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Cyclohexanones by Rh-Mediated Intramolecular C−H Insertion

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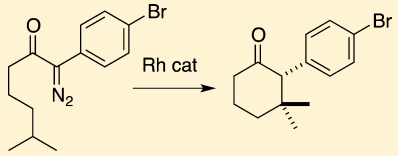
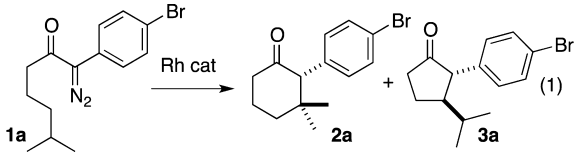
Supporting Information

ABSTRACT: Some long chain α-aryl α-diazo ketones under Rh catalysis cyclize efficiently to the corresponding cyclohexanones. This is in marked contrast to the cyclizations of α-diazo β-ketoesters, which consistently deliver cyclopentanone products.



INTRODUCTION

Rhodium carbenes derived from α-aryl ketones[1] can be electronically more discriminating than the Rh carbenes derived from β-ketoesters. We have found that when this discriminating carbene is applied in a intramolecular sense, with an electron rich C−H site six atoms away, C−H insertion to form the six-membered ring (eq 1) can dominate.[2] This is in marked contrast to the cyclization of analogous α-diazo β-ketoesters, which consistently deliver cyclopentanone products.[3,4]



RESULTS AND DISCUSSION

We had developed the Rh-mediated cyclization of α-aryl α-diazo ketones as a reliable protocol for preparing α-aryl cyclopentanones.[1] In the course of what we anticipated would be the routine cyclization of the diazo ketone **1a** (eq 1) to the cyclopentanone **3a** (^{13}C NMR δ 217.6), we observed a dominant product **2a** (^{13}C NMR δ 209.0) that was clearly cyclohexanone, from Rh-mediated C−H insertion into the more electron rich methine.[5] We have surveyed (Table 1) the influence of the catalyst on the yield of this cyclization and on the ratio of products. Catalysts with strong electron withdrawing ligands lead to diminished selectivity (entries 3 and 4). Electron withdrawing ligands increase the electrophilicity of the rhodium-stabilized carbene, leading to a more reactive carbene. Rh catalysts with more electron donating ligands lead to less electrophilic carbenes, thus allowing higher selectivity and yields for the insertion (entries 1, 2, and 5). Because the Du Bois[6] catalyst $Rh_2(esp)_2$ is commercially available and the pivalate is not, we used the $Rh_2(esp)_2$ catalyst for subsequent explorations.[7]

We next investigated the catalyst loading (Table 2). It was apparent that 5 mol % was optimal. We also investigated the diazo transfer reaction (Table 3). We found that 2,4,6-triisopropylbenzenesulfonyl azide (TIBSA) in toluene with 1,8-diazabicycloundec-7-ene (DBU) as the base delivered the diazo ketone **1a** most efficiently. *p*-Nitrobenzenesulfonyl azide (*p*NBSA) gave comparable yields, but the diazo ketone was more readily purified when TIBSA was used.

Table 1. Cyclization of 1a to 2a vs 3a

entry	catalyst[a]	2a:3a[b]	yield (%)[c]
1	$Rh_2(oct)_4$[d]	9.5:1.0	74
2	$Rh_2(piv)_4$[e]	11.7:1.0	92
3	$Rh_2(OAc)_4$[f]	7.5:1.0	18
4	$Rh_2(tfa)_4$[g]	5.3:1.0	74
5	$Rh_2(esp)_4$[h]	106:1.0	92

[a]Reaction conditions: **1a** (1.0 mmol) in hexanes (5.0 mL) was added to 0.003−0.005 equiv of Rh catalyst in hexanes (5.0 mL), rt. [b]Ratios are from GC−MS area %. [c]Combined chromatographed yield for the two ketones. [d]oct = octanoate. [e]piv = pivalate. [f]OAc = acetate. [g]tfa = trifluoroacetate. [h]esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate (ref 6).

Table 2. Catalyst Loading Screen

entry	catalyst loading (%)[a]	yield (%)[b]
1	1	50
2	3	70
3	5	92
4	10	90

[a]Reaction conditions: **1a** (1.0 mmol) in hexanes (5.0 mL) was added to $Rh_2(esp)_2$ in hexanes (5.0 mL), rt. [b]Combined chromatographed yield for the two ketones.

Preparation of the Substrates. With our first substrate optimized, we planned to investigate the effect of the electronics of the aromatic ring on the C−H insertion. To easily prepare these substrates in gram quantities, a general strategy was developed. The initial aryl bromide **4** (Scheme 1) was converted into the epoxide **6** by conversion to the Grignard reagent and coupling with allyl bromide and then exposure to *m*-chloroperoxybenzoic acid (*m*CPBA). Cu-catalyzed opening

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Table 3. Diazo Transfer Optimization

entry	reagent[a]	solvent	base	yield (%)[b]
1	*p*NBSA[c]	DCM	DBU[e]	75
2	*p*NBSA[c]	toluene	DBU[e]	78
3	*p*NBSA[c]	acetonitrile	DBU[e]	78
4	*p*NBSA[c]	DCM	TEA[f]	40
5	*p*NBSA[c]	THF	NaH	60
6	TIBSA[d]	toluene	DBU[e]	84

[a]Reaction conditions: The liquid base was added dropwise over 5 min to the α-aryl ketone (1.0 mmol) and diazo transfer reagent (1.5 equiv) in solvent (5.0 mL), rt. [b]Yields are for pure chromatographed diazo ketone **1a**. [c]*p*NBSA = *p*-nitrobenzenesulfonyl azide. [d]TIBSA = 2,4,6-triisopropylbenzenesulfonyl azide. [e]DBU = 1,8-diazabicyclo[5.4.0]-unde-7-ene. [f]TEA = triethylamine.

of the epoxide with the Grignard reagent derived from 1-bromo-3-methylbutane followed by oxidation delivered the α-aryl ketone **7** that was carried on to the diazo ketone **1**.

