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Palladium-catalyzed, asymmetric Baeyer–Villiger oxidation of prochiral cyclobutanones with PHOX ligands

Kimberly S. Petersen, Brian M. Stoltz *

Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125, United States

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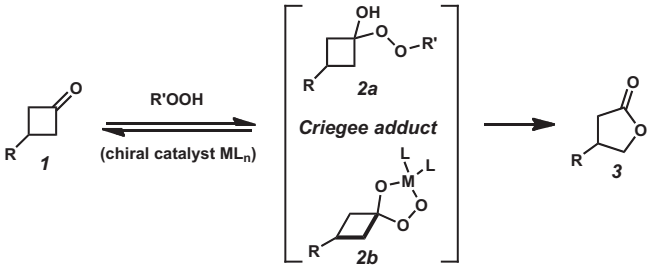
ABSTRACT

Described in this report is a general method for the conversion of prochiral 3-substituted cyclobutanones to enantioenriched γ-lactones through a palladium-catalyzed Baeyer–Villiger oxidation using phosphinooxazoline ligands in up to 99% yield and 81% ee. Lactones of enantiopurity ≥93% could be obtained through a single recrystallization step. Importantly, 3,3-disubtituted cyclobutanones produced enantioenriched lactones containing a β-quaternary center.

1. Introduction

Catalytic asymmetric oxidation chemistry has had a profound effect on modern organic synthesis. In particular, asymmetric epoxidations (e.g., Sharpless, Jacobsen and Shi)[1] and dihydroxylations (e.g., Sharpless)[2] are powerful tools that deliver enantioenriched products from prochiral starting materials with high levels of enantioselectivity. Our laboratory has been interested in asymmetric oxidation for some time and has developed a series of palladium-catalyzed asymmetric oxidation reactions.[3] Despite much progress in the field over the past 30 years there are still many oxidation methods for which no satisfactory catalytic asymmetric version exists.

A century after its discovery, the Baeyer–Villiger oxidation remains one of the most powerful methods to convert a ketone into an ester proceeding by insertion of an oxygen atom into a C–C bond (Scheme 1).[4] While much recent work has been devoted to developing catalytic asymmetric variants of this reaction, the results, except for a few examples, have been modest with respect to enantioselectivity.[5] By contrast, bio-catalyzed Baeyer–Villiger oxidations have been shown to proceed with high levels of enantioselectivity (>95% ee).[6] The Baeyer–Villiger reaction is believed to proceed by a two-step process whereby the hydrogen peroxide or peracid initially adds to the carbonyl group to give a tetrahedral intermediate, the Criegee adduct **2**. This intermediate then undergoes a rearrangement in which an alkyl substituent at the carbonyl carbon migrates to a peroxide oxygen atom resulting in an ester or lactone. The reaction is highly regioselective and stereospecific in that the more substituted alkyl substituent migrates and there is retention of stereochemistry of the migrating group. It is generally accepted that the reaction proceeds most smoothly when the migrating carbon atom of Criegee adduct **2** is antiperiplanar to both the O–O bond of the leaving group and the lone pair of electrons of the hydroxy group. Thus it can be assumed that interaction of the intermediate Criegee adduct **2** with a chiral catalyst is necessary for asymmetric induction in the reaction (see **2b**).



Scheme 1. Baeyer–Villiger oxidation.

The first examples of catalytic, asymmetric Baeyer–Villiger oxidations were reported independently by Bolm and Strukul in 1994.[7] Strukul and co-workers used a chiral platinum(II) complex in the presence of hydrogen peroxide to selectively oxidize racemic cyclic

* Corresponding author. E-mail address: stoltz@caltech.edu (B.M. Stoltz).

