to cool to rt. The reaction mixture was diluted with CH$_2$Cl$_2$ (10 mL) and concentrated *in vacuo*. A mixture of Et$_2$O/pentane (1:1; 80 mL) was added to the residue to precipitate

out metal salts, and filtered through a pad of celite. The filtrate was concentrated in vacuo. Purification by flash chromatography under the specified conditions afforded the desired bromide.

General Procedure B: Cyclization

DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 25 mg, 0.6 mmol, 1.2 equiv) which had been cooled to 0 °C. The requisite bromide **5** (0.5 mmol, 1.0 equiv) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 5 min. The reaction mixture was stirred at 0 °C for 1 h then 25 °C for 30 min. Saturated aq. NH$_4$Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (4 × 20 mL). The organic extracts were combined, dried (Na$_2$SO$_4$) and concentrated *in vacuo*. Purification by flash chromatography under the specified conditions afforded the desired dioxene.

(±)-Ethyl 2-(2-bromo-1-phenylethoxy)-3-oxobutanoate (5a) Prepared according to **General Procedure A** employing diazo **1** (187 mg, 1.2 mmol) and (±)-2-bromo-1-phenylethan-1-ol[18a] **4a** (201 mg, 1.0 mmol). Purification by flash chromatography (75% CH$_2$Cl$_2$ in pentane) afforded bromide **5a** as a pale yellow oil (300 mg, 91%, d.r. 52:48); R$_f$ = 0.29 (75% CH$_2$Cl$_2$ in pentane); IR (film) / cm^{-1} 3032, 2982, 2903, 1745 (C=O), 1723 (C=O), 1494, 1455, 1417, 1357, 1257, 1204, 1158, 1110, 1029, 921, 860, 757, 701, 669, 602, 551; *Diastereoisomer 1:* ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41–7.28 (m, 5 H, 5 × Ph-H), 4.71 (dd, *J* = 7.2, 5.3 Hz, 1 H, OCH(Ph)), 4.35–4.22 (m, 3 H, C*H*(CO$_2$Et)(COMe) and CO$_2$C*H$_2$*CH$_3$), 3.74 (dd, *J* = 10.6, 7.2 Hz, 1 H, C*H*HBr), 3.57 (dd, *J* = 10.6, 5.3 Hz, 1 H, CH*H*Br), 2.26 (s, 3 H, COCH$_3$), 1.32 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H$_3$*); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 202.5 (C=O ketone), 166.9 (C=O ester), 137.5 (Ph-C$_q$), 129.4 (Ph-CH), 129.0 (2 × Ph-CH), 127.2 (2 × Ph-CH), 82.8 (*C*H(CO$_2$Et)(COMe)), 81.6 (OCH(Ph)), 62.0 (CO$_2$*C*H$_2$CH$_3$), 35.0 (CH$_2$Br), 26.58 (CO*C*H$_3$), 14.1 (CO$_2$CH$_2$*C*H$_3$); *Diastereoisomer 2:* ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41–7.28 (m, 5 H, 5 × Ph-H), 4.61 (dd, *J* = 8.8, 3.8 Hz, 1 H, OCH(Ph)), 4.31 (s, 1 H, C*H*(CO$_2$Et)(COMe)), 4.04 (q, *J* = 7.1 Hz, 2 H, CO$_2$C*H$_2$*CH$_3$), 3.73 (dd, *J* = 11.0, 8.8 Hz, 1 H, C*H*HBr), 3.52 (dd, *J* = 11.0, 3.8 Hz, 1 H, CH*H*Br), 2.42

(s, 3 H, COCH$_3$), 1.14 (t, J = 7.1 Hz, 3 H, CO$_2$CH$_2$CH$_3$); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 201.1 (C=O ketone), 166.6 (C=O ester), 137.1 (Ph-C$_q$), 129.2 (Ph-CH), 128.8 (2 × Ph-CH), 127.1 (2 × Ph-CH), 84.2 (CH(CO$_2$Et)(COMe)), 83.5 (OCH(Ph)), 61.8 (CO$_2$CH$_2$CH$_3$), 35.3 (CH$_2$Br), 26.63 (COCH$_3$), 13.8 (CO$_2$CH$_2$CH$_3$); HRMS (ESI-TOF) m/z Calcd for C$_{14}$H$_{17}$BrO$_4$Na$^+$ [M+Na]$^+$: 351.0208, Found: 351.0194.

Ethyl 2-[(1S)-2-bromo-1-phenylethoxy]-3-oxobutanoate (((S)-5a) Prepared according to **General Procedure A** employing diazo **1** (187 mg, 1.2 mmol) and enantioenriched (1S)-2-bromo-1-phenylethan-1-ol[34] ((S)-4a) (201 mg, 1.0 mmol, 93% ee). Purification by flash chromatography (75% CH$_2$Cl$_2$ in pentane) afforded bromide (S)-5a as a pale yellow oil (297 mg, 90%, d.r. 50:50); $[\alpha]_D^{19}$ +66.0 (c. 0.67, CHCl$_3$).

(±)-Ethyl 3-methyl-6-phenyl-5,6-dihydro-1,4-dioxine-2-carboxylate (6a) Prepared according to **General Procedure B** employing bromide (±)-5a (165 mg, 0.5 mmol). Purification by flash chromatography (10% Et$_2$O in pentane) afforded dioxene **6a** as a white solid (113 mg, 91%); R$_f$= 0.23 (10% Et$_2$O in pentane); mp = 25–27 °C; IR (film) / cm^{-1} 2981, 2929, 1709 (C=O), 1634 (C=C), 1497, 1455, 1370, 1315, 1297, 1281, 1243, 1156, 1101, 1070, 1043, 924, 881, 757, 698, 610, 593; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43–7.34 (m, 5 H, 5 × Ph-H), 4.86 (dd, J = 8.3, 2.3 Hz, 1 H, OCH(Ph)), 4.32–4.25 (m, 3 H, OCHH and CO$_2$CH$_2$CH$_3$), 3.92 (dd, J = 11.2, 8.3 Hz, 1 H, OCHH), 2.29 (s, 3 H, CH$_3$), 1.34 (t, J = 7.1 Hz, 3 H, CO$_2$CH$_2$CH$_3$); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 164.1 (CO$_2$), 146.7 ((Me)C$_q$=C), 136.3 (Ph-C$_q$), 128.6 (2 × Ph-CH), 128.5 (Ph-CH), 126.5 (2 × Ph-CH), 125.6 ((EtO$_2$C)C$_q$=C), 73.7 (OCH(Ph)), 69.9 (OCH$_2$), 60.5 (CO$_2$CH$_2$CH$_3$), 17.6 (CH$_3$), 14.4 (CO$_2$CH$_2$CH$_3$); HRMS (ESI-TOF) m/z Calcd for C$_{14}$H$_{17}$O$_4^+$ [M+H]$^+$: 249.1127, Found: 249.1134.

Ethyl (6S)-3-methyl-6-phenyl-5,6-dihydro-1,4-dioxine-2-carboxylate ((S)-6a) Prepared according to **General Procedure B** employing enantioenriched bromide (S)-5a (164 mg, 0.5 mmol, 93% ee). Purification by flash chromatography (10% Et$_2$O in pentane) afforded dioxene (S)-6a as a

white solid (105 mg, 85%, 92% *ee*); $[\alpha]_D^{25}$ +157 (c. 0.98, CHCl$_3$); HPLC, Chiralpak ID column, 99.3:0.7 *n*hexane/IPA, flow 1.0 mLmin^{-1}, UV detection at 254 nm, 13.6 min ((*S*)-**6a**), 15.6 min ((*R*)-**6a**).

(±)-Ethyl 2-[2-bromo-1-(3-methoxyphenyl)ethoxy]-3-oxobutanoate (5b) Prepared according to **General Procedure A** employing diazo **1** (187 mg, 1.2 mmol) and (±)-2-bromo-1-(3-methoxyphenyl)ethan-1-ol[18a,35] **4b** (231 mg, 1.0 mmol). Purification by flash chromatography (50% to 60% to 70% CH$_2$Cl$_2$ in pentane) afforded bromide **5b** as a pale yellow oil (292 mg, 81%, dr 50:50); R$_f$ = 0.32 (60% CH$_2$Cl$_2$ in pentane); IR (film) / cm^{-1} 2981, 2939, 2839, 1745 (C=O), 1723 (C=O), 1587, 1489, 1456, 1436, 1357, 1322, 1283, 1257, 1156, 1111, 1035, 862, 788, 754, 704, 671, 564; *Diastereoisomer 1:* ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.34–7.26 (m, 1 H, Ar-H), 6.98–6.89 (m, 2 H, 2 × Ar-H), 6.89–6.83 (m, 1 H, Ar-H), 4.69 (dd, *J* = 7.4, 5.2 Hz, 1 H, OCH(Ar)), 4.36–4.22 (m, 3 H, C*H*(CO$_2$Et)(COMe) and CO$_2$C*H$_2$*CH$_3$), 3.82 (s, 3 H, OCH$_3$), 3.72 (dd, *J* = 10.7, 7.4 Hz, 1 H, C*H*HBr), 3.56 (dd, *J* = 10.7, 5.2 Hz, 1 H, CH*H*Br), 2.27 (s, 3 H, COCH$_3$), 1.32 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H$_3$*); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 202.5 (C=O ketone), 166.6 (C=O ester), 160.03 (Ar-*C$_q$*-OMe), 138.7 (Ar-*C$_q$*-CH(O)), 130.1 (Ar-CH), 119.5 (Ar-CH), 114.9 (Ar-CH), 112.9 (Ar-CH), 82.8 (*C*H(CO$_2$Et)(COMe)), 81.5 (OCH(Ar)), 62.0 (CO$_2$*C*H$_2$CH$_3$), 55.3 (OCH$_3$), 34.9 (CH$_2$Br), 26.59 (CO*C*H$_3$), 14.1 (CO$_2$CH$_2$*C*H$_3$); *Diastereoisomer 2:* ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.34–7.26 (m, 1 H, Ar-H), 6.98–6.89 (m, 2 H, 2 × Ar-H), 6.89–6.83 (m, 1 H, Ar-H), 4.59 (dd, *J* = 8.9, 3.7 Hz, 1 H, OCH(Ar)), 4.31 (s, 1 H, C*H*(CO$_2$Et)(COMe)), 4.11–4.03 (m, 2 H, CO$_2$C*H$_2$*CH$_3$), 3.82 (s, 3 H, OCH$_3$), 3.71 (dd, *J* = 11.0, 8.9 Hz, 1 H, C*H*HBr), 3.52 (dd, *J* = 11.0, 3.7 Hz, 1 H, CH*H*Br), 2.42 (s, 3 H, COCH$_3$), 1.16 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H$_3$*); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 201.0 (C=O ketone), 166.9 (C=O ester), 159.95 (Ar-*C$_q$*-OMe), 139.0 (Ar-*C$_q$*-CH(O)), 129.9 (Ar-CH), 119.4 (Ar-CH), 114.6 (Ar-CH), 112.3 (Ar-CH), 84.2 (*C*H(CO$_2$Et)(COMe)), 83.4 (OCH(Ar)), 61.8 (CO$_2$*C*H$_2$CH$_3$),

55.3 (OCH_3), 35.2 (CH_2Br), 26.61 (COCH_3), 13.8 (CO$_2$CH$_2$$CH_3$); HRMS (ESI-TOF) *m/z* Calcd for C$_{15}$H$_{19}$BrO$_5$Na$^+$ [M+Na]$^+$: 381.0314, Found: 381.0318.