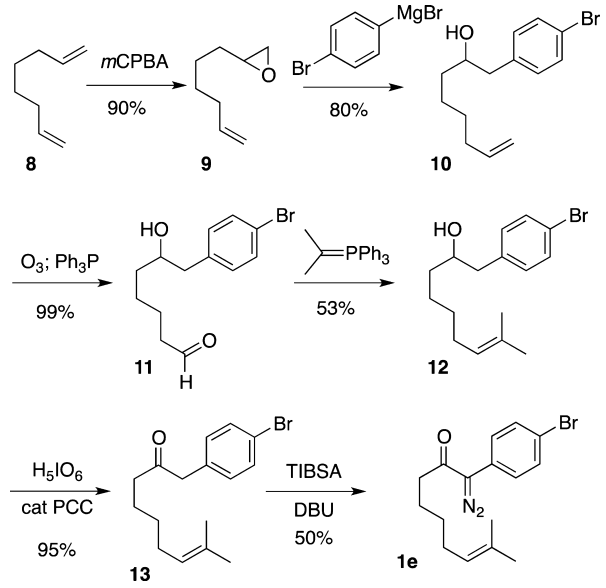
We also planned to explore the effect of different activating groups at the site of insertion. The diazo ketone **1e** (Scheme 2) was readily prepared from 1,7-octadiene. The mono epoxide formed by exposure to *m*CPBA was opened with the Grignard reagent derived from 1,4-dibromobenzene to give the secondary alcohol **10**. Ozonolysis followed by the Wittig reaction and finally oxidation and diazo transfer delivered the desired diazo ketone **1e**.

The aryl-substituted substrate **1f** (Scheme 3) was prepared by conversion of the commercial alcohol **14** to the bromide **15**. Epoxide **4a** was opened with the Grignard reagent derived from bromide **15**. Oxidation of the resulting secondary alcohol followed by diazo transfer delivered the diazo ketone **1f**.

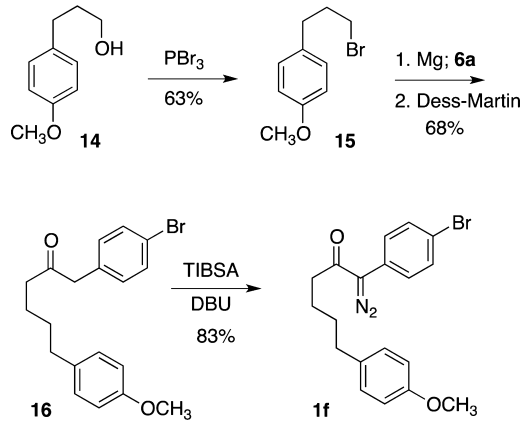
The synthesis of **19** (Scheme 4) proceeded from the commercial alcohol **17**. Epoxidation of the derived benzyl ether with *m*CPBA gave the epoxide **18**. Opening of the epoxide **18** with the Grignard reagent derived from 1,4-dibromobenzene followed by oxidation and diazo transfer delivered the diazo ketone **1g**.

Scope of the C−H Insertion. We explored the cyclization of the α-aryl α-diazo ketones (Table 4) we had prepared. In each case (entries 1−6), cyclohexanone formation proceeded

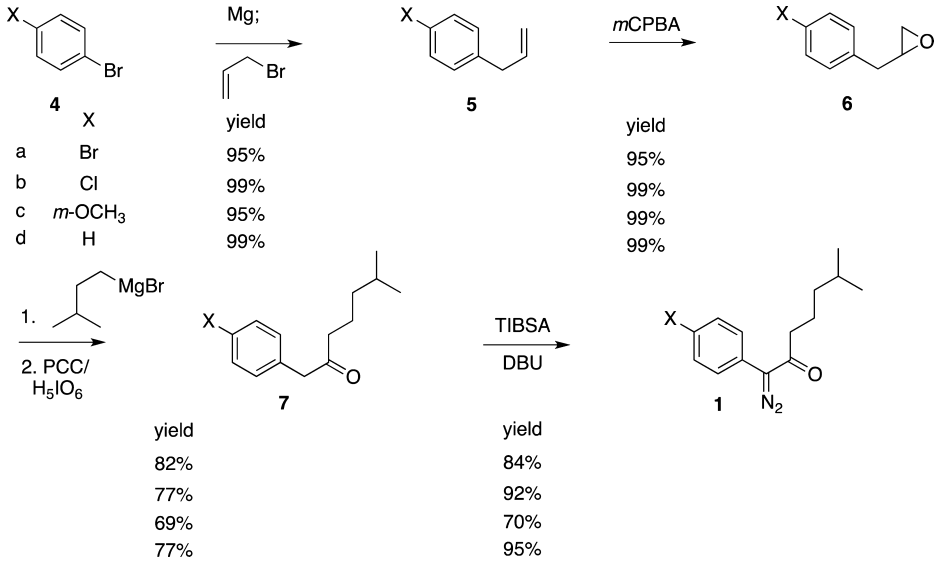
Scheme 2. Preparation of the Trisubstituted Alkene



Scheme 3. Synthesis of the Bis Arene



Scheme 1. Preparation of α-Diazo α-Aryl Ketones



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Scheme 4. Synthesis of the Benzyl Ether