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ketones (up to 58% ee).[7b] Bolm and co-workers found that 2-substituted cycloalkanones could be selectively oxidized in the presence of a sacrificial aldehyde and a catalytic Cu/oxazoline complex with molecular oxygen (up to 69% ee).[7a] The first catalytic, asymmetric Baeyer–Villiger oxidations of symmetric 3-substituted cyclobutanones (e.g., **1**) to enantioenriched γ-lactones (e.g., **3**) proceeded in only modest selectivities (≤65% ee).[8] More recently, work by Katsuki[9] and then Malkov and Kočovský[10] has been toward the development of a Baeyer–Villiger oxidation of such cyclobutanones using a chiral cationic palladium(II) complex and hydrogen peroxide/urea adduct as the oxidant. Both procedures use phosphinopyridine ligands (**4**–**6**, Fig. 1) and proceed with yields up to 100% and enantioselectivies up to 81% ee. This oxidation is postulated to occur via a metal/Criegee adduct, such as **2b**. Finally, a variety of non-transition metal catalyzed Baeyer–Villiger oxidations have been developed. Murahashi and Imada used chiral bisflavins to catalyze the asymmetric Baeyer–Villiger oxidation of prochiral cyclobutanones, such as **1** to lactones, such as **3** with up to 74% ee.[11] More recently, Ding and collaborators performed the same transformation using chiral Brønsted acids arriving at γ-lactones, such as **3** with up to 93% ee.[12] Additionally, Miller and co-workers have shown in preliminary results that chiral carboxylic acids can be used to desymmetrize prochiral ketones with modest selectivities (30 and 42% ee).[13]

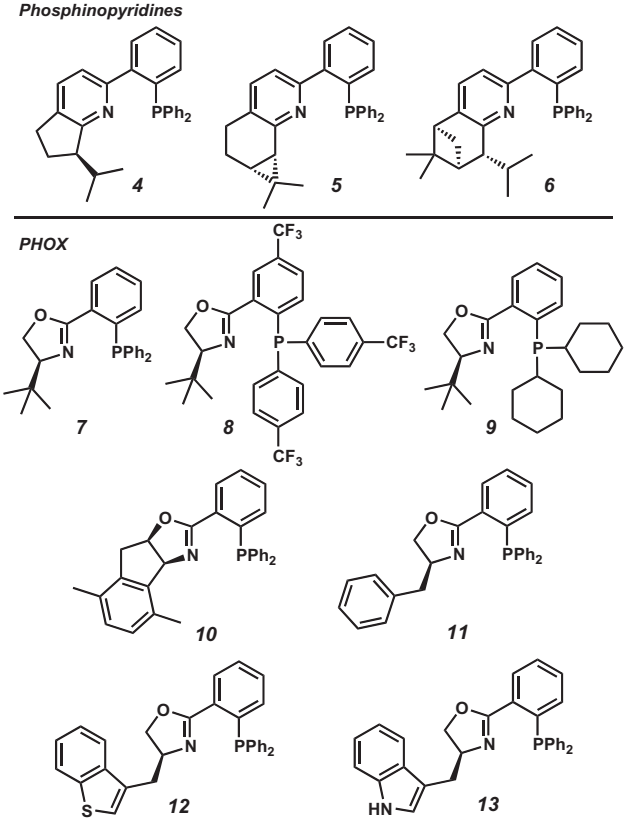


Fig. 1. *P,N*-ligands.

Our interest in the development of enantioselective oxidation processes along with our extensive experience with and collection of *P,N*-type phosphinooxazoline (PHOX) ligands (**7**–**13**, Fig. 1)[14] led us to examine the palladium-catalyzed Baeyer–Villiger oxidations of cyclic ketones. We have recently demonstrated the utility of PHOX ligands in palladium-catalyzed enantioselective decarboxylative alkylation[15] and protonation reactions.[16] Herein, we report the application of PHOX ligands in the palladium-catalyzed Baeyer–Villiger oxidation of *meso* cyclobutanones to produce enantioenriched γ-lactones in up to 99% yield and 81% ee. Several of these lactones (**3a** and **3b**) were recrystallized in ≥66% yield to give material with 93% ee. One of these lactones, (*R*)-(−)-3-(4′-chlorophenyl)-γ-butyrolactone (**3b**), can be further manipulated to produce the $GABA_B$ receptor agonist (*R*)-(−)-baclofen.

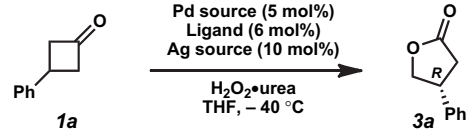
2. Results and discussions

Prochiral 3-substituted cyclobutanones **1a**–**f** were prepared through a [2+2] cycloaddition of dichloroketene to the appropriate alkene followed by dechlorination of the resulting 2,2-dichlorocyclobutanones with zinc (Scheme 2).[17]

Scheme 2. Preparation of *meso* cyclobutanones.