(±)-Ethyl   6-(3-methoxyphenyl)-3-methyl-5,6-dihydro-1,4-dioxine-2-carboxylate   (6b) Prepared according to **General Procedure B** employing bromide **5b** (180 mg, 0.5 mmol). Purification by flash chromatography (20% Et$_2$O in pentane) afforded dioxene **6b** as a white solid (131 mg, 94%); R$_f$= 0.32 (20% Et$_2$O in pentane); mp = 53–55 °C; IR (film) / cm^{-1} 2980, 2932, 2838, 1708 (C=O), 1635 (C=C), 1604, 1490, 1456, 1437, 1370, 1302, 1288, 1254, 1152, 1103, 1069, 1038, 927, 864, 782, 767, 696, 585; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.33–7.29 (m, 1 H, Ar-H), 6.98–6.92 (m, 2 H, 2 × Ar-H), 6.91–6.86 (m, 1 H, Ar-H), 4.83 (dd, *J* = 8.3, 2.3 Hz, 1 H, OCH(Ar)), 4.34–4.21 (m, 3 H, OC*H*H and CO$_2$C*H$_2$*CH$_3$), 3.91 (dd, *J* = 11.1, 8.3 Hz, 1 H, OCH*H*), 3.82 (s, 3 H, OCH$_3$), 2.28 (s, 3 H, CH$_3$), 1.33 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H$_3$*); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 164.0 (CO$_2$), 159.8 (Ar-C_q-OMe), 146.7 ((Me)C_q=C), 137.9 (Ar-C_q-CH(O)), 129.7 (Ar-CH), 125.5 ((EtO$_2$C)C_q=C), 118.7 (Ar-CH), 113.9 (Ar-CH), 112.1 (Ar-CH), 73.5 (OCH(Ar)), 69.8 (OCH$_2$), 60.5 (CO$_2$CH$_2$CH$_3$), 55.3 (OCH$_3$), 17.6 (CH$_3$), 14.4 (CO$_2$CH$_2$CH$_3$); HRMS (ESI-TOF) *m/z* Calcd for C$_{15}$H$_{19}$O$_5$$^+$ [M+H]$^+$: 279.1132, Found: 279.1125.

(±)-2-Bromo-1-(3,4-dichlorophenyl)ethan-1-ol (4c) Sodium borohydride (158 mg, 4.2 mmol) was added portionwise to a solution of 2-bromo-3',4'-dichloroacetophenone (1.61 g, 6.0 mmol) in MeOH (30 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h 30 min. The reaction mixture was concentrated in vacuo and water (20 mL) was added. The aqueous mixture was extracted with Et$_2$O (3 × 30 mL). The organic extracts were combined, washed with saturated aq. NH$_4$Cl (15 mL), brine (15 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by flash chromatography (20% Et2O in pentane) afforded alcohol **4c** as a white crystalline solid (1.33 g, 82%); R$_f$= 0.27 (20% Et$_2$O in pentane); mp = 49–51 °C (lit.[36] mp = 59–50 °C (petroleum ether)); IR (film) / cm^{-1} 3412 (br O-H), 2961, 2899, 1565, 1471, 1421, 1392, 1196, 1133, 1070, 1031, 993, 885, 823, 743, 675, 640, 581; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.52 (d, *J* = 2.0 Hz, 1 H, Ar-H), 7.46 (d, *J* = 8.3 Hz, 1 H, Ar-H), 7.22 (dd, *J*

= 8.3, 2.0 Hz, 1 H, Ar-H), 4.94–4.86 (m, 1 H, C*H*(OH)), 3.63 (dd, *J* = 10.6, 3.4 Hz, 1 H, C*H*HBr), 3.49 (dd, *J* = 10.6, 8.6 Hz, 1 H, CH*H*Br), 2.73 (d, *J* = 3.1 Hz, 1 H, OH); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 140.4 (Ar-*C$_q$*-CH(OH)), 132.9 (Ar-C$_q$-Cl), 132.4 (Ar-C$_q$-Cl), 130.6 (Ar-CH), 128.0 (Ar-CH), 125.3 (Ar-CH), 72.5 (CH(OH)), 39.6 (CH$_2$Br). Observed data (^{1}H and ^{13}C NMR) was consistent with that previously reported.[34] The reaction was performed on a larger scale (10 mmol acetophenone), which afforded an isolated yield of alcohol (2.28 g, 84%).

(±)-Ethyl 2-[2-bromo-1-(3,4-dichlorophenyl)ethoxy]-3-oxobutanoate (5c) Prepared according to **General Procedure A** employing diazo **1** (188 mg, 1.2 mmol) and **4c** (269 mg, 1.0 mmol). Purification by flash chromatography (40% to 50% to 60% CH$_2$Cl$_2$ in pentane) afforded bromide **5c** as a colorless oil (302 mg, 76%, d.r. 52:48); R$_f$ = 0.23 (50% CH$_2$Cl$_2$ in pentane); IR (film) / cm^{-1} 2984, 2939, 2912, 1746 (C=O), 1724 (C=O), 1565, 1470, 1403, 1357, 1258, 1202, 1158, 1110, 1062, 1031, 883, 824, 754, 710, 676, 644, 573, 541; *Diastereoisomer 1:* ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51–7.45 (m, 2 H, 2 × Ar-H), 7.22 (dd, *J* = 8.3, 2.0 Hz, 1 H, Ar-H), 4.58 (dd, *J* = 8.2, 4.3 Hz, 1 H, OCH(Ar)), 4.34 (s, 1 H, C*H*(CO$_2$Et)(COMe)), 4.11 (q, *J* = 7.1 Hz, 2 H, CO$_2$C*H$_2$*CH$_3$), 3.66 (dd, *J* = 11.0, 8.2 Hz, 1 H, C*H*HBr), 3.49 (dd, *J* = 11.0, 4.3 Hz, 1 H, CH*H*Br), 2.40 (s, 3 H, COCH$_3$), 1.19 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H$_3$*); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 200.1 (C=O ketone), 166.5 (C=O ester), 137.9 (Ar-*C$_q$*-CH(O)), 133.3 (Ar-C$_q$-Cl), 133.2 (Ar-C$_q$-Cl), 130.8 (Ar-CH), 129.0 (Ar-CH), 126.3 (Ar-CH), 84.4 (*C*H(CO$_2$Et)(COMe)), 81.9 (OCH(Ar)), 62.1 (CO$_2$*C*H$_2$CH$_3$), 34.6 (CH$_2$Br), 26.6 (CO*C*H$_3$), 13.8 (CO$_2$CH$_2$*C*H$_3$); *Diastereoisomer 2:* ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51–7.45 (m, 1 H, Ar-H), 7.42 (d, *J* = 2.0 Hz, 1 H, Ar-H), 7.18 (dd, *J* = 8.3, 2.0 Hz, 1 H, Ar-H), 4.68 (t, *J* = 6.2 Hz, 1 H, OCH(Ar)), 4.32–4.23 (m, 3 H, C*H*(CO$_2$Et)(COMe) and CO$_2$C*H$_2$*CH$_3$), 3.71 (dd, *J* = 10.6, 6.4 Hz, 1 H, C*H*HBr), 3.54 (dd, *J* = 10.6, 6.0 Hz, 1 H, CH*H*Br), 2.27 (s, 3 H, COCH$_3$), 1.32 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H$_3$*); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 201.6 (C=O ketone), 166.3 (C=O ester), 137.4 (Ar-*C$_q$*-CH(O)), 133.5 (Ar-C$_q$-Cl), 133.0 (Ar-C$_q$-Cl), 131.0 (Ar-CH), 129.2 (Ar-CH), 126.4 (Ar-CH), 82.9

(CH(CO$_2$Et)(COMe)), 80.1 (OCH(Ar)), 62.2 (CO$_2$$CH_2CH_3$), 34.4 ($CH_2$Br), 26.5 (CO$CH_3$), 14.1 (CO$_2CH_2$$CH_3$); HRMS (FTMS +pNSI) *m/z* Calcd for C$_{14}$H$_{15}$BrCl$_2$O$_4$Na$^+$ [M+Na]$^+$: 418.9423, Found: 418.9422. The reaction was performed on a larger scale (8.0 mmol alcohol **4c**) using a microwave vial (10–20 mL volume) equipped with an Ar balloon, which afforded an improved isolated yield of bromide **5c** (2.91 g, 91%).

(±)-Ethyl   6-(3,4-dichlorophenyl)-3-methyl-5,6-dihydro-1,4-dioxine-2-carboxylate   (6c)
Prepared according to **General Procedure B** employing bromide **5c** (199 mg, 0.5 mmol). Purification by flash chromatography (15% Et$_2$O in pentane) afforded dioxene **6c** as a white crystalline solid (133 mg, 84%); R$_f$ = 0.29 (15% Et$_2$O in pentane); mp = 84–86 °C; IR (film) / cm^{-1} 2982, 2928, 2875, 1709 (C=O), 1636 (C=C), 1565, 1473, 1385, 1371, 1343, 1318, 1297, 1252, 1162, 1132, 1103, 1071, 1032, 930, 822, 767, 707, 681, 660, 582; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.49 (d, *J* = 2.0 Hz, 1 H, Ar-H), 7.47 (d, *J* = 8.3 Hz, 1 H, Ar-H), 7.22 (dd, *J* = 8.3, 2.0 Hz, 1 H, Ar-H), 4.83 (dd, *J* = 8.0, 2.3 Hz, 1 H, OCH(Ar)), 4.33–4.23 (m, 3 H, OCHH and CO$_2$CH_2CH$_3$), 3.88 (dd, *J* = 11.2, 8.0 Hz, 1 H, OCHH), 2.27 (s, 3 H, CH$_3$), 1.34 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$CH_3); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 163.7 (CO$_2$), 146.9 ((Me)C_q=C), 136.5 (Ar-C_q-CH(O)), 133.0 (Ar-C$_q$-Cl), 132.7 (Ar-C$_q$-Cl), 130.7 (Ar-CH), 128.5 (Ar-CH), 125.7 (Ar-CH), 125.6 ((EtO$_2$C)C_q=C), 72.4 (OCH(Ar)), 69.2 (OCH_2), 60.7 (CO$_2$$CH_2CH_3$), 17.5 (CH$_3$), 14.4 (CO$_2CH_2$$CH_3$); HRMS (ESI-TOF) *m/z* Calcd for C$_{14}$H$_{15}$Cl$_2$O$_4$$^+$ [M+H]$^+$: 317.0347, Found: 317.0356. The reaction was performed on a larger scale (5.0 mmol bromide **5c**) which afforded an isolated yield of dioxene **6c** (1.28 g, 80%).

(±)-2-Bromo-1-cyclohexylethan-1-ol (4d) and (±)-2-bromo-2-cyclohexylethan-1-ol (4g)
Using conditions developed by Ward,[37] *N*-bromosuccinimide (3.56 g, 20.0 mmol) was added to a solution of vinylcyclohexane (1.37 mL, 10.0 mmol) in DMSO (12.5 mL) and water (0.4 mL) at 10 ºC. The reaction mixture was warmed to 25 ºC and stirred for 1 h 15 min. Saturated aq. NaHCO$_3$ (20 mL) was then added, followed by EtOAc (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 30 mL). The organic extracts were combined, dried (Na$_2$SO$_4$) and

concentrated *in vacuo*. Purification by flash chromatography (10% Et$_2$O in pentane) afforded alcohol **4d** as a pale yellow oil (601 mg, 29%) followed by alcohol **4g** as a pale yellow oil (784 mg, 38%); *Alcohol 4d:* R$_f$ = 0.37 (10% EtOAc in hexanes); IR (film) / cm^{-1} 3385 (br O-H), 2923, 2852, 1449, 1096, 1039, 986, 893, 659; ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.62 (dd, *J* = 9.5, 1.9 Hz, 1 H, C*H*HBr), 3.58–3.40 (m, 2 H, C*H*OH and CH*H*Br), 2.08 (d, *J* = 4.6 Hz, 1 H, OH), 1.99–1.86 (m, 1 H, Cy-CH), 1.84–1.72 (m, 2 H, 2 × Cy-CH), 1.72–1.63 (m, 2 H, 2 × Cy-CH), 1.56–1.46 (m, 1 H, Cy-CH), 1.35–0.98 (m, 5 H, 5 × Cy-CH); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 75.2 (CHOH), 42.1 (Cy-CH$_2$), 39.5 (CH$_2$Br), 29.0 (Cy-CH), 28.3 (Cy-CH$_2$), 26.2 (Cy-CH$_2$), 26.0 (Cy-CH$_2$), 25.9 (Cy-CH$_2$); HRMS (EI-TOF) *m/z* Calcd for C$_8$H$_{13}$Br$^+$ [M-H$_2$O]$^+$: 188.0201, Found: 188.0201. *Alcohol 4g*: R$_f$ = 0.21 (10% EtOAc in hexanes); IR (film) / cm^{-1} 3349 (br O-H), 2925, 2853, 1449, 1068, 1015, 891, 658; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.09 (q, *J* = 5.7 Hz, 1 H, CHBr), 3.86 (dd, *J* = 6.6, 5.7 Hz, 2 H, C*H$_2$*OH), 2.00 (t, *J* = 6.6 Hz, 1 H, OH), 1.95–1.84 (m, 1 H, Cy-CH), 1.84–1.62 (m, 5 H, 5 × Cy-CH), 1.39–1.04 (m, 5 H, 5 × Cy-CH); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 67.4 (CHBr), 65.3 (CH$_2$OH), 41.3 (Cy-CH), 30.9 (Cy-CH$_2$), 30.3 (Cy-CH$_2$), 26.1 (Cy-CH$_2$), 26.0 (Cy-CH$_2$), 25.9 (Cy-CH$_2$). Observed data (IR, ^{1}H and ^{13}C NMR) for alcohol **4g** was consistent with that previously reported.[38]