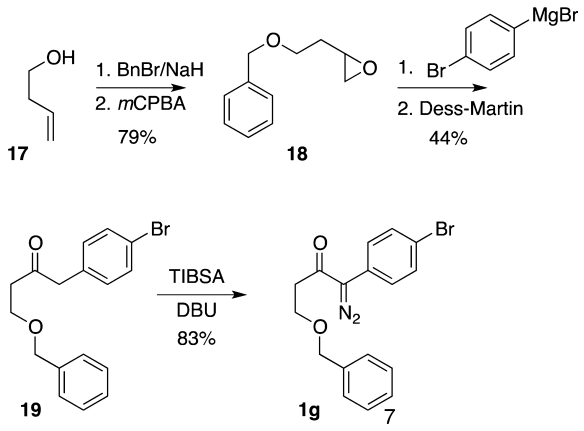
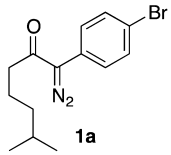
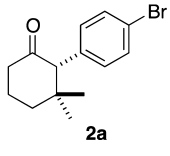
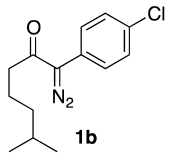
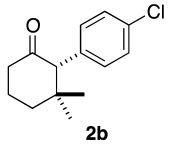
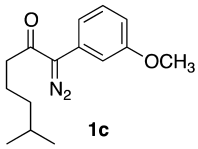
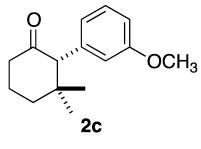
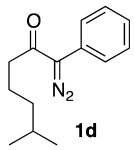
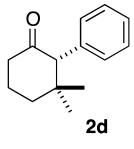
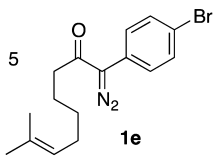
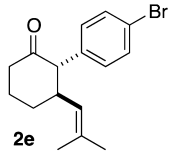
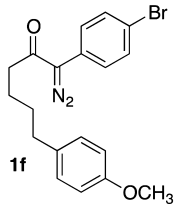
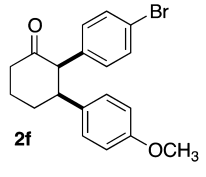


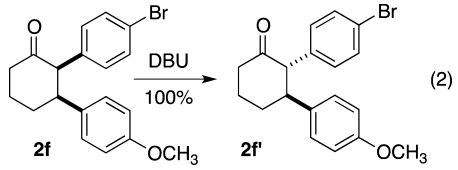
Table 4. Cyclization of Diazo Ketones

	Diazo Ketone	Product	Yield[a]	2 : 3[b]
1	 1a	 2a	94%	10.8:1
2	 1b	 2b	82%	15.8:1
3	 1c	 2c	69%	8.6:1
4	 1d	 2d	79%	13.3:1
5	 1e	 2e	86%[c]	11.5:1
6	 1f	 2f	72%	> 99:1

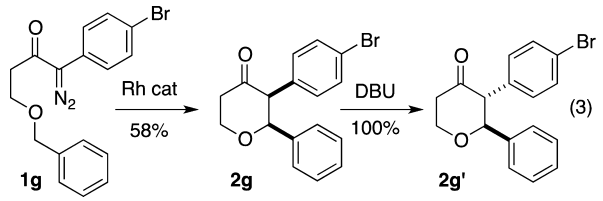
[a]Yields are for the pure chromatographed mixture of ketones. [b]Ratios are by GC–MS of the product mixture. [c]The initial mixture of diastereomers was equilibrated by exposure to DBU before purification.

well with the $Rh_2(esp)_2$ catalyst. The electronic contribution at the benzene ring was investigated (entries 1–4). Halogens in the para position stabilize the carbene, leading to very good selectivities and yields. We also investigated the effect of a meta methoxy group (entry 3). We observed a slight decrease in selectivity for the insertion, suggesting that the meta methoxy arene is not quite as good at stabilizing the electron deficient carbene, making it more reactive, and thus less selective.

With a pendant trisubstituted alkene, we observed the C–H insertion product (entry 5) with no cyclopropane.[8] With a 4-methoxyphenyl substituent (entry 6), we observed exceptional selectivity for the formation of the cyclohexanone. As had been previously observed[9] with conjugate addition to α-aryl cyclohexenones, the kinetic product was predominantly cis, **2f**. This smoothly equilibrated (eq 2) to the trans product **2f′** upon exposure to DBU.



We also observed formation of the tetrahydropyranone (eq 3) on exposure of the diazo ketone **1g** to the $Rh_2(esp)_2$ catalyst. The kinetically formed cis product **2g** was readily equilibrated to trans **2g′** upon exposure to DBU.

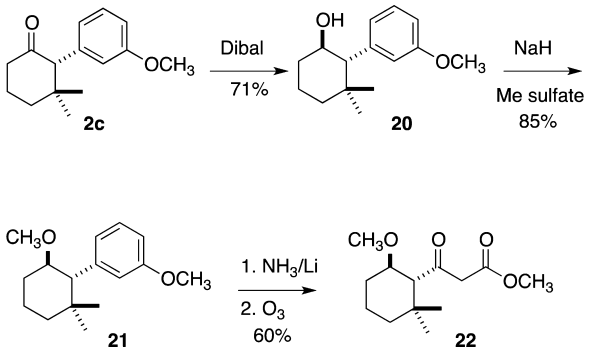


The α-aryl cyclohexanones prepared following this protocol will have many applications in target-directed synthesis. The arene is also a useful starting point for further manipulation. Following the procedure of Evans,[10] for instance, Birch reduction of **21** (Scheme 5) followed by ozonolysis delivered the β-keto ester **22**.

Mechanism of the Cyclization.

The results observed in this study are in marked contrast to those we reported[1b] for the cyclization of α-diazo β-keto esters. With $Rh_2(OAc)_4$, for instance, **23** (eq 4) cleanly cyclized to **24**.

Scheme 5. Cleavage of the Aromatic Ring



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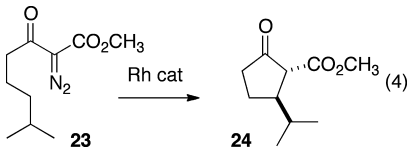
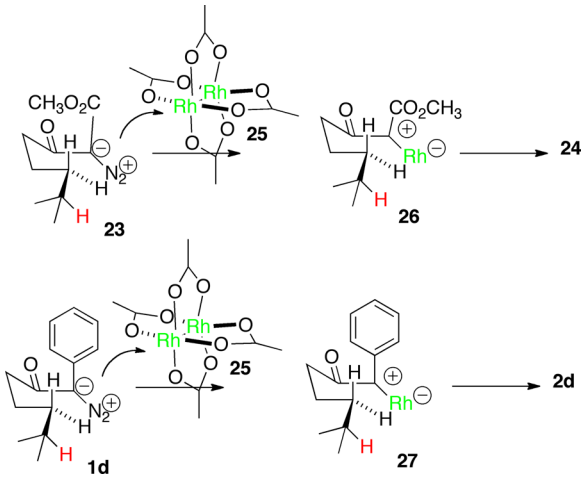
These results can be understood upon considering (Scheme 6) the competing transition states **26** and **27**.