In order to optimize the reaction using PHOX ligands we first examined the Baeyer–Villiger oxidation of 3-phenylcyclobutanone (**1a**, Table 1). Little difference in reactivity and selectivity was observed by varying the palladium source (entries 1–5). Interestingly, we found that tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$, entry 4) was competent in the reaction suggesting that either a cationic Pd(II) species is responsible for the observed chemistry, or that hydroxide or peroxide is serving as a ligand on palladium during the course of the reaction, even when Cl^- is present in the catalyst precursor.[18] Based on these results we chose to focus on $Pd(CH_3CN)_2Cl_2$ as the palladium source simply because of convenience. Silver is necessary in the reaction as shown in entry 6, however silver trifluoromethanesulfonimide (entry 8) gave results similar to silver hexafluoroantimonate. With the optimized palladium and silver sources we next focused on a ligand screen. The electronics of the phosphorous made little difference in the reaction with both the electron poor ligand **8** and the electron rich ligand **9** yielding lactone **3a** in 76% and 64% ee, respectively (entries 12 and 14). However, the

Table 1
Screen of palladium source, silver source, and ligand[a]



Entry	Pd source	Ligand	Silver source	Yield[b,c] (%)	ee[d] (%)
1	$Pd(PhCN)_2Cl_2$	**7**	$AgSbF_6$	95[b]	78
2	$Pd(nbd)Cl_2$	**7**	$AgSbF_6$	98[b]	73
3	$Pd(CH_3CN)_2Cl_2$	**7**	$AgSbF_6$	100[b]	79
4	$Pd_2(dba)_3$	**7**	$AgSbF_6$	96[b]	78
5	$PdBr_2$	**7**	$AgSbF_6$	93[b]	77
6	$Pd(CH_3CN)_2Cl_2$	**7**	None	0[b]	n.d.[e]
7	$Pd(CH_3CN)_2Cl_2$	**7**	$AgPF_6$	79[b]	66
8	$Pd(CH_3CN)_2Cl_2$	**7**	$AgNTf_2$	100[b]	76
9	$Pd(CH_3CN)_2Cl_2$	**7**	AgOTf	83[b]	66
10	$Pd(CH_3CN)_2Cl_2$	**7**	$AgClO_4$	94[b]	70
11	$Pd(CH_3CN)_2Cl_2$	**7**	$AgSbF_6$	91[c]	80 (93)[f]
12	$Pd(CH_3CN)_2Cl_2$	**8**	$AgSbF_6$	93[c]	76
13	$Pd(CH_3CN)_2Cl_2$	**10**	$AgSbF_6$	99[c]	81
14	$Pd(CH_3CN)_2Cl_2$	**9**	$AgSbF_6$	97[b]	64
15	$Pd(CH_3CN)_2Cl_2$	**11**	$AgSbF_6$	92[b]	56
16	$Pd(CH_3CN)_2Cl_2$	**12**	$AgSbF_6$	39[b]	64
17	$Pd(CH_3CN)_2Cl_2$	**13**	$AgSbF_6$	88[b]	71

[a] Reaction conditions: 0.1 mmol **1a**, 0.005 mmol Pd source, 0.006 mmol ligand, 0.01 mmol silver source, and 0.13 mmol H_2O_2·urea in 0.5 mL THF for 24–100 h.
[b] Yield determined by GC conversion.
[c] Isolated yield on scale of 0.34 mmol of **1a**.
[d] Determined by chiral GC analysis and absolute configuration determined by comparison of sign of rotation to published reports.
[e] n.d.=not determined.
[f] ee % after recrystallization from hexanes/Et_2O.

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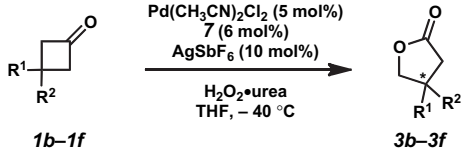
substitution at the 4-position of the oxazoline ring was found to be important, with aryl and heteroaryl alanine derived PHOX ligands leading to product **3a** with lower enantioselectivity (entries 15–17). We also explored a number of other solvents (e.g., CH_2Cl_2, toluene, and Et_2O), however with the exception of 2-methyl THF these were found to be inferior. Finally, lowering the temperature led to significant retardation of reaction rate. Fortuitously, the crystalline product, γ-lactone **3a**, was easily recrystallized from diethyl ether and hexanes to yield material with an ee of 93% in 66% yield.