(±)-Ethyl 2-(2-bromo-1-cyclohexylethoxy)-3-oxobutanoate (5d) Prepared according to **General Procedure A** employing diazo **1** (188 mg, 1.2 mmol) and **4d** (209 mg, 1.0 mmol). Purification by flash chromatography (15% Et$_2$O in pentane) afforded bromide **5d** as a pale yellow oil as a mixture of keto and enol tautomers (283 mg, 84%; 67% keto; d.r. 64:36); R$_f$ = 0.26 (15% Et$_2$O in pentane); IR (film) / cm^{-1} 2926, 2854, 1748 (C=O), 1726 (C=O), 1655, 1449, 1255, 1180, 1112, 1035, 1015; *Diastereomer 1 (keto tautomer)*: ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.51 (s, 1 H, C*H*(CO$_2$Et)(COMe)), 4.46–4.40 (m, 2 H, CO$_2$C*H$_2$*CH$_3$), 3.75–3.37 (m, 3 H, CH$_2$Br and OCH(Cy)), 2.35 (s, 3 H, COCH$_3$), 2.04–1.53 (m, 6 H, 6 × Cy-CH), 1.44–0.98 (m, 8 H, CO$_2$CH$_2$C*H$_3$* and 5 × Cy-CH); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 202.7 (C=O ketone), 167.4 (C=O ester), 84.7

($CH(CO_2Et)(COMe)$), 84.4 ($OCH(Cy)$), 61.9 ($CO_2CH_2CH_3$), 40.8 (Cy-CH), 32.4 (CH_2Br), 29.0 (Cy-CH_2), 28.4 (2 × Cy-CH_2), 26.6 (Cy-CH_2), 26.3 (Cy-CH_2), 26.03 ($COCH_3$), 25.98 (Cy-CH_2), 14.1 ($CO_2CH_2CH_3$); *Diastereomer 2 (keto tautomer):* ^1H NMR (400 MHz, CDCl$_3$) δ 4.44 (s, 1 H, $CH(CO_2Et)(COMe)$), 4.46–4.40 (m, 2 H, $CO_2CH_2CH_3$), 3.75–3.37 (m, 3 H, CH_2Br and $OCH(Cy)$), 2.30 (s, 3 H, $COCH_3$), 2.04–1.53 (m, 6 H, 6 × Cy-CH), 1.44–0.98 (m, 8 H, $CO_2CH_2CH_3$ and 5 × Cy-CH); $^{13}C\{^1H\}$ NMR (101 MHz, CDCl$_3$) δ 202.0 (C=O ketone), 167.6 (C=O ester), 86.0 ($CH(CO_2Et)(COMe)$), 85.6 ($OCH(Cy)$), 62.0 ($CO_2CH_2CH_3$), 42.1 (Cy-CH_2), 40.5 (Cy-CH_2), 39.5 (Cy-CH), 32.5 (CH_2Br) 28.3 (Cy-CH_2), 27.7 (Cy-CH_2), 26.6 ($COCH_3$), 25.9 (Cy-CH_2), 14.1 ($CO_2CH_2CH_3$); *Enol tautomer:* ^1H NMR (400 MHz, CDCl$_3$) δ 11.3 (s, 1 H, OH), 4.46–4.40 (m, 2 H, $CO_2CH_2CH_3$), 3.75–3.37 (m, 3 H, CH_2Br and $OCH(Cy)$), 2.11 (s, 3 H, $COCH_3$), 2.04–1.53 (m, 6 H, 6 × Cy-CH), 1.44–0.98 (m, 8 H, $CO_2CH_2CH_3$ and 5 × Cy-CH); HRMS (ESI-TOF) *m/z* Calcd for $C_{14}H_{23}O_4BrNa^+$ [M+Na]$^+$: 357.0677, Found: 357.0683. *Signals for enol tautomer were very weak by ^{13}C NMR.*

(±)-Ethyl 6-cyclohexyl-3-methyl-5,6-dihydro-1,4-dioxine-2-carboxylate (6d) Prepared according to **General Procedure B** employing bromide **5d** (168 mg, 0.5 mmol). Purification by flash chromatography (10% Et$_2$O in pentane) afforded dioxene **6d** as a white crystalline solid (100 mg, 78%); R$_f$ = 0.28 (10% Et$_2$O in pentane); mp = 32–33 °C; IR (film) / cm^{-1} 2988, 2924, 2855, 1709 (C=O), 1639 (C=C), 1210, 1297, 1247, 1176, 1126, 1081, 1053, 1027, 922, 767; ^1H NMR (400 MHz, CDCl$_3$) δ 4.25 (dq, *J* = 7.1, 1.5 Hz, 2 H, $CO_2CH_2CH_3$), 4.19 (dd, *J* = 11.0, 2.1 Hz, 1 H, OC*H*H), 3.87 (dd, *J* = 11.0, 7.3 Hz, 1 H, OCH*H*), 3.57 (td, *J* = 7.3, 2.1 Hz, 1 H, $OCH(Cy)$), 2.23 (s, 3 H, CH$_3$), 2.10–1.97 (m, 1 H, Cy-CH), 1.85–1.54 (m, 5 H, 5 × Cy-CH), 1.34 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.31–0.97 (m, 5 H, 5 × Cy-CH); $^{13}C\{^1H\}$ NMR (101 MHz, CDCl$_3$) δ 164.3 (CO$_2$), 146.7 ((Me)C_q=C), 124.8 ((EtO$_2$C)C_q=C), 75.9 ($OCH(Cy)$), 67.0 (OCH$_2$), 60.3 ($CO_2CH_2CH_3$), 38.3 (Cy-CH), 28.9 (Cy-CH_2), 28.3 (Cy-CH_2), 26.3 (Cy-CH_2), 25.8 (Cy-CH_2), 25.7 (Cy-CH_2), 17.5 (CH$_3$), 14.4 ($CO_2CH_2CH_3$); HRMS (ESI-TOF) *m/z* Calcd for $C_{14}H_{23}O_4^+$ [M+H]$^+$: 255.1596, Found: 255.1606.

(±)-Ethyl 2-({1-[(*tert*-butyldimethylsilyl)oxy]-3-chloropropan-2-yl}oxy)-3-oxobutanoate (5e) Prepared according to **General Procedure A** employing diazo **1** (187 mg, 1.2 mmol) and (±)-1-[(*tert*-butyldimethylsilyl)oxy]-3-chloropropan-2-ol[18a,39] **4e** (225 mg, 1.0 mmol). Purification by flash chromatography (5% EtOAc in pentane) afforded chloride **5e** as a colorless oil (251 mg, 71%, d.r. 52:48); R_f = 0.28 (5% EtOAc in pentane); IR (film) / cm^{-1} 2956, 2931, 2858, 1749 (C=O), 1729 (C=O), 1472, 1359, 1339, 1253, 1183, 1114, 1062, 1008, 974, 939, 900, 835, 777, 669, 555; *Diastereoisomer 1:* ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.69 (s, 1 H, C*H*(CO$_2$Et)(COMe)), 4.31–4.24 (m, 2 H, CO$_2$C*H*$_2$CH$_3$), 3.88–3.78 (m, 2 H, C*H*HOTBS and C*H*HCl), 3.76–3.67 (m, 3 H, OC*H*(CH$_2$OTBS) and CH*H*OTBS and CH*H*Cl), 2.32 (s, 3 H, COC*H*$_3$), 1.307 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H*$_3$), 0.89 (s, 9 H, C(C*H*$_3$)$_3$), 0.07 (s, 6 H, OSi(C*H*$_3$)$_2$(*t*Bu)); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 201.8 (C=O ketone), 167.23 (C=O ester), 85.1 (*C*H(CO$_2$Et)(COMe)), 81.0 (O*C*H(CH$_2$OTBS)), 62.9 (*C*H$_2$OTBS), 61.96 (CO$_2$*C*H$_2$CH$_3$), 44.0 (*C*H$_2$Cl), 26.6 (CO*C*H$_3$), 25.8 (C(*C*H$_3$)$_3$), 18.2 (*C$_q$*(CH$_3$)$_3$), 14.1 (CO$_2$CH$_2$*C*H$_3$), −5.5 (OSi(*C*H$_3$)(C'H$_3$)(*t*Bu), −5.6 (OSi(CH$_3$)(*C'*H$_3$)(*t*Bu); *Diastereoisomer 2:* ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.72 (s, 1 H, C*H*(CO$_2$Et)(COMe)), 4.31–4.24 (m, 2 H, CO$_2$C*H*$_2$CH$_3$), 3.88–3.78 (m, 2 H, C*H*HOTBS and C*H*HCl), 3.76–3.67 (m, 3 H, OC*H*(CH$_2$OTBS) and CH*H*OTBS and CH*H*Cl), 2.30 (s, 3 H, COC*H*$_3$), 1.310 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H*$_3$), 0.89 (s, 9 H, C(C*H*$_3$)$_3$), 0.08 (s, 6 H, OSi(C*H*$_3$)$_2$(*t*Bu)); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 201.7 (C=O ketone), 167.22 (C=O ester), 85.2 (*C*H(CO$_2$Et)(COMe)), 80.8 (O*C*H(CH$_2$OTBS)), 63.0 (*C*H$_2$OTBS), 61.99 (CO$_2$*C*H$_2$CH$_3$), 43.2 (*C*H$_2$Cl), 26.4 (CO*C*H$_3$), 25.8 (C(*C*H$_3$)$_3$), 18.2 (*C$_q$*(CH$_3$)$_3$), 14.1 (CO$_2$CH$_2$*C*H$_3$), −5.5 (OSi(*C*H$_3$)(C'H$_3$)(*t*Bu), −5.6 (OSi(CH$_3$)(*C'*H$_3$)(*t*Bu); HRMS (ESI-TOF) *m/z* Calcd for C$_{15}$H$_{30}$ClO$_5$Si$^+$ [M+H]$^+$: 353.1551, Found: 353.1548.

(±)-Ethyl 6-{[(tert-butyldimethylsilyl)oxy]methyl}-3-methyl-5,6-dihydro-1,4-dioxine-2-carboxylate (6e) Prepared according to **General Procedure B** employing chloride **5e** (177 mg, 0.5 mmol). Purification by flash chromatography (10% Et$_2$O in pentane) afforded dioxene **6e** as a white solid (143 mg, 90%); R_f = 0.26 (10% Et$_2$O in pentane); mp = 20–21 °C; IR (film) / cm^{-1} 2954, 2931,

2886, 2858, 1714 (C=O), 1638 (C=C), 1464, 1370, 1300, 1253, 1175, 1139, 1107, 1052, 973, 919, 837, 779, 668; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.29–4.19 (m, 3 H, OC*H*H and CO$_2$C*H$_2$*CH$_3$), 4.01–3.85 (m, 3 H, OC*H*(CH$_2$OTBS) and OCH*H* and C*H*HOTBS), 3.70 (dd, J = 10.5, 7.0 Hz, 1 H, CH*H*OTBS), 2.22 (s, 3 H, CH$_3$), 1.32 (t, J = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H$_3$*), 0.89 (s, 9 H, C(C*H$_3$*)$_3$), 0.080 (s, 3 H, OSi(C*H$_3$*)(C'H$_3$)(*t*Bu)), 0.076 (s, 3 H, OSi(CH$_3$)(C'*H$_3$*)(*t*Bu)); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 164.0 (*C*O$_2$), 146.9 ((Me)*C$_q$*=C), 124.6 ((EtO$_2$C)*C$_q$*=C), 71.8 (O*C*H(CH$_2$OTBS)), 66.3 (O*C*H$_2$), 61.5 (*C*H$_2$OTBS), 60.5 (CO$_2$*C*H$_2$CH$_3$), 25.8 (C(*C*H$_3$)$_3$), 18.2 (*C$_q$*(CH$_3$)$_3$), 17.7 (*C*H$_3$), 14.3 (CO$_2$CH$_2$*C*H$_3$), −5.44 (OSi(*C*H$_3$)(C'H$_3$)(*t*Bu)), −5.46 (OSi(CH$_3$)(*C'*H$_3$)(*t*Bu); HRMS (ESI-TOF) *m/z* Calcd for C$_{15}$H$_{29}$O$_5$Si$^+$ [M+H]$^+$: 317.1784, Found: 317.1783.