Scheme 6. Competing Transition States for C−H Insertion



It is generally[11] thought that the selectivity of Rh-mediated C−H functionalization is due to the transient formation of σ complexes between the electrophilic Rh carbene and the several target C−H bonds. Carbon−carbon bond formation proceeds as the carbene center commits to the electron density in a particular C−H bond. It has recently been shown[12] that the Rh- and Ag-catalyzed intermolecular C−H insertions of push−pull stabilized carbenes, such as **27**, are significantly more tertiary selective than the same insertions of Rh carbene **26** derived from an α-diazo β-keto ester. This may be due to the more ready polarization of the intermediate metal carbene complex **27**, compared to **26**, as they proceed to withdraw the electron density from a target C−H bond. These initial observations[12] were of an increased preference for tertiary C−H insertion. Applied in an intramolecular sense, the result is a preference for cyclohexanone rather than cyclopentanone formation.

CONCLUSION

The cyclization of, for example, **1e** to **2e**, represents a significant increase in molecular complexity.[13] Cyclopentanone construction by Rh-mediated intramolecular C−H insertion has been found to have many applications in target-directed synthesis.[3,4] We expect that the cyclohexanone construction described here will similarly be useful.

EXPERIMENTAL SECTION

General Experimental Information. ^{1}H NMR and ^{13}C NMR spectra were recorded as solutions in deuteriochloroform ($CDCl_3$) at 400 and 100 MHz, respectively. ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "d" from methylene and quaternary carbons as "u". The infrared (IR) spectra were determined as neat oils. The R_f values indicated refer to thin layer chromatography (TLC:) on 2.5 × 10 cm, analytical plates coated with silica gel GF 250 μm, unless otherwise noted, and developed in the solvent system indicated. All glassware was oven dried and rinsed with dry solvent before use. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium metal/benzophenone ketyl under dry nitrogen. MTBE is methyl *tert*-butyl ether and PE is 30−60 petroleum ether. TIBSA is 2,4,6-triisopropylbenzenesulfonyl azide. All reactions were conducted under N_2 and stirred magnetically. Product ratios (i.e., cyclohexanone versus cyclopentanone) were determined via GC−MS by integrating the product peaks directly. The method was an initial start of 70 °C for 2 min and then a 20 °C/min ramp to 230 °C and a hold at 230 °C for 3 min. HRMS were obtained by an electron ionization (EI) method of ionization with a double focusing sector detector. Commercial *m*-chloroperoxybenzoic acid (*m*CPBA) was purified by dissolving in Et_2O and washing with K_2HPO_4 buffer pH = 7.5. The organic fraction was dried (Na_2SO_4) and concentrated.

1-(4-Bromophenyl)-6-methylheptan-2-one (7a). To a solution of 1,4-dibromobenzene (10.0 g, 42.7 mmol) in dry Et_2O (200 mL) were added Mg turnings (1.50 g, 64.0 mmol). A chip of I_2 was added, and the mixture was brought to reflux. After the reaction initiated, brown color developed, the heating was stopped, and the reaction was allowed to complete. After the exotherm stopped and most of the Mg was consumed, the mixture was cooled to 0 °C. Allyl bromide (10.2 g, 85.0 mmol) was added neat dropwise over 5 min. The mixture was allowed to warm to rt for 2 h. The mixture was quenched with saturated aqueous NH_4Cl and then partitioned between Et_2O and, sequentially, 1 M aqueous HCl, and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield the alkene **5a** (7.98 g, 95% yield) as a colorless oil. TLC:: R_f (5% MTBE/PE) = 0.80. ^{1}H NMR, δ: 3.34 (d, J = 6.9 Hz, 2H), 5.14−5.05 (m, 2H), 6.02−5.87 (m, 1H), 7.07 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H). ^{13}C NMR, δ: u 136.7, 120.1, 119.1, 116.3, 39.6; d 133.1, 131.4. The ^{1}H NMR data matches published spectra.[14]

To a solution of the alkene **5a** (7.98 g, 40.72 mmol) in dry CH_2Cl_2 (150 mL) at 0 °C was added *m*CPBA (8.43 g, 48.86 mmol). After stirring at 0 °C for 2 h, the reaction mixture was quenched with 1 M aqueous NaOH and then partitioned between CH_2Cl_2 and, sequentially, water and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield the epoxide **6a** (8.20 g, 95% yield) as a colorless oil. TLC:: R_f (5% MTBE/PE) = 0.38. ^{1}H NMR, δ: 2.51 (dd, J = 2.4, 4.8 Hz, 1H), 2.76−2.82 (m, 3H), 3.08−3.14 (m, 1H), 7.10−7.14 (d, J = 8.4 Hz, 2H), 7.40−7.43 (d, J = 8.4 Hz, 2H). ^{13}C NMR, δ: u 136.2, 120.7, 46.8, 38.1; d 131.7, 130.9, 52.2. The ^{1}H NMR data matches published spectra.[15]