Under our optimized conditions we sought to explore the reaction with other prochiral 3-substituted cyclobutanones (Table 2). We were pleased to see that both aryl and aliphatic substituents produced lactones in high yield and similar enantioselectivities. Importantly, (*R*)-(−)-3-(4′-chlorophenyl)-γ-butyrolactone (**3b**), which was obtained in 90% yield and 75% ee could easily be recrystallized to yield material with 93% ee. Excitingly 3,3-disubtituted cyclobutanones were also competent substrates in the Baeyer–Villiger oxidation producing lactones with a β-quaternary center in moderate selectivities (**3e** and **3f**, entries 4 and 5). The substrate scope highlights the potential utility of this method in the synthesis of biologically active molecules.

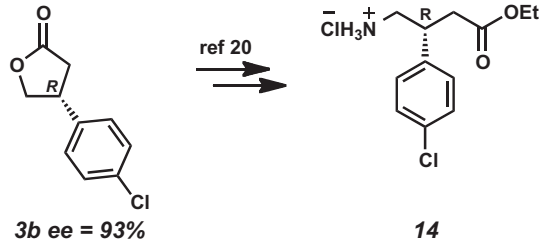
Table 2
Substrate screen[a]



Entry	R^1, R^2	Yield[b] (%)	ee[c,d] (%)
1	**1b**/**3b**: R^1=4-Cl–Ph, R^2=H	90	75 (93)[d,e]
2	**1c**/**3c**: R^1=4-CF_3–Ph, R^2=H	99	65[d]
3	**1d**/**3d**: R^1=*t*-Bu, R^2=H	80	75[c]
4	**1e**/**3e**: R^1=Ph, R^2=Me	83	52[c]
5	**1f**/**3f**: R^1=*t*-Bu, R^2=Me	57	29[f]

[a] Reaction conditions: 0.34 mmol **1b**–**f**, 0.017 mmol $Pd(CH_3CN)_2Cl_2$, 0.021 mmol ligand, 0.034 mmol $AgSbF_6$, and 0.445 mmol H_2O_2·urea in 1 mL THF for 24–100 h.
[b] Isolated yield on 0.34 mmol scale of ketone.
[c] Determined by chiral GC analysis.
[d] Determined by chiral HPLC analysis.
[e] ee % after recrystallization from hexanes/Et_2O.
[f] Determined by chiral HPLC analysis of the dibenzoate of the reduced diol (see Experimental section).

The hydrochloride salt of (*R*)-(−)-baclofen (**14**, Scheme 3) is a potent $GABA_B$ receptor agonist.[19] The racemic form is commercially available and used to treat spasticity and alcoholism, however the (*R*)-isomer has been shown to be predominantly responsible for the molecule's bioactivity. The molecule has been the target of many asymmetric syntheses. Several of these strategies start from enantioenriched lactone **3b** generated from either an enzymatic Baeyer–Villiger[20] or from an enantioselective C–H insertion.[21] We have demonstrated that via our method we could generate γ-lactone **3b** in 93% ee and 72% yield after a single recrystallization. Transformation of enantioenriched lactone **3b** to (*R*)-(−)-baclofen (**14**) can be completed as previously described.[22]



Scheme 3. Synthesis of (*R*)-(−)-baclofen.

3. Conclusion

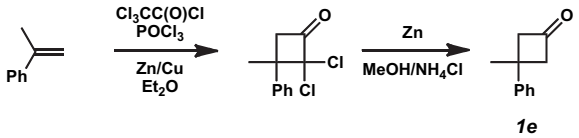
We have successfully employed PHOX ligands to effect a palladium-catalyzed asymmetric Baeyer–Villiger oxidation of prochiral 3-substituted cyclobutanones **1** to enantioenriched γ-lactones **3** in yields up to 99% and enantioselectivities up to 81% ee. Of note, 3,3-disubtituted cyclobutanones (**1e** and **1f**) produced lactones with a β-quaternary center with moderate selectivity (**3e** and **3f**). Furthermore, we found that γ-lactones, such as **3a** and **3b** were easily recrystallized to material with enantiopurity of 93% ee. Lactone **3b** can easily be manipulated to provide enantioenriched $GABA_B$ receptor agonsist (*R*)-(−)-baclofen (**14**).[22] Efforts to expand the scope and improve the selectivity of the reaction are the focus of ongoing studies.