(±)-Ethyl 2-[(1,3-dichloropropan-2-yl)oxy]-3-oxobutanoate (5f) Prepared according to **General Procedure A** employing diazo **1** (189 mg, 1.2 mmol) and 1,3-dichloropropan-2-ol[18a,40] **4f** (129 mg, 1.0 mmol). Purification by flash chromatography (5% to 10% EtOAc in pentane) afforded chloride **5f** as a colorless oil (171 mg, 67%); R$_f$ = 0.31 (10% EtOAc in pentane); IR (film) / cm^{-1} 2984, 2905, 1747 (C=O), 1726 (C=O), 1427, 1358, 1340, 1257, 1211, 1182, 1157, 1121, 1016, 860, 837, 757, 704, 613, 560; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.64 (s, 1 H, C*H*(CO$_2$Et)(COMe)), 4.33–4.24 (m, 2 H, CO$_2$C*H$_2$*CH$_3$), 3.92–3.86 (m, 1 H, OC*H*(CH$_2$Cl)$_2$), 3.82–3.78 (m, 2 H, CH$_2$Cl), 3.77–3.70 (m, 2 H, C'H$_2$Cl), 2.32 (s, 3 H, COCH$_3$), 1.32 (t, J = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H$_3$*); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 200.8 (C=O ketone), 166.8 (C=O ester), 85.1 (*C*H(CO$_2$Et)(COMe)), 79.9 (O*C*H(CH$_2$Cl)$_2$), 62.3 (CO$_2$*C*H$_2$CH$_3$), 43.4 (*C*H$_2$Cl), 43.2 (*C'*H$_2$Cl), 26.6 (CO*C*H$_3$), 14.1 (CO$_2$CH$_2$*C*H$_3$); HRMS (CI) *m/z* Calcd for C$_9$H$_{18}$Cl$_2$NO$_4^+$ [M+NH$_4$]$^+$: 274.0613, Found: 274.0619.

(±)-Ethyl 6-(chloromethyl)-3-methyl-5,6-dihydro-1,4-dioxine-2-carboxylate (6f) Prepared according to **General Procedure B** employing chloride **5f** (129 mg, 0.5 mmol). Purification by flash chromatography (15% to 20% Et$_2$O in pentane) afforded dioxene **6f** as a colorless oil (100 mg, 90%); R$_f$ = 0.33 (20% Et$_2$O in pentane); IR (film) / cm^{-1} 2981, 2932, 1708 (C=O), 1635 (C=C), 1446, 1371, 1307, 1249, 1164, 1123, 1075, 961, 931, 852, 767, 728, 692, 588, 579; ^{1}H NMR (400 MHz, CDCl$_3$) δ

4.32–4.24 (m, 3 H, OC*H*H and CO$_2$C*H$_2$*CH$_3$), 4.24–4.17 (m, 1 H, OC*H*(CH$_2$Cl)), 4.07 (dd, *J* = 11.1, 5.7 Hz, 1 H, OCH*H*), 3.76 (dd, *J* = 11.3, 4.6 Hz, 1 H, C*H*HCl), 3.61 (dd, *J* = 11.3, 8.2 Hz, 1 H, CH*H*Cl), 2.25 (s, 3 H, CH$_3$), 1.35 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H$_3$*); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 163.6 (*C*O$_2$), 147.0 ((Me)*C$_q$*=C), 124.3 ((EtO$_2$C)*C$_q$*=C), 71.0 (O*C*H(CH$_2$Cl)), 65.6 (O*C*H$_2$), 60.7 (CO$_2$*C*H$_2$CH$_3$), 40.8 (*C*H$_2$Cl) 17.6 (*C*H$_3$), 14.3 (CO$_2$CH$_2$*C*H$_3$); HRMS (ESI-TOF) *m/z* Calcd for C$_9$H$_{14}$ClO$_4$$^+$ [M+H]$^+$: 221.0581, Found: 221.0580.

(±)-Ethyl 2-(2-bromo-2-cyclohexylethoxy)-3-oxobutanoate (5g) Prepared according to **General Procedure A** employing diazo **1** (188 mg, 1.2 mmol) and **4g** (209 mg, 1.0 mmol). Purification by flash chromatography (15% Et$_2$O in pentane) afforded bromide **5g** as a pale yellow oil as a mixture of keto and enol tautomers (291 mg, 87%; 71% keto; d.r. 56:44); R$_f$ = 0.26 (15% Et$_2$O in pentane); IR (film) / cm^{-1} 2928, 2854, 1747 (C=O), 1728 (C=O), 1449, 1369, 1258, 1149, 1128, 1016; *Diastereomer 1 (keto tautomer):* ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.41 (s, 1 H, C*H*(CO$_2$Et)(COMe)), 4.37–4.21 (m, 2 H, CO$_2$C*H$_2$*CH$_3$), 4.19–3.61 (m, 3 H, CH(Cy)Br and OCH$_2$), 2.32 (s, 3 H, COCH$_3$), 1.96–1.61 (m, 6 H, 6 × Cy-CH), 1.46–1.08 (m, 8 H, CO$_2$CH$_2$C*H$_3$* and 5 × Cy-CH); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 201.6 (C=O ketone), 166.9 (C=O ester), 85.7 (*C*H(CO$_2$Et)(COMe)), 73.5 (O*C*H$_2$), 62.0 (CO$_2$*C*H$_2$CH$_3$), 59.9 (*C*H(Cy)Br), 40.9 (Cy-CH), 30.96 (Cy-CH$_2$), 29.1 (Cy-CH$_2$), 28.7 (Cy-CH$_2$), 26.6 (Cy-CH$_2$), 26.11 (Cy-CH$_2$), 26.08 (CO*C*H$_3$), 25.86 (Cy-CH$_2$), 14.1 (CO$_2$CH$_2$*C*H$_3$); *Diastereomer 2 (keto tautomer):* ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.40 (s, 1 H, C*H*(CO$_2$Et)(COMe)), 4.37–4.21 (m, 2 H, CO$_2$C*H$_2$*CH$_3$), 4.19–3.61 (m, 3 H, CH(Cy)Br and OCH$_2$), 2.31 (s, 3 H, COCH$_3$), 1.96–1.61 (m, 6 H, 6 × Cy-CH), 1.46–1.08 (m, 8 H, CO$_2$CH$_2$C*H$_3$* and 5 × Cy-CH); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 201.6 (C=O ketone), 166.8 (C=O ester), 85.6 (*C*H(CO$_2$Et)(COMe)), 72.8 (O*C*H$_2$), 62.0 (CO$_2$*C*H$_2$CH$_3$), 59.3 (*C*H(Cy)Br), 40.6 (Cy-CH), 30.93 (Cy-CH$_2$), 29.1 (Cy-CH$_2$), 26.5 (Cy-CH$_2$), 26.13 (Cy-CH$_2$), 26.08 (CO*C*H$_3$), 25.87 (Cy-CH$_2$), 14.1 (CO$_2$CH$_2$*C*H$_3$); *Enol tautomer:* ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.1 (s, 1 H, OH), 4.37–4.21 (m, 2 H, CO$_2$C*H$_2$*CH$_3$), 4.19–3.61 (m, 3 H, CH(Cy)Br and OCH$_2$), 2.11 (s, 3 H,

COCH$_3$), 1.96–1.61 (m, 6 H, 6 × Cy-CH), 1.46–1.08 (m, 8 H, CO$_2$CH$_2$CH_3 and 5 × Cy-CH); HRMS (ESI-TOF) m/z Calcd for C$_{14}$H$_{23}$O$_4$BrNa$^+$ [M+Na]$^+$: 357.0677, Found: 357.0669. *Signals for enol tautomer were very weak by ^{13}C NMR.*

(±)-Ethyl 5-cyclohexyl-3-methyl-5,6-dihydro-1,4-dioxine-2-carboxylate (6g) Prepared according to **General Procedure B** employing bromide **5g** (168 mg, 0.5 mmol). Purification by flash chromatography (10% Et$_2$O in pentane) afforded dioxene **6g** as a white crystalline solid (113 mg, 89%); R$_f$ = 0.16 (10% Et$_2$O in pentane); mp = 35–37 °C; IR (film) / cm^{-1} 2982, 2930, 2857, 1706 (C=O), 1633 (C=C), 1446, 1372, 1306, 1287, 1270, 1241, 1166, 1123, 1082, 1066, 1015, 976, 964, 769; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.33–4.21 (m, 2 H, CO$_2$CH_2CH$_3$), 4.19–4.11 (m, 1 H, OCHH), 3.79–3.71 (m, 2 H, OCHH and OCH(Cy)), 2.24 (CH$_3$), 1.95–1.88 (m, 1 H, Cy-CH), 1.76 (m, 2 H, 2 × Cy-CH), 1.73–1.64 (m, 2 H, 2 × Cy-CH), 1.64–1.58 (m, 1 H, Cy-CH), 1.34 (t, J = 7.1 Hz, 3 H, CO$_2$CH$_2$CH_3), 1.30–1.02 (m, 5 H, 5 × Cy-CH); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 164.0 (CO$_2$), 147.5 ((Me)C_q=C), 124.7 ((EtO$_2$C)C_q=C), 78.3 (OCH(Cy)), 65.2 (OCH$_2$), 60.4 (CO$_2$CH$_2$CH$_3$), 38.6 (Cy-CH), 28.4 (Cy-CH$_2$), 28.3 (Cy-CH$_2$), 26.2 (Cy-CH$_2$), 25.8 (Cy-CH$_2$), 25.7 (Cy-CH$_2$), 17.8 (CH$_3$), 14.4 (CO$_2$CH$_2$CH$_3$); HRMS (ESI-TOF) m/z Calcd for C$_{14}$H$_{23}$O$_4$$^+$ [M+H]$^+$: 255.1596, Found: 255.1601.

(±)-*trans*-Ethyl 2-[(2-bromocyclopentyl)oxy]-3-oxobutanoate (5h) Prepared according to **General Procedure A** employing diazo **1** (187 mg, 1.2 mmol) and (±)-*trans*-2-bromocyclopentan-1-ol^{18a,41} **4h** (165 mg, 1.0 mmol). Purification by flash chromatography (5% to 10% Et$_2$O in pentane) afforded bromide **5h** as a colorless oil (213 mg, 73%, d.r. 50:50); R$_f$ = 0.13 (5% Et$_2$O in pentane); IR (film) / cm^{-1} 2980, 2876, 1747 (C=O), 1726 (C=O), 1436, 1411, 1356, 1335, 1256, 1182, 1159, 1114, 1070, 1031, 960, 848, 810, 618, 537; *Diastereoisomer 1:* ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.52 (s, 1 H, CH(CO$_2$Et)(COMe)), 4.33–4.21 (m, 3 H, CHBr and CO$_2$CH_2CH$_3$), 4.20–4.13 (m, 1 H, OCH), 2.45–2.32 (m, 1 H, CHH), 2.29 (s, 3 H, COCH$_3$), 2.23–2.14 (m, 1 H, CHH), 2.04–1.97 (m, 1 H, CHH), 1.91–1.76 (m, 3 H, CHH and CH$_2$), 1.32 (t, J = 7.1 Hz, 3 H, CO$_2$CH$_2$CH_3); ^{13}C{^{1}H} NMR (101 MHz,

CDCl$_3$) δ 201.8 (C=O ketone), 167.2 (C=O ester), 89.3 (O*C*H), 84.4 (*C*H(CO$_2$Et)(COMe)), 62.1 (CO$_2$*C*H$_2$CH$_3$), 53.5 (*C*HBr), 34.64 (*C*H$_2$), 29.9 (*C*H$_2$), 26.4 (CO*C*H$_3$), 21.5 (*C*H$_2$), 14.1 (CO$_2$CH$_2$*C*H$_3$);

Diastereoisomer 2: ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.47 (s, 1 H, C*H*(CO$_2$Et)(COMe)), 4.33–4.21 (m, 3 H, CHBr and CO$_2$C*H$_2$CH$_3$), 4.20–4.13 (m, 1 H, OC*H*), 2.45–2.32 (m, 1 H, C*H*H), 2.25 (s, 3 H, COC*H$_3$*), 2.23–2.14 (m, 1 H, C*H*H), 2.04–1.97 (m, 1 H, CH*H*), 1.91–1.76 (m, 3 H, CH*H* and C*H$_2$*), 1.31 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H$_3$*); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 201.7 (C=O ketone), 167.2 (C=O ester), 89.1 (O*C*H), 84.5 (*C*H(CO$_2$Et)(COMe)), 62.0 (CO$_2$*C*H$_2$CH$_3$), 52.9 (*C*HBr), 34.57 (*C*H$_2$), 29.8 (*C*H$_2$), 26.3 (CO*C*H$_3$), 21.6 (*C*H$_2$), 14.1 (CO$_2$CH$_2$*C*H$_3$); HRMS (CI) *m/z* Calcd for C$_{11}$H$_{21}$BrNO$_4$$^+$ [M+NH$_4$]$^+$: 310.0654, Found: 310.0650.