To a solution of 1-bromo-3-methylbutane (11.68 g, 77.36 mmol) in dry THF (200 mL) were added Mg turnings (2.32 g, 96.7 mmol). The reaction was initiated with an I_2 chip and heating to reflux. Once the exotherm stopped, the mixture was cooled to −30 °C. A CuBr·Me_2S complex (0.279 g, 3.87 mmol) was added, followed by a solution of the epoxide **6a** (8.20 g, 38.68 mmol) in THF (50 mL) added dropwise over 5 min. After being allowed to warm to rt, the mixture was quenched with saturated aqueous NH_4Cl and then partitioned between Et_2O and, sequentially, 1 M aqueous HCl and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield the alcohol (10.21 g, 93% yield) as a colorless oil. TLC:: R_f (10% MTBE/PE) = 0.40. To a solution of the alcohol (10.21 g, 35.97 mmol) in CH_3CN (150 mL) was added pyridinium chlorochromate (PCC) (0.155 g, 0.72 mmol) followed by periodic acid (9.84 g, 43.16 mmol).[16] After 30 min, the mixture was filtered through a short pad of Celite eluting with Et_2O. The filtrate was concentrated, and the residue was chromatographed to yield ketone **7a** (9.02 g, 74% yield from 1,4-dibromobenzene) as a clear oil. TLC:: R_f (10% MTBE/PE) = 0.42. ^{1}H NMR, δ: 0.83 (s, 3H), 0.86 (s, 3H), 1.09−1.14 (m, 2H), 1.47−1.59 (m, 3H), 2.40−2.44 (m, 2H), 3.63 (s, 2H), 7.06−7.09 (d, J = 8.4 Hz, 2H), 7.43−7.46 (d, J = 8.4 Hz, 2H). ^{13}C NMR, δ: u 207.8, 133.3, 121.0, 49.3, 42.5, 38.3, 21.6; d 131.8, 131.1, 27.8, 22.5 (2). IR (film): 2953, 1711, 1488, 1069, 799 cm^{-1}. HRMS Calcd $C_{14}H_{20}BrO$ [M + H] 283.0698. Found: 283.0687.

2-(4-Bromophenyl)-3,3-dimethylcyclohexanone (2a). To a solution of the ketone **7a** (0.10 g, 0.35 mmol) in toluene (3.0 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.11 g, 0.71 mmol)

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followed by triisopropylbenzenesulfonyl azide (TIBSA) (0.13 g, 0.42 mmol). The mixture was kept in the dark for 30 min. The mixture was then chromatographed directly to yield the diazo ketone **1a** (0.092 g, 84% yield) as orange crystals. TLC:: R_f (10% MTBE/PE) = 0.39. ^{1}H NMR, δ: 0.84 (s, 3H), 0.90 (s, 3H), 1.20−1.30 (m, 2H), 1.52−1.58 (m, 1H), 1.67−1.75 (m, 2H), 2.56−2.59 (m, 2H), 7.40−7.43 (d, J = 7.8 Hz, 2H), 7.50−7.53 (d, J = 7.8 Hz, 2H). ^{13}C NMR, δ: u 192.6, 124.7, 120.4, 39.4, 38.4, 22.5; d 132.1, 127.0, 27.9, 22.5. The diazo ketone **1a** (0.092 g, 0.29 mmol) was then taken into a glovebox. To a slurry of $Rh_2(esp)_2$ (0.011 g, 0.014 mmol) in hexanes (10 mL) was added the diazo ketone **1a** in hexanes (10 mL) dropwise over 10 min. After 5 min, the mixture was removed from the glovebox, and the solution was chromatographed directly to obtain a mixture of the cyclized products **2a** with a little **3a** (0.078 g, 79% yield from **7a**). TLC: R_f (10% MTBE/PE) = 0.42. ^{1}H NMR, δ: 0.77 (s, 3H), 0.82 (s, 3H), 1.65−1.68 (m, 1H), 1.78−1.81 (m, 1H), 1.92−1.95 (m, 2H), 2.34−2.42 (m, 2H), 3.39 (s, 1H), 6.99 (d, J = 8.4 Hz, 2H), 7.34−7.38 (d, J = 8.4 Hz, 2H). ^{13}C NMR, δ: u 209.0, 132.9, 121.0, 41.5, 40.9, 40.7, 22.5; d 132.9, 130.6, 66.8, 30.5, 21.8. IR (film): 2957, 1709, 1265, 754 cm^{-1}. HRMS [M + Na] Calcd $C_{14}H_{17}BrNaO$ 303.0360. Found: 303.0350. GC−MS R_t for **2a** was 12.00 min, and for **3a**, the R_t was 11.89 min. The integrated ratio of the peaks was 10.6:1.0. Upon closer inspection of the ^{13}C NMR, we observed a peak at δ 217.6 corresponding to the cyclopentanone.

1-(4-Chlorophenyl)-6-methylheptan-2-one (7b). To a solution of 1-bromo-4-chlorobenzene (4.00 g, 20.9 mmol) in dry Et_2O (100 mL) were added Mg turnings (0.75 g, 31.4 mmol). A chip of I_2 was added, and the mixture was brought to reflux. After the reaction initiated, a brown color developed, the heating was stopped, and the reaction was allowed to complete. After the exotherm stopped and most of the Mg was consumed, the mixture was cooled to 0 °C. Allyl bromide (3.05 g, 25.4 mmol) was added neat dropwise over 5 min. The mixture was allowed to warm to rt for 2 h. The mixture was quenched with saturated aqueous NH_4Cl and then partitioned between Et_2O and, sequentially, 1 M aqueous HCl and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield the alkene **5b** (3.17 g, 99% yield) as a colorless oil. TLC: R_f (5% MTBE/PE) = 0.85. ^{1}H NMR, δ: 3.32 (d, J = 6.6 Hz, 2H), 5.09−5.03 (m, 2H), 5.98−5.85 (m, 1H), 7.09 (d, J = 8.4 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H). ^{13}C NMR, δ: u 39.51, 116.26, 131.82, 138.45; d 128.24, 129.06, 136.90. The ^{1}H NMR data matches published spectra.[17]

To a solution of the alkene **5b** (3.17 g, 20.8 mmol) in dry CH_2Cl_2 (100 mL) at 0 °C was added *m*CPBA (4.31 g, 24.04 mmol). After stirring at 0 °C for 2 h, the mixture was quenched with 1 M aqueous NaOH and then partitioned between CH_2Cl_2 and, sequentially, water and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield the epoxide **6b** (3.45 g, 99% yield) as a colorless oil. TLC: R_f (5% MTBE/PE) = 0.42. ^{1}H NMR, δ: 2.48−2.60 (m, 1H), 2.82 (t, J = 4.2 Hz, 1H), 2.87 (d, J = 5.3 Hz, 2H), 3.11−3.20 (m, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.26−7.36 (m, 2H). ^{13}C NMR, δ: u 135.5, 132.5, 46.7, 38.0; d 130.3, 128.6, 52.1. IR (film): 3029, 2917, 1446, 1454, 1409 cm^{-1}. The ^{1}H NMR data matches published spectra.[18]