4. Experimental

4.1. General

Unless stated otherwise, reactions were performed in oven-dried or flame-dried glassware under a nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Commercially obtained reagents were used as received, unless specified otherwise. Low-temperature reactions were controlled by a ThermoNeslab CB80 cryocool. Zinc/copper couple was made as previously described.[23] Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F_{254} pre-coated plates (0.25 mm) and visualized using a combination of UV light (254 nm), *p*-anisaldehyde, potassium permanganate, or phosphomolybdic acid staining. SiliaFlash® P60 Academic Silica Gel (particle size 40–63 μm; pore diameter 60 Å) was used for flash column chromatography. Analytical chiral HPLC analyses were performed with an Agilent 1100 Series HPLC instrument utilizing a Chiralcel AD or OD-H column (4.6 mm×25 cm) obtained from Daicel Chemical Industries, Ltd with detection at either λ=210 or 254 nm. Chiral GC analysis was performed with an Agilent 6850 GC utilizing a Supleco Chiraldex G-TA or Betadex (30 m×0.25cm) column (1.0 mL/min carrier gas flow). ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz, 75 MHz, and 282 MHz, respectively) or a Varian Inova 500 (at 500 MHz and 125 MHz, respectively) instrument and are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). IR spectra were recorded on a Perkin–Elmer Spectrum BXII spectrometer and are reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-1010 polarimeter, using a 100 mm path-length cell. High-resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility.

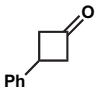
4.2. Representative procedure for the synthesis of cyclobutanones



*4.2.1. Cyclobutanone **1e**.* To a 100 mL 2-neck round-bottomed flask equipped with a magnetic stir bar and a 25 mL addition funnel were added α-methylstyrene (0.62 mL, 4.75 mmol), zinc–copper couple (0.92 g, 7.12 mmol), and ether (10 mL). A solution of trichloroacetyl chloride (0.79 mL, 7.12 mmol) and phosphorus oxychloride (0.44 mL, 4.75 mmol) in ether (5 mL) was added dropwise via addition funnel over 20 min. A reflux condenser was added to the flask and the resulting solution was heated at 40 °C for 10 h. After cooling to 23 °C the mixture was filtered over Celite and washed with ether (20 mL). The filtrate was then quenched with satd $NaHCO_3$ and the

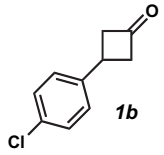
layers separated. The aqueous layer is extracted with ether (1×10 mL) and the combined organics are rinsed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (3 cm×7 in silica, 5→7% EtOAc in hexanes) to afford 2,2-dichloro-3-phenylcyclobutanone as a clear and colorless oil (780 mg, 72% yield).

In a 50 mL round-bottom flask equipped with a reflux condenser is placed 2,2-dichloro-3-phenylcyclobutanone (775 mg, 3.38 mmol) from above and activated zinc (885 mg 13.53 mmol) in a satd methanolic NH_4Cl solution (5 mL). The suspension is refluxed for 6 h, then cooled to 23 °C, and filtered through Celite. The Celite is rinsed with ether (20 mL) and organics are rinsed with H_2O (10 mL), satd $NaHCO_3$ (10 mL), and brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (3 cm×7 in silica, 2→10% EtOAc in hexanes) to afford cyclobutanone **1e** as a clear and colorless oil (350 mg, 65% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5H), 3.48 (m, 2H), 3.13 (m, 2H), 1.62 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.6, 148.3, 128.6, 126.3, 125.6, 59.3, 34.0, 31.1; IR (neat film, NaCl) ν 3549, 3059, 3025, 2958, 2921, 2866, 1784, 1601, 1496, 1445, 1381, 1302, 1186, 1142, 1080, 1029, 764, 701 cm^{-1}; HRMS (EI^+) m/z calcd for $C_{11}H_{12}O$ $[M]^+$: 160.0888, found 160.0905.