(±)-*cis*-Ethyl   3-methyl-4aH,5H,6H,7H,7aH-cyclopenta[b][1,4]dioxine-2-carboxylate   (6h) Prepared according to **General Procedure B** employing bromide **5h** (147 mg, 0.5 mmol). Purification by flash chromatography (20% Et$_2$O in pentane) afforded dioxene **6h** as a colorless oil (97 mg, 91%); R$_f$ = 0.30 (20% Et$_2$O in pentane); IR (film) / cm^{-1} 2978, 2945, 2878, 1707 (C=O), 1635 (C=C), 1447, 1370, 1347, 1303, 1252, 1157, 1127, 1082, 1041, 1021, 936, 886, 861, 768, 739; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.33–4.21 (m, 3 H, OCH and CO$_2$C*H$_2$CH$_3$), 4.19–4.14 (td, *J* = 5.2, 3.4 Hz, 1 H, OC'H), 2.24 (s, 3 H, CH$_3$), 1.96–1.85 (m, 4 H, 2 × C*H*H and CH$_2$), 1.82–1.72 (m, 1 H, CH*H*), 1.68–1.58 (m, 1 H, CH*H*), 1.33 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H$_3$*); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 164.3 (CO$_2$), 146.0 ((Me)*C$_q$*=C), 122.5 ((EtO$_2$C)*C$_q$*=C), 76.7 (O*C*H), 74.0 (O*C*'H), 60.5 (CO$_2$*C*H$_2$CH$_3$), 28.0 (*C*H$_2$), 27.2 (*C*H$_2$), 18.8 (*C*H$_2$), 17.9 (*C*H$_3$), 14.4 (CO$_2$CH$_2$*C*H$_3$); HRMS (ESI-TOF) *m/z* Calcd for C$_{11}$H$_{17}$O$_4$$^+$ [M+H]$^+$: 213.1127, Found: 213.1127.

(±)-*trans*-Ethyl 2-[(2-bromo-2,3-dihydro-1H-inden-1-yl)oxy]-3-oxobutanoate (5i) Prepared according to **General Procedure A** employing diazo **1** (188 mg, 1.2 mmol) and (±)-*trans*-2-bromo-1-indanol **4i** (213 mg, 1.0 mmol). Purification by flash chromatography (10% Et$_2$O in pentane) afforded bromide **5i** as a yellow oil as a mixture of keto and enol tautomers (298 mg, 87%; 58% keto; d.r.

62:38); R_f = 0.20 (10% Et_2O in pentane); IR (film) / cm^{-1} 2983, 1728 (C=O), 1656 (C=O), 1621, 1478, 1464, 1409, 1337, 1254, 1216, 1179, 1123, 1061, 1019, 961, 936, 915, 861, 820, 755, 734, 615, 545; *Diastereoisomer 1 (keto tautomer):* ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.63–7.58 (m, 1 H, Ar-CH), 7.47–7.20 (m, 3 H, 3 × Ar-H), 5.23 (d, *J* = 5.2 Hz, 1 H, OCH(Ar)), 5.00 (s, 1 H, C*H*(CO$_2$Et)(COMe)), 4.51–4.44 (m, 1 H, CHBr), 4.41–4.24 (m, 2 H, CO$_2$C*H$_2$*CH$_3$), 3.65 (d, *J* = 16.4, 7.3 Hz, 1 H, C*H*H(Ar)), 3.31–3.19 (m, 1 H, CH*H*(Ar)), 2.34 (s, 3 H, COCH$_3$), 1.33 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H$_3$*); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 201.1 (C=O ketone), 167.2 (C=O ester), 140.0 (Ar-C$_q$), 139.2 (Ar-C$_q$), 129.5 (Ar-CH), 127.6 (Ar-CH), 125.4 (Ar-CH), 124.4 (Ar-CH), 90.8 (OCH(Ar)), 84.6 (*C*H(CO$_2$Et)(COMe)), 62.1 (CO$_2$*C*H$_2$CH$_3$), 51.0 (CHBr), 41.2 (CH$_2$(Ar)), 26.7 (CO*C*H$_3$), 14.1 (CO$_2$CH$_2$*C*H$_3$); *Diastereoisomer 2 (keto tautomer):* ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.47–7.20 (m, 4 H, 4 × Ar-H), 5.21 (d, *J* = 3.5 Hz, 1 H, OCH(Ar)), 4.74 (s, 1 H, C*H*(CO$_2$Et)(COMe)), 4.64–4.60 (m, 1 H, CHBr), 4.41–4.24 (m, 2 H, CO$_2$C*H$_2$*CH$_3$), 3.75 (d, *J* = 16.9, 6.5 Hz, 1 H, C*H*H(Ar)), 3.31–3.19 (m, 1 H, CH*H*(Ar)), 2.24 (s, 3 H, COCH$_3$), 1.35 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H$_3$*); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 201.5 (C=O ketone), 167.0 (C=O ester), 141.0 (Ar-C$_q$), 138.4 (Ar-C$_q$), 129.8 (Ar-CH), 127.4 (Ar-CH), 125.5 (Ar-CH), 125.0 (Ar-CH), 91.2 (OCH(Ar)), 84.0 (*C*H(CO$_2$Et)(COMe)), 62.2 (CO$_2$*C*H$_2$CH$_3$), 51.2 (CHBr), 41.6 (CH$_2$(Ar)), 26.4 (CO*C*H$_3$), 14.1 (CO$_2$CH$_2$*C*H$_3$); *Enol tautomer:* ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.25 (br s, 1 H, C=C(OH)), 7.47–7.20 (m, 4 H, 4 × Ar-H), 5.32 (d, *J* = 2.6 Hz, 1 H, OCH(Ar)), 4.68–4.64 (m, 1 H, CHBr), 4.41–4.24 (m, 2 H, CO$_2$C*H$_2$*CH$_3$), 3.80 (dd, *J* = 17.1, 6.3 Hz, 1 H, C*H*H(Ar)), 3.31–3.19 (m, 1 H, CH*H*(Ar)), 1.80 (d, *J* = 0.7 Hz, 3 H, CH$_3$), 1.39 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H$_3$*); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 169.5 ((EtO$_2$C)*C$_q$*=C(OH)), 167.3 (CO$_2$), 141.3 (Ar-C$_q$), 138.8 (Ar-C$_q$), 129.7 (Ar-CH), 127.2 (Ar-CH), 126.0 (Ar-CH), 124.9 (Ar-CH), 123.1 ((EtO$_2$C)C=*C$_q$*(OH)), 92.0 (OCH(Ar)), 61.1 (CO$_2$*C*H$_2$CH$_3$), 51.1 (CHBr), 41.7 (CH$_2$(Ar)), 16.5 (CH$_3$), 14.3 (CO$_2$CH$_2$*C*H$_3$); HRMS (ESI-TOF) *m/z* Calcd for C$_{17}$H$_{20}$BrNO$_4$Na$^+$ [M+CH$_3$CN+Na]$^+$: 404.0473, Found: 404.0490.

(±)-*cis*-Ethyl 2-methyl-4aH,9H,9aH-indeno[1,2-b][1,4]dioxine-3-carboxylate (6i) Prepared according to **General Procedure B** employing bromide **5i** (171 mg, 0.5 mmol). Purification by flash chromatography (20% Et_2O in pentane) afforded dioxene **6i** as a pale yellow oil (125 mg, 96%); R_f = 0.29 (20% Et_2O in pentane); IR (film) / cm^{-1} 2979, 2954, 1708 (C=O), 1640 (C=C), 1462, 1444, 1370, 1305, 1250, 1160, 1149, 1084, 1010, 960, 933, 888, 862, 834, 751, 668, 627, 602; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48–7.44 (m, 1 H, Ar-H), 7.33–7.23 (m, 3 H, 3 × Ar-H), 5.36 (d, J = 3.9 Hz, 1 H, OCH(Ar)), 4.74 (q, J = 3.9 Hz, 1 H, OCH(CH$_2$Ar)), 4.28 (q, J = 7.1 Hz, 2 H, CO$_2$CH_2CH$_3$), 3.14–3.08 (m, 2 H, CH$_2$Ar), 2.15 (s, 3 H, CH$_3$), 1.35 (t, J = 7.1 Hz, 3 H, CO$_2$CH$_2$CH_3); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.1 (CO$_2$), 147.6 ((Me)C_q=C), 139.6 (Ar-C$_q$), 139.3 (Ar-C$_q$), 129.1 (Ar-CH), 127.2 (Ar-CH), 125.7 (Ar-CH), 124.7 (Ar-CH), 122.9 ((EtO$_2$C)C_q=C), 76.6 (OCH(Ar)), 75.9 (OCH(CH$_2$Ar)), 60.4 (CO$_2$CH$_2$CH$_3$), 36.7 (CH$_2$Ar), 17.9 (CH$_3$), 14.4 (CO$_2$CH$_2$CH$_3$); HRMS (ESI-TOF) m/z Calcd for $C_{15}H_{17}O_4^+$ [M+H]$^+$: 261.1127, Found: 261.1130.

(±)-Ethyl 2-[(1-chloro-2-methylpropan-2-yl)oxy]-3-oxobutanoate (5j) Prepared according to **General Procedure A** employing diazo **1** (188 mg, 1.2 mmol) and 1-chloro-2-methyl-2-propanol **4j** (109 mg, 1.0 mmol). Purification by flash chromatography (15% to 20% Et_2O in pentane) afforded chloride **5j** as a pale yellow oil (111 mg, 47%); R_f = 0.22 (20% Et_2O in pentane); IR (film) / cm^{-1} 2983, 2941, 1745 (C=O), 1723 (C=O), 1467, 1423, 1387, 1370, 1356, 1337, 1257, 1208, 1158, 1123, 1107, 1033, 901, 856, 784, 735, 554; ^1H NMR (400 MHz, $CDCl_3$) δ 4.51 (s, 1 H, CH(CO$_2$Et)(COMe)), 4.28–4.22 (m, 2 H, CO$_2$CH_2CH$_3$), 3.54 (s, 2 H, CH$_2$Cl), 2.30 (s, 3 H, COCH$_3$), 1.333 (s, 3 H, CH$_3$), 1.326 (s, 3 H, CH$_3$), 1.32 (t, J = 7.1 Hz, 3 H, CO$_2$CH$_2$CH_3); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 203.4 (C=O ketone), 168.4 (C=O ester), 79.0 (CH(CO$_2$Et)(COMe)), 77.9 (OC_q(CH$_3$)$_2$), 61.9 (CO$_2$CH$_2$CH$_3$), 51.8 (CH$_2$Cl), 26.2 (COCH$_3$), 24.1 (CH$_3$), 23.4 (CH$_3$), 14.0 (CO$_2$CH$_2$CH$_3$); HRMS (ESI-TOF) m/z Calcd for $C_{10}H_{17}ClO_4Na^+$ [M+Na]$^+$: 259.0713, Found: 259.0707.