To a solution of 1-bromo-3-methylbutane (6.22 g, 41.18 mmol) in dry THF (100 mL) were added Mg turnings (1.23 g, 51.47 mmol). The reaction was initiated with an I_2 chip and heating to reflux. Once the exotherm stopped, the mixture was cooled to −30 °C. A CuBr·Me_2S complex (0.42 g, 2.06 mmol) was added, followed by a solution of the epoxide **6b** (3.45 g, 20.59 mmol) in THF (0 mL) added dropwise over 5 min. After being allowed to warm to rt, the mixture was quenched with saturated aqueous NH_4Cl and then partitioned between Et_2O and, sequentially, 1 M aqueous HCl and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield the alcohol (4.69 g, 95% yield) as a colorless oil. TLC: R_f (10% MTBE/PE) = 0.42. To a solution of the alcohol (4.69 g, 23.45 mmol) in CH_3CN (100 mL) was added PCC (0.084 g, 0.39 mmol) followed by H_5IO_6 (5.34 g, 6.93 mmol). After 30 min, the mixture was filtered through a short pad of Celite eluting with Et_2O. The filtrate was concentrated, and the residue was chromatographed to yield the ketone **7b** (4.58 g, 72% yield from 1-bromo-4-chlorobenzene) as a yellow oil. TLC: R_f (10% MTBE/PE) = 0.5. ^{1}H NMR, δ: 0.77 (s, 3H), 0.92 (s, 3H), 1.14 (dd, J = 8.6, 7.3 Hz, 2H), 1.47−1.67 (m, 3H), 2.45 (t, J = 7.4 Hz, 2H), 3.68 (s, 2H), 7.11−7.19 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H). ^{13}C NMR, δ: u 208.0, 132.9, 132.7, 49.2, 42.4, 38.3, 21.5; d 129.2, 128.8, 27.0, 22.4. IR (film): 2938, 1712, 1491, 1461, 1407 cm^{-1}. HRMS Calcd $C_{14}H_{19}ClO$ 238.1124. Found: 238.1131.

2-(4-Chlorophenyl)-3,3-dimethylcyclohexanone (2b). To a solution of the ketone **7b** (0.20 g, 0.84 mmol) in toluene (4.0 mL) was added DBU (0.16 g, 1.05 mmol) followed by TIBSA (0.39 g, 1.26 mmol). The mixture was kept in the dark for 30 min. The mixture was then chromatographed directly to yield the diazo ketone **1b** (0.20 g, 92% yield) as orange crystals. TLC: R_f (10% MTBE/PE) = 0.40. ^{1}H NMR, δ: 0.88 (s, 3H), 0.94 (s, 3H), 1.20−1.34 (m, 3H), 1.59 (m, 2H), 1.67−1.78 (m, 2H), 2.60 (t, J = 7.5 Hz, 2H), 7.36−7.43 (d, J = 7.8 Hz, 2H), 7.46−7.52 (d, J = 7.8 Hz, 2H). ^{13}C NMR, δ: u 192.6, 124.7, 120.4, 39.4, 38.4, 22.5; d 132.1, 127.0, 27.9, 22.5. The diazo ketone **1b** (0.20 g, 0.75 mmol) was then taken into a glovebox. To a slurry of $Rh_2(esp)_2$ (0.028 g, 0.037 mmol) in hexanes (10 mL) was added the diazo ketone **1b** in hexanes (10 mL) dropwise over 10 min. After 5 min, the mixture was removed from the glovebox and chromatographed directly to obtain the mixture of cyclized products **2b** and **3b** (0.150 g, 75% yield from **7b**). TLC: R_f (30% MTBE/PE) = 0.62. ^{1}H NMR, δ: 0.89 (s, 3H), 0.94 (s, 3H), 1.70−1.81 (m, 1H), 1.83−1.94 (m, 1H), 1.98−2.12 (m, 2H), 2.40−2.57 (m, 2H), 3.51 (s, 1H), 7.15 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H). ^{13}C NMR, δ: u 209.2, 133.2, 132.4, 41.5, 40.8, 40.7, 25.6; d 131.6, 127.6, 27.5, 66.6, 30.5, 21.3. IR (film): 2948, 2859, 1707, 1491, 1451 cm^{-1}. HRMS Calcd $C_{14}H_{17}ClO$ 236.0968. Found: 236.0962. GC−MS R_t for **2b** was 11.94 min, and for **3b**, the R_t was 11.83 min. The integrated ratio of the peaks was 15.6:1.0. Upon closer inspection of the ^{13}C NMR, we observed a peak at δ 216.9 corresponding to the cyclopentanone.

1-(3-Methoxyphenyl)-6-methylheptan-2-one (7c). To a solution of 3-bromoanisole (4.00 g, 21.4 mmol) in dry Et_2O (100 mL) were added Mg turnings (0.77 g, 32.0 mmol). A chip of I_2 was added, and the mixture was brought to reflux. After the reaction initiated, a brown color developed, the heating was stopped, and the reaction was allowed to complete. After the exotherm stopped and most of the Mg was consumed, the mixture was cooled to 0 °C. Allyl bromide (3.10 g, 25.7 mmol) was added neat dropwise over 5 min. The mixture was allowed to warm to rt for 2 h. The mixture was quenched with saturated aqueous NH_4Cl and then partitioned between Et_2O and, sequentially, 1 M aqueous HCl and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield the alkene **5c** (3.00 g, 95% yield) as a colorless oil. TLC: R_f (10% MTBE/PE) = 0.69. ^{1}H NMR, δ: 3.37 (d, J = 6.7 Hz, 2H), 3.80 (s, 3H), 5.12−5.06 (m, 2H), 5.96 (ddt, J = 6.6, 10.5, 16.9 Hz, 1H), 6.74 (s, 1H), 6.80−6.76 (m, 2H), 7.23−7.19 (m, 1H). ^{13}C NMR, δ: u 159.6, 142.7, 115.9, 40.28; d 137.2, 129.4, 121.0, 114.2, 111.5, 55.16. The ^{1}H NMR data matches published spectra.[19]