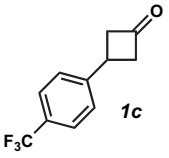
1a

4.2.2. Cyclobutanone ***1a***. Material was prepared from styrene in 42% overall yield as a clear and colorless oil as described above for **1e**. The characterization data matches that in literature.[10]



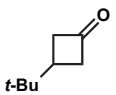
1b

4.2.3. Cyclobutanone ***1b***. Material was prepared from 4-chlorostyrene in 21% overall yield as a clear and colorless oil as described above for **1e**. The characterization data matches that in literature.[10]



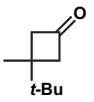
1c

4.2.4. Cyclobutanone ***1c***. Material was prepared from 4-(trifluoromethyl)styrene in 56% overall yield as a clear and colorless oil as described above for **1e**. ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J=8.1 Hz, 2H), 7.42 (d, J=8.5 Hz, 2H), 3.75 (quintet, J=8.1 Hz, 1H), 3.55 (m, 2H), 3.36 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.4, 147.5, 129.1 (q, J=32.4 Hz), 126.9, 125.7 (q, J=3.8 Hz), 124.1 (q, J=271.8 Hz), 54.7, 28.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ −62.5; IR (neat film, NaCl) ν 3560, 3049, 2980, 2928, 1791, 1619, 1425, 1387, 1327, 1165, 1123, 1069, 1017, 834, 723 cm^{-1}; HRMS (EI^+) m/z calcd for $C_{11}H_9OF_3$ $[M]^+$: 214.0606, found 214.0603.



1d

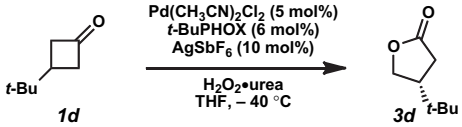
4.2.5. Cyclobutanone ***1d***. Material was prepared from 3,3-dimethyl-1-butene in 32% overall yield as a clear and colorless oil as described above for **1e**. The characterization data matches that in literature.[24]



1f

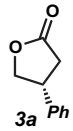
4.2.6. Cyclobutanone ***1f***. Material was prepared from 2,3,3-trimethyl-1-butene in 4% overall yield as a clear and colorless oil described above for **1e**. The characterization data matches that in literature.[25]

4.3. Representative procedure for the synthesis of γ-lactones



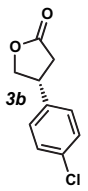
1d *3d*

4.3.1. γ-Lactone ***3d***. To a solution of dichlorobis(acetonitrile)palladium(II) (4.4 mg, 17 μmol) in THF (1 mL) was added ligand **7** (8.1 mg, 21 μmol) and the solution was stirred for 1 h at 23 °C. To another flask containing silver hexafluoroantimonate (11.7 mg, 34 μmol) was added the above palladium(II) complex solution. After stirring 1 h at 23 °C the mixture was filtered through a pad of Celite under Ar into a new flask containing cyclobutanone **1d** (43 mg, 0.34 mmol) and cooled to −40 °C. To the cooled solution was added urea·hydrogenperoxide (42 mg, 0.45 mmol) and the mixture was further stirred at the temperature for 90 h. The mixture was directly purified by flash chromatography on silica gel (2 cm×7 in silica, 2→10% EtOAc in hexanes) to afford γ-lactone **3d** as a clear and colorless oil (39 mg, 80% yield). Observed 75% ee as determined by chiral GC analysis (Chiraldex® GTA, 100 °C, t_R (minor)=52.4 min; t_R (major)=52.8 min). ^1H NMR (500 MHz, $CDCl_3$) δ 4.31 (m, 1H), 4.09 (m, 1H), 2.43 (m, 2H), 2.35 (m, 1H), 0.91 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.4, 69.8, 45.9, 31.3, 30.1, 26.8; IR (neat film, NaCl) ν 3537, 2962, 2873, 1780, 1477, 1419, 1400, 1369, 1175, 1033, 999, 987, 841 cm^{-1}; HRMS (EI^+) m/z calcd for $C_8H_{14}O_2$ $[M]^+$: 142.0994, found 142.0991.



3a

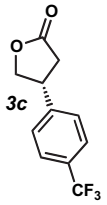
4.3.2. γ-Lactone ***3a***. Material was prepared from **1a** in 91% yield as a white solid as described above for **3d**. Observed 80% ee as determined by chiral GC analysis (Chiraldex® GTA, 150 °C, t_R (minor)=35.4 min; t_R (major)=36.0 min). The characterization data matches that in literature.[10] $[\alpha]_{D^{25}}$ −39.3 (c 0.99, $CHCl_3$).