Ethyl 3,6,6-trimethyl-5,6-dihydro-1,4-dioxine-2-carboxylate (6j) and (±)-ethyl 2-acetyl-4,4-dimethyloxetane-2-carboxylate (7) Prepared according to a scaled down **General Procedure B**

employing chloride **5j** (71 mg, 0.3 mmol). Purification by flash chromatography (10% to 20% Et$_2$O in pentane) afforded dioxene **6j** as a colorless oil which solidified upon storage at –25 °C (20 mg, 34%) followed by oxetane **7** as a pale yellow oil (12 mg, 20%). *Dioxene 6j*: R$_f$ = 0.31 (20% Et$_2$O in pentane); mp = 18–20 °C; IR (film) / cm^{-1} 2981, 2934, 2880, 1709 (C=O), 1634 (C=C), 1461, 1382, 1367, 1311, 1286, 1273, 1238, 1156, 1078, 1027, 985, 940, 923, 897, 865, 835, 770, 721, 598; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.25 (q, *J* = 7.1 Hz, 2 H, CO$_2$C*H$_2$*CH$_3$), 3.74 (s, 2 H, OCH$_2$), 2.23 (s, 3 H, CH$_3$), 1.32 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H$_3$*), 1.28 (s, 6 H, OC(C*H$_3$*)$_2$); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 164.5 (CO$_2$), 145.0 ((Me)*C$_q$*=C), 123.4 ((EtO$_2$C)*C$_q$*=C), 72.4 (OCH$_2$), 70.2 (O*C$_q$*(CH$_3$)$_2$), 60.5 (CO$_2$CH$_2$CH$_3$), 22.7 (C$_q$(*CH$_3$*)$_2$), 17.5 (CH$_3$), 14.4 (CO$_2$CH$_2$*CH$_3$*); HRMS (FTMS +pAPCI) *m/z* Calcd for C$_{10}$H$_{17}$O$_4{}^+$ [M+H]$^+$: 201.1121, Found: 201.1123. *Oxetane 7*: R$_f$ = 0.20 (20% Et$_2$O in pentane); IR (film) / cm^{-1} 2973, 2933, 2875, 1745 (C=O), 1727 (C=O), 1448, 1372, 1355, 1283, 1215, 1158, 1123, 1060, 1015, 971, 843, 771, 744, 580; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.31–4.24 (m, 2 H, CO$_2$C*H$_2$*CH$_3$), 2.82 (d, *J* = 11.8 Hz, 1 H, C*H*H), 2.74 (d, *J* = 11.8 Hz, 1 H, CH*H*), 2.29 (s, 3 H, COCH$_3$), 1.51 (s, 3 H, CH$_3$), 1.39 (s, 3 H, CH$_3$), 1.30 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H$_3$*); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 204.8 (C=O ketone), 169.9 (C=O ester), 82.0 (*C$_q$*(CO$_2$Et)(COMe)), 81.6 (O*C$_q$*(CH$_3$)$_2$), 62.1 (CO$_2$CH$_2$CH$_3$), 39.5 (CH$_2$Cl), 29.3 (CH$_3$), 29.0 (CH$_3$), 24.5 (CO*CH$_3$*), 14.0 (CO$_2$CH$_2$*CH$_3$*); HRMS (ESI-TOF) *m/z* Calcd for C$_{10}$H$_{17}$O$_4{}^+$ [M+H]$^+$: 201.1127, Found: 201.1136.

Synthesis of Diazo Compound **8a**

Ethyl 2-diazo-4-methyl-3-oxopentanoate (8a) Cesium carbonate (1.63 g, 5 mmol) was added portionwise to a stirring solution of tosyl azide (986 mg, 5 mmol) and ethyl isobutyrylacetate (0.81 mL, 5 mmol) in THF (50 mL) at 25 °C. The resulting mixture was stirred at 25 °C for 3 h. The reaction mixture was filtered through celite, and the precipitate washed with Et$_2$O (100 mL). The filtrate was concentrated *in vacuo*. Pentane (100 mL) was added to the residue to precipitate out the sulphonamide by-product. The mixture was filtered through celite and the filtrate concentrated *in vacuo*. Purification by flash chromatography (30% to 50% to 70% CH$_2$Cl$_2$ in pentane) afforded diazo **8a** as a yellow liquid

(801 mg, 87%); R_f = 0.26 (50% CH$_2$Cl$_2$ in pentane); IR (film) / cm^{-1} 2979, 2938, 2875, 2131 (C=N=N out-of-phase), 1713 (C=O), 1655, 1467, 1383, 1372 (C=N=N in-phase),1355, 1292, 1207, 1173, 1128, 1101, 1017, 987, 873, 829, 753, 724, 672, 536; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.29 (q, J = 7.1 Hz, 2 H, CO$_2$C*H*$_2$CH$_3$), 3.57 (sep, J = 6.8 Hz, 1 H, COC*H*(CH$_3$)$_2$), 1.33 (t, J = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H*$_3$), 1.12 (d, J = 6.8 Hz, 6 H, 2 × CH$_3$); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 197.1 (C=O ketone), 161.2 (C=O ester), 61.3 (CO$_2$*C*H$_2$CH$_3$), 36.8 (CO*C*H(CH$_3$)$_2$), 18.5 (2 × CH$_3$), 14.3 (CO$_2$CH$_2$*C*H$_3$); HRMS (ESI-TOF) *m/z* Calcd for C$_8$H$_{13}$N$_2$O$_3$$^+$ [M+H]$^+$: 185.0926, Found: 185.0927.

Synthesis of dioxenes **10a-e**

(±)-Ethyl 2-(2-bromoethoxy)-4-methyl-3-oxopentanoate (9a) Prepared according to **General Procedure A** employing diazo **8a** (221 mg, 1.2 mmol) and 2-bromoethanol (124 mg, 1.0 mmol). Purification by flash chromatography (15% Et$_2$O in pentane) afforded bromide **9a** as a pale yellow oil (234 mg, 84%); R_f = 0.19 (15% Et$_2$O in pentane); IR (film) / cm^{-1} 2975, 2937, 2876, 1747 (C=O), 1721 (C=O), 1467, 1385, 1369, 1334, 1259, 1204, 1180, 1139, 1022, 859, 806, 738, 679, 582; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.57 (s, 1 H, C*H*(CO$_2$Et)(COMe)), 4.32–4.21 (m, 2 H, CO$_2$C*H*$_2$CH$_3$), 4.04 (dt, J = 10.6, 5.5 Hz, 1 H, OC*H*H), 3.78 (dt, J = 10.6, 6.4 Hz, 1 H, OCH*H*), 3.58–3.51 (m, 2 H, CH$_2$Br), 3.15 (sep, J = 6.9 Hz, 1 H, COC*H*(CH$_3$)$_2$), 1.30 (t, J = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H*$_3$), 1.14 (d, J = 6.9 Hz, 3 H, CH$_3$), 1.11 (d, J = 6.9 Hz, 3 H, CH$_3$); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 206.9 (C=O ketone), 167.1 (C=O ester), 84.1 (*C*H(CO$_2$Et)(COMe)), 70.9 (OCH$_2$), 61.9 (CO$_2$*C*H$_2$CH$_3$), 37.2 (CO*C*H(CH$_3$)$_2$), 29.6 (CH$_2$Br), 17.99 (CH$_3$), 17.96 (CH$_3$), 14.1 (CO$_2$CH$_2$*C*H$_3$); HRMS (ESI-TOF) *m/z* Calcd for C$_{12}$H$_{20}$BrNO$_4$Na$^+$ [M+CH$_3$CN+Na]$^+$: 344.0473, Found: 344.0463.

Ethyl 3-(propan-2-yl)-5,6-dihydro-1,4-dioxine-2-carboxylate (10a) Prepared according to a scaled down **General Procedure B** employing bromide **9a** (112 mg, 0.4 mmol). Purification by flash chromatography (25% Et$_2$O in pentane) afforded dioxene **10a** a colorless oil (71 mg, 89%); R_f = 0.31 (25% Et$_2$O in pentane); IR (film) / cm^{-1} 2972, 2936, 2874, 1708 (C=O), 1619 (C=C), 1459, 1370, 1337, 1303, 1276, 1260, 1236, 1174, 1133, 1101, 1086, 1028, 974, 901, 863, 811, 770; ^{1}H NMR (400 MHz,

CDCl$_3$) δ 4.26 (q, J = 7.1 Hz, 2 H, CO$_2$CH_2CH$_3$), 4.16–4.12 (m, 2 H, OCH_2CH$_2$O), 4.08–4.03 (m, 2 H, OCH$_2$CH_2O), 3.74 (sep, J = 6.9 Hz, 1 H, CH(CH$_3$)$_2$), 1.33 (t, J = 7.1 Hz, 3 H, CO$_2$CH$_2$CH_3), 1.09 (d, J = 6.9 Hz, 6 H, 2 × CH$_3$); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 163.8 (CO$_2$), 155.1 ((Me)C_q=C), 123.9 ((EtO$_2$C)C_q=C), 65.0 (OCH$_2$CH$_2$O), 63.2 (OCH$_2$$CH_2$O), 60.5 (CO$_2$$CH_2CH_3$), 28.4 ($C$H(CH$_3$)$_2$), 19.8 (2 × CH$_3$), 14.3 (CO$_2CH_2$$CH_3$); HRMS (ESI-TOF) m/z Calcd for C$_{10}$H$_{17}$O$_4^+$ [M+H]$^+$: 201.1127, Found: 201.1133.

(±)-Ethyl 2-(2-bromoethoxy)-3-oxo-3-phenylpropanoate (9b) Prepared according to **General Procedure A** employing diazo **8b** (262 mg, 1.2 mmol) and 2-bromoethanol (125 mg, 1.0 mmol). Purification by flash chromatography (15% to 20% Et$_2$O in pentane) afforded bromide **9b** as a pale yellow oil (268 mg, 85%); R$_f$ = 0.32 (20% Et$_2$O in pentane); IR (film) / cm^{-1} 2986, 1752 (C=O), 1690 (C=O), 1598, 1449, 1373, 1342, 1280, 1200, 1132, 1017, 774, 691, 600, 579; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.11–8.06 (m, 2 H, 2 × Ph-H), 7.65–7.58 (m, 1 H, Ph-H), 7.52–7.46 (m, 2 H, 2 × Ph-H), 5.13 (s, 1 H, CH(CO$_2$Et)(COPh)), 4.25 (q, J = 7.1 Hz, 2 H, CO$_2$CH_2CH$_3$), 4.07 (dt, J = 10.5, 6.1 Hz, 1 H, OCHH), 3.93 (dt, J = 10.5, 6.5 Hz, 1 H, OCHH), 3.55–3.49 (m, 2 H, CH$_2$Br), 1.22 (t, J = 7.1 Hz, 3 H, CO$_2$CH$_2$CH_3); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 191.9 (C=O ketone), 167.4 (C=O ester), 134.1 (Ph-CH), 129.5 (2 × Ph-CH), 128.7 (2 × Ph-CH), 128.2 (Ph-C$_q$), 83.5 (CH(CO$_2$Et)(COPh)), 70.9 (OCH$_2$), 62.1 (CO$_2$$CH_2CH_3$), 29.3 ($CH_2$Br), 14.0 (CO$_2CH_2$$CH_3$); HRMS (ESI-TOF) m/z Calcd for C$_{15}$H$_{18}$BrNO$_4$Na$^+$ [M+CH$_3$CN+Na]$^+$: 378.0317, Found: 378.0315.

Ethyl 3-phenyl-5,6-dihydro-1,4-dioxine-2-carboxylate (10b) Prepared according to a scaled down **General Procedure B** employing bromide **9b** (126 mg, 0.4 mmol). Purification by flash chromatography (40% Et$_2$O in pentane) afforded dioxene **10b** a white crystalline solid (75 mg, 80%); R$_f$ = 0.25 (40% Et$_2$O in pentane); mp = 62–65 °C; IR (film) / cm^{-1} 2982, 2933, 2877, 1710 (C=O), 1627 (C=C), 1600,1578, 1493, 1446, 1373, 1318, 1294, 1269, 1236, 1170, 1128, 1110, 1076, 1030, 976, 917, 883, 865, 809, 760, 698, 683, 575; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.44–7.31 (m, 5 H, 5 × Ph-H),

4.35–4.30 (m, 2 H, OCH_2CH$_2$O), 4.28–4.23 (m, 2 H, OCH$_2$CH_2O), 4.07 (q, *J* = 7.1 Hz, 2 H, CO$_2$CH_2CH$_3$), 1.03 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$CH_3); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 163.5 (CO$_2$), 147.4 ((Ph)C_q=C), 134.4 (Ph-C$_q$), 129.1 (3 × Ph-CH), 127.7 (2 × Ph-CH), 126.4 ((EtO$_2$C)C_q=C), 65.6 (OCH$_2$CH$_2$O), 63.8 (OCH$_2$$CH_2$O), 60.6 (CO$_2$$CH_2CH_3$), 13.7 (CO$_2CH_2$$CH_3$); HRMS (ESI-TOF) *m/z* Calcd for C$_{13}$H$_{15}$O$_4$$^+$ [M+H]$^+$: 235.0970, Found: 235.0975.