To a solution of the alkene **5c** (3.00 g, 20.28 mmol) in dry CH_2Cl_2 (100 mL) at 0 °C was added *m*CPBA (4.19 g, 24.33 mmol). After stirring at 0 °C for 2 h, the mixture mixture was quenched with 1 M aqueous NaOH and then partitioned between CH_2Cl_2 and, sequentially, water and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield the epoxide **6c** (3.29 g, 99% yield) as a colorless oil. TLC: R_f (5% MTBE/PE) = 0.33. ^{1}H NMR, δ: 2.59 (dd, J = 4.9, 2.6 Hz, 1H), 2.77−2.85 (m, 2H), 2.88−3.00 (m, 1H), 3.13−3.21 (m, 1H), 3.83 (s, 3H), 6.78−6.91 (m, 3H), 7.20−7.27 (m, 1H). ^{13}C NMR, δ: u 159.7, 138.7, 46.9, 38.8; d 129.5, 121.3, 114.7, 111.9, 55.3, 52.4. IR (film): 3078, 2939, 1600, 1489, 1259 cm^{-1}. The ^{1}H NMR data matches published spectra.[20]

To a solution of 1-bromo-3-methylbutane (6.06 g, 40.15 mmol) in dry THF (100 mL) were added Mg turnings (1.20 g, 50.17 mmol). The reaction was initiated with an I_2 chip and heating to reflux. Once the exotherm stopped, the mixture was cooled to −30 °C. A CuBr·Me_2S complex (0.412 g, 2.01 mmol) was added, followed by a solution of the epoxide (3.29 g, 20.07 mmol) in THF (50 mL) added dropwise

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over 5 min. After being allowed to warm to rt, the mixture was quenched with saturated aqueous NH_4Cl and then partitioned between Et_2O and, sequentially, 1 M aqueous HCl and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield the alcohol (4.64 g, 98% yield) as a yellow oil. TLC: R_f (30% MTBE/PE) = 0.63. To a solution of the alcohol (4.64 g, 19.66 mmol) in CH_3CN (100 mL) was added PCC (0.084 g, 0.0.39 mmol) followed by H_5IO_6 (5.38 g, 23.59 mmol). After 30 min, the mixture was filtered through a short pad of Celite eluting with Et_2O. The filtrate was concentrated, and the residue was chromatographed to yield the ketone **7c** (3.34 g, 67% yield from 3-bromoanisole) as a yellow oil. TLC: R_f (30% MTBE/PE) = 0.69. ^{1}H NMR, δ: 0.84 (s, 3H), 0.87 (s, 3H), 1.07−1.18 (m, 2H), 1.44−1.63 (m, 4H), 2.44 (t, J = 7.4 Hz, 2H), 3.67 (s, 2H), 3.82 (s, 3H), 6.73−6.88 (m, 3H), 7.26 (d, J = 7.8 Hz, 1H). ^{13}C NMR, δ: u 208.6, 159.7, 135.8, 50.2, 42.1, 38.3, 21.6; d 129.7, 121.7, 114.9, 112.4, 55.2, 27.8, 22.4. IR (film): 2948, 1707, 1594, 1486, 1456 cm^{-1}. HRMS Calcd $C_{15}H_{22}O_2$ 234.1620. Found: 234.1612.

2-(3-Methoxyphenyl)-3,3-dimethylcyclohexanone (2c). To a solution of the ketone **7c** (0.200 g, 0.85 mmol) in toluene (4.0 mL) was added DBU (0.17 g, 1.18 mmol) followed by TIBSA (0.40 g, 1.28 mmol). The mixture was kept in the dark for 30 min. The mixture was then chromatographed directly to yield the diazo ketone **1c** (0.156 g, 70% yield) as orange crystals. TLC: R_f (30% MTBE/PE) = 0.69. ^{1}H NMR, δ: 0.91 (s, 3H), 0.93 (s, 3H), 1.19−1.34 (m, 2H), 1.52−1.64 (m, 2H), 1.64−1.78 (m, 2H), 2.60 (t, J = 7.4 Hz, 2H), 3.95 (s, 3H), 6.82 (dd, J = 8.3, 2.2 Hz, 2H), 7.03 (d, J = 7.8 Hz, 2H), 7.20−7.25 (m, 1H). ^{13}C NMR, δ: u 192.6, 160.0, 124.1, 39.5, 38.4, 22.5; d 129.9, 121.9, 115.2, 112.6, 55.3, 27.9, 22.5. The diazo ketone **1c** (0.15 g, 0.57 mmol) was then taken into a glovebox. To a slurry of $Rh_2(esp)_2$ (0.021 g, 0.028 mmol) in hexanes (10 mL) was added the diazo ketone **1c** in hexanes (10 mL) dropwise over 10 min. After 5 min, the mixture was removed from the glovebox and chromatographed directly to obtain the cyclized products **2c** with a little **3c** (0.097 g, 48% yield from **7c**) as a white solid. Mp = 54−55 °C. TLC: R_f (30% MTBE/PE) = 0.66. ^{1}H NMR, δ: 0.89 (s, 3H), 0.96 (s, 3 H), 1.71−1.91 (m, 2H), 2.03 (dt, J = 6.2, 3.9 Hz, 2H), 2.38−2.59 (m, 2H), 3.48 (s, 1H), 3.82 (s, 3H), 6.73−6.87 (m, 3H), 7.25 (t, J = 7.8 Hz, 1H). ^{13}C NMR, δ: u 209.5, 158.7, 136.4, 41.5, 40.7, 40.6, 22.3; d 132.4, 128.3, 123.6, 117.3, 111.9, 67.4, 55.1, 30.6, 22.5. IR (film): 2954, 2870, 1711, 1601, 1583 cm^{-1}. HRMS Calcd $C_{15}H_{20}O_2$ 232.1463. Found: 232.1468. GC−MS R_t for **2c** was 11.59 min, and for **3c**, R_t was 11.53 min. By integration, the ratio of the peaks was 8.6:1.0. Upon closer inspection of the ^{13}C NMR we observed a peak at δ 217.6 corresponding to the cyclopentanone.