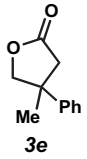
3b

4.3.3. γ-Lactone ***3b***. Material was prepared from **1b** in 90% yield as a white solid as described above for **3d**. Observed 75% ee as determined by chiral HPLC analysis (Chiralpak® AD, 4% 2-propanol/

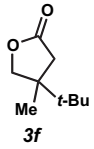
hexanes, 1 mL/min, 210 nm, t_R (minor)=29.8 min; t_R (major)=31.4 min). The characterization data matches that in literature.[12]



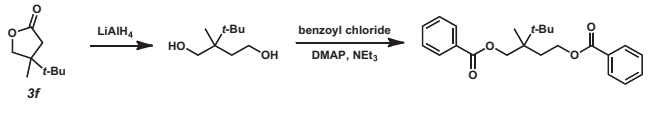
*4.3.4. γ-Lactone **3c**.* Material was prepared from **1c** in 79% yield as an off white solid as described above for **3d**. Observed 74% ee as determined by chiral HPLC analysis (Chiralpak® AD, 4% 2-propanol/hexanes, 1 mL/min, 254 nm, t_R (minor)=19.3 min; t_R (major)=20.1 min). The characterization data matches that in literature.[26]



*4.3.5. γ-Lactone **3e**.* Material was prepared from **1e** in 83% yield as a clear and colorless oil as described above for **3d**. Observed 51% ee as determined by chiral GC analysis (BetaDex, 145 °C, t_R (minor)=45.1 min; t_R (major)=45.9 min). The characterization data matches that in literature.[12]



*4.3.6. γ-Lactone **3f**.* Material was prepared from **1f** in 57% yield as a clear and colorless oil as described above for **3d**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30 (d, J=9.1 Hz, 1H), 3.87 (d, J=9.1 Hz, 1H), 2.64 (d, J=17.5 Hz, 1H), 2.10 (d, J=17.5 Hz, 1H), 1.18 (s, 3H), 0.94 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.4, 75.7, 45.5, 38.1, 34.0, 25.7, 21.9; IR (neat film, NaCl) 2967, 1777, 1468, 1363, 1281, 1179, 1010, 1022, 847 ν cm^{-1}; HRMS (EI$^+$) m/z calcd for $C_9H_{16}O_2$ [M+H]$^+$: 157.1229, found 157.1180.



Observed 29% ee as determined by chiral HPLC analysis of the derived dibenzoate. To a mixture of lactone **3f** (3 mg, 0.03 mmol) in Et_2O (1 mL) was added $LiAlH_4$ (11 mg, 0.30 mmol) and the mixture was refluxed for 4 h. After cooling to 23 °C the reaction mixture was diluted with Et_2O (5 mL) and 1 N HCl (5 mL). The layers were separated and the aqueous layer was re-extracted with Et_2O (2×5 mL). The combined organic phases were rinsed with brine (5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude diol was dissolved in NEt_3 (0.5 mL) and DMAP (3 mg, 0.02 mmol) and benzoyl chloride (35 mL, 0.3 mmol) were added. After stirring 4 h the reaction mixture was directly purified by flash chromatography on silica gel (2 cm×4 in silica, 2→20% EtOAc in hexanes) to yield the dibenzoate as a clear and colorless oil (2 mg, 20% yield). Chiralpak® OD-H, 3% 2-propanol/hexanes, 1 mL/min, 254 nm, t_R (major)=6.4 min; t_R (minor)=7.2 min).

4.4. Procedure for the recrystallization of γ-lactones

*4.4.1. γ-Lactone **3a**.* Lactone **3a** (152 mg, 77% ee) was dissolved in warm Et_2O (~4 mL). This solution was then diluted with warm hexanes (~20 mL) and the solution was allowed to cool to 23 °C then stored at 0 °C for 8 h. The mother liquor was decanted and the solids were rinsed with cold Et_2O (1×3 mL) and hexanes (3×5 mL). Solids were dried to yield white crystals in 66% yield (101 mg, 93% ee).

*4.4.2. γ-Lactone **3b**.* Lactone **3b** (116 mg, 71% ee) was dissolved in warm Et_2O (~2 mL). This solution was then diluted with warm hexanes (~20 mL) and the solution was allowed to cool to 23 °C then stored at 0 °C for 8 h. The mother liquor was decanted and the solids were rinsed with cold Et_2O (1×3 mL) and hexanes (3×5 mL). Solids were dried to yield white crystals in 72% yield (83 mg, 93% ee).

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