(±)-1-(Benzenesulfonyl)-1-(2-bromoethoxy)propan-2-one (9c)

Procedure using [Rh$_2$(OAc)$_4$]: A mixture of diazo **8c** (123 mg, 0.55 mmol), 2-bromoethanol (63 mg, 0.5 mmol) and dirhodium(II)tetraacetate (1.1 mg, 0.0025 mmol) in benzene (5 mL) was heated at 80 °C for 90 min. The reaction mixture was allowed to cool to rt. Water (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The organic extracts were combined, dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by flash chromatography (50% Et$_2$O in pentane) afforded bromide **9c** as a pale yellow oil (135 mg, 84%).

Procedure using [CpRu(MeCN)$_3$][PF$_6$]: Prepared according to **General Procedure A** employing diazo **8c** (270 mg, 1.2 mmol) and 2-bromoethanol (125 mg, 1.0 mmol). Purification by flash chromatography (40% Et$_2$O in pentane) afforded bromide **9c** as a pale yellow oil (105 mg, 33%); R$_f$ = 0.13 (40% Et$_2$O in pentane); IR (film) / cm^{-1} 3064, 2968, 2923, 1721 (C=O), 1584, 1448, 1418, 1357, 1321, 1309, 1191, 1147, 1115, 1077, 1009, 999, 816, 751, 721, 685, 615, 602, 566; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.90–7.85 (m, 2 H, 2 × Ph-H), 7.74–7.68 (m, 1 H, Ph-H), 7.62–7.55 (m, 2 H, 2 × Ph-H), 4.88 (s, 1 H, CH(SO$_2$Ph)(COMe)), 4.46 (dt, *J* = 11.3, 4.9 Hz, 1 H, OCHH), 4.03–3.95 (m, 1 H, OCHH), 3.56–3.46 (m, 2 H, CH$_2$Br), 2.19 (s, 3 H, COCH$_3$); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 298.9 (C=O), 135.7 (Ph-C$_q$), 134.7 (Ph-CH), 129.6 (2 × Ph-CH), 129.2 (2 × Ph-CH), 99.1 (CH(SO$_2$Ph)(COMe)), 73.9 (OCH$_2$), 29.8 (CH$_2$Br), 27.7 (COCH$_3$); HRMS (CI) *m/z* Calcd for C$_{11}$H$_{17}$BrNO$_4$S$^+$ [M+NH$_4$]$^+$: 338.0062, Found: 338.0068.

5-(Benzenesulfonyl)-6-methyl-2,3-dihydro-1,4-dioxine (10c) Prepared according to **General Procedure B** employing bromide **9c** (101 mg, 0.3 mmol). Purification by flash chromatography (50% Et$_2$O in pentane) afforded dioxene **10c** as an off-white crystalline solid (59 mg, 79%); R$_f$ = 0.28 (50% Et$_2$O in pentane); mp = 61–63 °C; IR (film) / cm^{-1} 3064, 2988, 2932, 2884, 1637 (C=C), 1585, 1447, 1386, 1362, 1319, 1308, 1275, 1255, 1232, 1184, 1140, 1120, 1080, 1028, 930, 906, 876, 758, 723, 688, 623, 600, 555; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.93–7.88 (m, 2 H, 2 × Ph-H), 7.63–7.58 (m, 1 H, Ph-H), 7.55–7.49 (m, 2 H, 2 × Ph-H), 4.14–4.09 (m, 2 H, OC*H$_2$*CH$_2$O), 3.97–3.92 (m, 2 H, OCH$_2$C*H$_2$*O), 2.29 (s, 3 H, CH$_3$); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 144.5 ((Me)*C$_q$*=C), 140.7 (Ph-*C$_q$*), 133.1 (Ph-CH), 132.2 ((PhO$_2$S)*C$_q$*=C), 128.9 (2 × Ph-H), 127.3 (2 × Ph-H), 65.2 (O*C*H$_2$CH$_2$O), 64.2 (OCH$_2$*C*H$_2$O), 16.5 (CH$_3$); HRMS (CI) *m/z* Calcd for C$_{11}$H$_{16}$NO$_4$S$^+$ [M+NH$_4$]$^+$: 258.0800, Found: 258.0800.

(±)-Diethyl [1-(2-bromoethoxy)-2-oxopropyl]phosphonate (9d) Prepared according to **General Procedure A** employing diazo **8d** (264 mg, 1.2 mmol) and 2-bromoethanol (125 mg, 1.0 mmol). Purification by flash chromatography (60% to 70% EtOAc in pentane) afforded bromide **9d** as a pale yellow oil (193 mg, 61%); R$_f$ = 0.15 (60% EtOAc in pentane); IR (film) / cm^{-1} 2984, 2932, 1719 (C=O), 1444, 1423, 1393, 1357, 1252, 1164, 1115, 1018, 972, 799, 675, 579, 568, 543; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.31 (d, J_{P-H} = 19.0 Hz, 1 H, C*H*(PO(OEt)$_2$)(COMe)), 4.28–4.16 (m, 4 H, 2 × OC*H$_2$*CH$_3$), 4.02–3.89 (m, 2 H, OCH$_2$), 3.53 (t, J = 5.9 Hz, 2 H, CH$_2$Br), 2.36 (s, 3 H, COCH$_3$), 1.39–1.32 (m, 6 H, 2 × OCH$_2$C*H$_3$*); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 203.3 (C=O), 84.2 (d, J_{C-P} = 150.1 Hz, *C*H(PO(OEt)$_2$)(COMe)), 72.6 (d, J_{C-P} = 9.4 Hz, OCH$_2$), 63.8 (d, J_{C-P} = 6.8 Hz, O*C*H$_2$CH$_3$), 63.7 (d, J_{C-P} = 6.8 Hz, O*C*H$_2$CH$_3$), 29.8 (CH$_2$Br), 27.5 (CO*C*H$_3$), 16.39 (d, J_{C-P} = 6.1 Hz, OCH$_2$*C*H$_3$), 16.35 (d, J_{C-P} = 6.1 Hz, OCH$_2$*C*H$_3$); ^{31}P{^{1}H} NMR (162 MHz, CDCl$_3$) δ 13.7; HRMS (ESI-TOF) *m/z* Calcd for C$_9$H$_{19}$BrO$_5$P$^+$ [M+H]$^+$: 317.0153, Found: 317.0161.

Diethyl (3-methyl-5,6-dihydro-1,4-dioxin-2-yl)phosphonate (10d) Prepared according to a scaled down **General Procedure B** employing bromide **9d** (127 mg, 0.4 mmol) and 2-bromoethanol. Purification by flash chromatography (60% EtOAc in pentane) afforded dioxene **10d** as pale yellow oil (85 mg, 90%); R_f = 0.25 (60% EtOAc in pentane); IR (film) / cm^{-1} 2983, 2931, 1638 (C=C), 1444, 1387, 1367, 1268, 1231, 1175, 1116, 1099, 1018, 961, 908, 877, 792, 754, 668, 612, 591, 532; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.18–4.03 (m, 6 H, OCH_2CH$_2$O and 2 × OCH_2CH$_3$), 4.01–3.97 (m, 2 H, OCH$_2$CH_2O), 2.13 (d, $J_{\text{P-H}}$ = 2.5 Hz, 3 H, CH$_3$), 1.332 (t, J = 7.1 Hz, 3 H, OCH$_2$CH_3), 1.331 (t, J = 7.1 Hz, 3 H, OCH$_2$CH_3); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 147.9 (d, $J_{\text{C-P}}$ = 39.2 Hz, (Me)C_q=C), 122.3 (d, $J_{\text{C-P}}$ = 243.2 Hz, ((EtO)$_2$OP)C_q=C), 65.1 (OCH$_2$CH$_2$O), 63.4 (d, $J_{\text{C-P}}$ = 7.0 Hz, 2 × OCH$_2$CH$_3$), 62.1 (d, $J_{\text{C-P}}$ = 5.2 Hz, OCH$_2$$CH_2$O), 16.5 (CH$_3$), 16.2 (d, $J_{\text{C-P}}$ = 6.5 Hz, 2 × OCH$_2$$CH_3$); ^{31}P{^{1}H} NMR (162 MHz, CDCl$_3$) δ 12.5; HRMS (ESI-TOF) m/z Calcd for C$_9$H$_{18}$O$_5$P$^+$ [M+H]$^+$: 237.0892, Found: 237.0896.

(±)-2-(2-Bromoethoxy)cyclohexane-1,3-dione (9e) and **2,3,5,6,7,8-hexahydro-1,4-benzodioxin-5-one (10e)** Prepared according to **General Procedure A** employing diazo **8e** (166 mg, 1.2 mmol) and 2-bromoethanol (125 mg, 1.0 mmol). Purification by flash chromatography (5% to 10% to 20% EtOAc in CH$_2$Cl$_2$) afforded bromide **9e** as a pale yellow oil (2 mg, 1%) followed by dioxene **10e** as a yellow oil (32 mg, 21%). *Bromide 9e:* R_f = 0.55 (20% EtOAc in CH$_2$Cl$_2$); IR (film) / cm^{-1} 2949, 1652 (C=O), 1606 (C=O), 1455, 1426, 1397, 1367, 1329, 1216, 1184, 1137, 1003, 962, 866, 828, 566; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.34 (s, 1 H, CH(CO)$_2$), 4.19–4.14 (m, 2 H, OCH$_2$), 3.63–3.57 (m, 2 H, CH$_2$(CO)), 2.49–2.44 (m, 2 H, CH$_2$(CO)), 2.40–2.34 (m, 2 H, CH$_2$Br), 2.01 (quin, J = 6.5 Hz, 2 H, CH$_2$); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 199.5 (C=O), 176.9 (C=O), 103.1 (CH(CO)$_2$), 67.8 (OCH$_2$), 36.7 (CH$_2$Br), 28.7 (CH$_2$(CO)), 27.9 (CH$_2$(CO)), 21.1 (CH$_2$); HRMS (CI) m/z Calcd for C$_8$H$_{12}$BrO$_3$$^+$ [M+H]$^+$: 234.9970, Found: 234.9976. *Dioxene 10e:* R_f = 0.39 (20% EtOAc in CH$_2$Cl$_2$); IR (film) / cm^{-1} 2945, 2879, 1667 (C=O), 1622 (C=C), 1459, 1434, 1391, 1341, 1276, 1230, 1194, 1148, 1095, 1038,

1000, 919, 865, 703, 627, 550, 524; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.24–4.18 (m, 2 H, OCH_2CH$_2$O), 4.17–4.11 (m, 2 H, OCH$_2$CH_2O), 2.51–2.46 (m, 2 H, CH$_2$(C=C)), 2.46–2.40 (m, 2 H, CH$_2$(CO)), 1.96 (quin, J = 6.3 Hz, 2 H, CH$_2$); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 191.9 (C=O), 154.6 ((H$_2$C)C_q=C), 132.4 ((OC)C_q=C), 65.8 (OCH_2CH$_2$O), 63.5 (OCH$_2$$CH_2$O), 36.7 ($CH_2$(CO)), 27.5 ($CH_2$(C=C)), 20.3 (CH$_2$); HRMS (ESI-TOF) m/z Calcd for C$_8$H$_{11}$O$_3^+$ [M+H]$^+$: 155.0708, Found: 155.0703.

Synthesis of Compounds 11-15

(±)-7-Acetyl-1-azabicyclo[4.2.0]octan-8-one (11) A mixture of diazo amide **8f** (213 mg, 1.1 mmol), 2-bromoethanol (124 mg, 1.0 mmol) and dirhodium(II) tetraacetate (2.3 mg, 0.005 mmol) in benzene (10 mL) was heated at 80 °C for 2 h. The reaction mixture was allowed to cool to rt, then concentrated *in vacuo*. Purification by flash chromatography (30% to 40% to 50% EtOAc in pentane) afforded β-lactam **11** as a colorless oil as a single diastereoisomer (73 mg, 40%); R$_f$ = 0.11 (30% EtOAc in pentane); IR (film) / cm^{-1} 2915, 2849, 1710 (C=O ketone), 1635 (C=O β-lactam), 1577, 1480, 1448, 1360, 1271, 1230, 1210, 1177, 1124, 1082, 827, 704, 624, 512; ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.84 (d, J = 1.7 Hz, 1 H, CH(COMe)(CON)), 3.81 (dd, J = 14.4, 4.7 Hz, 1 H, NCHH), 3.75 (ddd, J = 10.9, 4.5, 1.7 Hz, 1 H, NCH), 2.80–2.70 (m, 1 H, NCHH), 2.30 (s, 3 H, COCH_3), 2.12–2.02 (m, 1 H, CHH), 1.94–1.86 (m, 1 H, C'HH), 1.71–1.63 (m, 1 H, C''HH), 1.49–1.34 (m, 2 H, C'HH and C''HH), 1.32–1.20 (m, 1 H, CHH); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 200.7 (C=O ketone), 161.5 (C=O β-lactam), 70.7 (CH(CON)(COMe)), 49.1 (NCH), 39.2 (NCH$_2$), 29.6 (COCH$_3$), 29.5 (CH$_2$), 24.3 (C''H$_2$), 21.9 (C'H$_2$); HRMS (ESI-TOF) m/z Calcd for C$_9$H$_{14}$NO$_2^+$ [M+H]$^+$: 168.1025, Found: 168.1017.

(±)-1-[6-(3,4-Dichlorophenyl)-3-methyl-5,6-dihydro-1,4-dioxine-2-carbonyl]pyrrolidine (13) A microwave vial (0.5–2.0 mL volume) was charged with dioxene **6c** (63 mg, 0.20 mmol). The reaction vial was flushed with argon, sealed with a cap and then further flushed with argon. Ethanol (1.0 mL) was added followed by 1 N aq. NaOH (0.11 mL, 0.22 mmol). The reaction mixture was

stirred in an oil bath at 110 °C for 1 h. The reaction mixture was diluted with EtOAc (10 mL) and concentrated *in vacuo* to afford (±)-6-(3,4-dichlorophenyl)-3-methyl-5,6-dihydro-1,4-dioxine-2-carboxylate sodium salt **12** as a white solid which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (dd, J = 2.0 Hz, 1 H, Ar-H), 7.64 (dd, J = 8.3 Hz, 1 H, Ar-H), 7.41 (dd, J = 8.3, 2.0 Hz, 1 H, Ar-H), 4.85 (dd, J = 6.8, 2.1 Hz, 1 H, OCH(Ar)), 4.11 (dd, J = 10.9, 2.1 Hz, 1 H, OC*H*H), 3.78 (dd, J = 10.9, 6.8 Hz, 1 H, OCH*H*), 2.15 (s, 3 H, CH$_3$). HATU (91 mg, 0.24 mmol) was added to a flask containing (±)-6-(3,4-dichlorophenyl)-3-methyl-5,6-dihydro-1,4-dioxine-2-carboxylate sodium salt **12** (0.20 mmol) in DMF (2 mL). The reaction mixture was stirred at 40 °C for 10 min. Pyrrolidine (20 µL, 0.24 mmol) was added and the reaction mixture was stirred at 40 °C for a further 20 min. *N,N*-Diisopropylethylamine (0.11 mL, 0.63 mmol) was then added dropwise and the reaction mixture was stirred at 40 °C for 20 h. Saturated aq. NH$_4$Cl (10 mL) was added. The aqueous mixture was extracted with CH$_2$Cl$_2$ (4 × 10 mL). The organic extracts were combined, dried (Na$_2$SO$_4$) and concentrated *in vacuo*. Purification by flash chromatography (30% EtOAc in pentane) afforded dioxene **13** as an off-white crystalline solid (63 mg, 92% over 2 steps); R$_f$ = 0.10 (30% EtOAc in pentane); mp = 118–120 °C; IR (film) / cm^{-1} 2972, 2953, 2924, 2877, 1664 (C=O), 1611 (C=C), 1469, 1431, 1343, 1307, 1242, 1211, 1183, 1164, 1126, 1082, 1049, 1031, 943, 927, 826, 771, 682, 665, 589; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.45 (d, J = 8.3 Hz, 1 H, Ar-H), 7.43 (d, J = 2.0 Hz, 1 H, Ar-H), 7.18 (dd, J = 8.3, 2.0 Hz, 1 H, Ar-H), 4.75 (dd, J = 8.6, 2.3 Hz, 1 H, OCH(Ar)), 4.20 (dd, J = 11.2, 2.3 Hz, 1 H, OC*H*H), 3.81 (dd, J = 11.2, 8.6 Hz, 1 H, OCH*H*), 3.57–3.47 (m, 3 H, NCH$_2$ and NC*H*H), 3.46–3.38 (m, 1 H, NCH*H*), 2.04 (s, 3 H, CH$_3$),1.92–1.79 (m, 4 H, 2 × NCH$_2$C*H$_2$*); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 163.5 (C=O), 139.0 ((Me)C_q=C), 136.6 (Ar-C_q-CH(O)), 132.9 (Ar-C$_q$-Cl), 132.7 (Ar-C$_q$-Cl), 130.7 (Ar-CH), 128.5 ((NOC)C_q=C), 128.4 (Ar-CH), 125.6 (Ar-CH), 72.5 (OCH(Ar)), 69.3 (OCH$_2$), 47.8 (NCH$_2$), 46.2 (NCH$_2$), 26.2 (NCH$_2$*C*H$_2$), 24.0 (NCH$_2$*C*H$_2$), 16.0 (CH$_3$); HRMS (ESI-TOF) *m/z* calcd for C$_{16}$H$_{18}$Cl$_2$NO$_3$$^+$ [M+H]$^+$: 342.0664, Found: 342.0677.

(±)-6-(3,4-Dichlorophenyl)-3-methyl-N-(3-methylphenyl)-5,6-dihydro-1,4-dioxine-2-carboxamide (14) A microwave vial (0.5–2.0 mL volume) was charged with dioxene **6c** (64 mg, 0.20 mmol). The reaction vial was flushed with argon, sealed with a cap and then further flushed with argon. Ethanol (1.0 mL) was added followed by 1 N aq. NaOH (0.11 mL, 0.22 mmol). The reaction mixture was stirred in an oil bath at 110 °C for 1 h. The reaction mixture was diluted with EtOAc (10 mL) and concentrated *in vacuo* to afford (±)-6-(3,4-dichlorophenyl)-3-methyl-5,6-dihydro-1,4-dioxine-2-carboxylate sodium salt **12** as a white solid which was used without further purification. HATU (91 mg, 0.24 mmol) was added to a flask containing (±)-6-(3,4-dichlorophenyl)-3-methyl-5,6-dihydro-1,4-dioxine-2-carboxylate sodium salt **12** (0.20 mmol) in DMF (2 mL). The reaction mixture was stirred at 40 °C for 10 min. 3-Toluidine (26 µL, 0.24 mmol) was added and the reaction mixture was stirred at 40 °C for a further 20 min. *N,N*-Diisopropylethylamine (0.11 mL, 0.63 mmol) was then added dropwise and the reaction mixture was stirred at 40 °C for 20 h. Saturated aq. NH$_4$Cl (10 mL) was added. The aqueous mixture was extracted with CH$_2$Cl$_2$ (4 × 10 mL). The organic extracts were combined, dried (Na$_2$SO$_4$) and concentrated *in vacuo*. Purification by flash chromatography (8% Et$_2$O in CH$_2$Cl$_2$) afforded dioxene **14** as a viscous yellow oil (71 mg, 93% over 2 steps); R$_f$ = 0.84 (8% Et$_2$O in CH$_2$Cl$_2$); IR (film) / cm^{-1} 3413 (N-H), 2925, 2875, 1683 (C=O), 1635 (C=C), 1611, 1532, 1489, 1452, 1407, 1298, 1241, 1153, 1131, 1103, 1048, 1032, 905, 822, 778, 725, 690, 647, 596; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.16 (br s, 1 H, NH), 7.51 (d, J = 8.3 Hz, 1 H, Ar-H), 7.48 (d, J = 2.0 Hz, 1 H, Ar-H), 7.46–7.42 (m, 1 H, Ar-H), 7.36–7.30 (m, 1 H, Ar-H), 7.23 (dd, J = 8.3, 2.0 Hz, 1 H, Ar-H), 7.21–7.16 (m, 1 H, Ar-H), 6.95–6.88 (m, 1 H, Ar-H), 4.82 (dd, J = 8.5, 2.3 Hz, 1 H, OCH(Ar)), 4.25 (dd, J = 11.3, 2.3 Hz, 1 H, OC*H*H), 3.88 (dd, J = 11.3, 8.5 Hz, 1 H, OCH*H*), 2.40 (s, 3 H, CH$_3$), 2.33 (s, 3 H, Ar-CH$_3$); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 160.9 (C=O), 144.8 ((Me)C_q=C), 138.7 (Ar-C$_q$-Me), 137.5 (Ar-C$_q$-NH), 136.1 (Ar-C_q-CH(O)), 133.1 (2 × Ar-C$_q$-Cl), 130.8 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 126.1 ((ArHNOC)C_q=C), 125.8 (Ar-CH), 124.8 (Ar-CH), 120.5 (Ar-CH), 117.0 (Ar-CH), 73.0

(OCH(Ar)), 69.3 (OCH$_2$), 21.4 (Ar-CH$_3$), 16.9 (CH$_3$); HRMS (ESI-TOF) *m/z* calcd for C$_{19}$H$_{18}$Cl$_2$NO$_3^+$ [M+H]$^+$: 378.0664, Found: 378.0673.

(±)-[6-(3,4-Dichlorophenyl)-3-methyl-5,6-dihydro-1,4-dioxin-2-yl]methanol **(15)**

Diisobutylaluminium hydride (1 M in THF, 0.7 mL, 0.70 mmol) was added dropwise to a stirring solution of dioxene **6c** (63 mg, 0.20 mmol) in toluene (3.5 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 40 min, then at 0 °C for 20 min. Saturated aq. Rochelle salt (8 mL) was added and the resulting aqueous mixture was vigourously stirred at rt for 20 min. The aqueous mixture was extracted with EtOAc (4 × 10 mL). The organic extracts were combined, dried (Na$_2$SO$_4$) and concentrated *in vacuo*. Purification by flash chromatography (20% EtOAc in pentane) afforded dioxene **15** as a viscous colorless oil (49 mg, 89%); R$_f$ = 0.18 (20% EtOAc in pentane); IR (film) / cm^{-1} 3422 (br O-H), 2925, 2871, 1699 (C=C), 1565, 1468, 1388, 1342, 1307, 1243, 1207, 1125, 1081, 1031, 996, 905, 821, 726, 678, 647, 590, 528; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.49–7.39 (m, 2 H, 2 × Ar-H), 7.18 (dd, *J* = 8.3, 1.9 Hz, 1 H, Ar-H), 4.84 (dd, *J* = 8.2, 2.2 Hz, 1 H, OCH(Ar)), 4.21 (s, 2 H, C*H$_2$*OH), 4.14 (dd, *J* = 11.2, 2.2 Hz, 1 H, OC*H*H), 3.75 (dd, *J* = 11.2, 8.2 Hz, 1 H, OCH*H*), 2.06 (br s, 1 H, OH), 1.88 (s, 3 H, CH$_3$); ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 137.3 (Ar-*C$_q$*-CH(O)), 132.8 ((HOH$_2$C)*C$_q$*=C), 132.4 ((Me)*C$_q$*=C), 131.9 (Ar-C$_q$-Cl), 131.0 (Ar-C$_q$-Cl), 130.5 (Ar-CH), 128.3 (Ar-CH), 125.6 (Ar-CH), 73.4 (OCH(Ar)), 69.0 (OCH$_2$), 60.0 (CH$_2$OH), 14.9 (CH$_3$); HRMS (ESI-TOF) *m/z* Calcd for C$_{12}$H$_{11}$Cl$_2$O$_2$ [M-OH]: 257.0136, Found: 257.0146.

SUPPORTING INFORMATION

Further detail on the optimization of the Ru-catalyzed O-H insertion, copies of ^{1}H and ^{13}C NMR spectra for novel compounds, and HPLC traces for enantioenriched compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) See supporting information for further details and discussion on the optimization of the O–H insertion reaction.

(22) The reaction scope was performed using the bromohydrin substrates due to ease of preparation.

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