6-Methyl-1-phenylheptan-2-one (7d). To a solution of bromobenzene (4.00 g, 25.5 mmol) in dry Et_2O (100 mL) were added Mg turnings (0.92 g, 38.2 mmol). A chip of I_2 was added, and the mixture was brought to reflux. After the reaction initiated, a brown color developed, the heating was stopped and the reaction was allowed to complete. After the exotherm stopped and most of the Mg was consumed, the mixture was cooled to 0 °C. Allyl bromide (3.69 g, 30.6 mmol) was added neat dropwise over 5 min. The mixture was allowed to warm to rt for 2 h. The mixture was quenched with saturated aqueous NH_4Cl and then partitioned between Et_2O and, sequentially, 1 M aqueous HCl and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield the alkene **5d** (2.97 g, 99% yield) as a colorless oil. TLC: R_f (5% MTBE/PE) = 0.80. ^{1}H NMR, δ: 3.37 (d, J = 6.7 Hz, 2H), 5.10−5.03 (m, 2H), 6.03−5.89 (m, 1H), 7.30−7.16 (m, 5H). ^{13}C NMR, δ: u 120.2, 115.8, 40.2; d 137.5, 128.8, 127.1, 126.7. The ^{1}H NMR data matches published spectra.[20]

To a solution of the alkene **5d** (2.97 g, 25.19 mmol) in dry CH_2Cl_2 (100 mL) at 0 °C was added *m*CPBA (5.21 g, 30.23 mmol). After stirring at 0 °C for 2 h, the mixture mixture was quenched with 1 M aqueous NaOH and then partitioned between CH_2Cl_2 and, sequentially, water and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield the epoxide **6d** (3.34 g, 99% yield) as a colorless oil. TLC: R_f (5% MTBE/PE) = 0.38. ^{1}H NMR, δ: 2.58 (dd, J = 4.9, 2.6 Hz, 1H), 2.78−2.89 (m, 2H), 2.91−3.01 (m, 1H), 3.19 (dd, J = 3.5, 2.8 Hz, 1H), 7.26−7.30 (m, 3H), 7.34 (d, J = 6.5 Hz, 2H). ^{13}C NMR, δ: u 137.1, 46.9, 38.7; d 129.0, 128.5, 126.6, 52.4. IR (film): 3029, 2917, 1496, 1459 cm^{-1}. The ^{1}H NMR data matches published spectra.[21]

To a solution of 1-bromo-3-methylbutane (7.53 g, 49.86 mmol) in dry THF (150 mL) were added Mg turnings (1.49 g, 62.35 mmol). The mixture was initiated with an I_2 chip and heating to reflux. Once the exotherm stopped, the mixture was cooled to −30 °C. A CuBr·Me_2S complex (0.51 g, 2.49 mmol) was added, followed by a solution of the epoxide **6d** (3.34 g, 24.94 mmol) in THF (50 mL) added dropwise over 5 min. After being held overnight, the mixture was quenched with saturated aqueous NH_4Cl and then partitioned between Et_2O and, sequentially, 1 M aqueous HCl and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield the alcohol (4.36 g, 85% yield) as a colorless oil. TLC: R_f (10% MTBE/PE) = 0.50. To a solution of the alcohol (4.36 g, 21.20 mmol) in CH_3CN (20 mL) was added PCC (0.091 g, 0.424 mmol) followed by H_5IO_6 (5.80 g, 25.44 mmol). After 30 min, the mixture was filtered through a short pad of Celite eluting with Et_2O. The filtrate was concentrated, and the residue was chromatographed to yield the ketone **7d** (3.09 g, 75% yield from bromobenzene) as a clear oil. TLC: R_f (10% MTBE/PE) = 0.55. ^{1}H NMR, δ: 0.83 (s, 3H), 0.87 (s, 3H), 1.08−1.16 (m, 2H), 1.45−1.63 (m, 3H), 2.45 (t, J = 7.5 Hz, 2H), 3.70 (s, 2H), 7.20−7.25 (m, 3H), 7.35 (d, J = 7.6 Hz, 2H). ^{13}C NMR, δ: u 208.7, 129.4, 50.1, 42.2, 38.3, 21.6; d 129.4, 128.7, 126.9, 27.8, 22.4. IR (film): 2938, 1707, 1594, 1486, 1461 cm^{-1}. HRMS Calcd $C_{14}H_{20}O$ 204.1514. Found: 204.1519.

3,3-Dimethyl-2-phenylcyclohexanone (2d). To a solution of the ketone **7d** (0.20 g, 0.98 mmol) in toluene (5.0 mL) was added DBU (0.20 g, 1.31 mmol) followed by TIBSA (0.46 g, 1.48 mmol). The mixture was kept in the dark for 30 min. The mixture was then chromatographed directly to yield the diazo ketone **1d** (0.21 g, 95% yield) as orange crystals. TLC: R_f (10% MTBE/PE) = 0.46. ^{1}H NMR, δ: 0.88 (s, 3H), 0.94 (s, 3H), 1.21−1.31 (m, 3H), 1.58 (m, 2H), 1.67−1.78 (m, 2H), 2.60 (t, J = 7.4 Hz, 2H), 7.27−7.30 (m, 1H), 7.40−7.47 (d, J = 7.8 Hz, 2H), 7.54 (d, J = 7.8 Hz, 2H). ^{13}C NMR, δ: u 132.1, 124.7, 39.1, 29.3, 27.1, 25.7; d 131.9, 128.7, 124.0, 25.7, 17.7. The diazo ketone **1d** (0.224 g, 0.91 mmol) was then taken into a glovebox. To a slurry of $Rh_2(esp)_2$ (0.034 g, 0.045 mmol) in hexanes (10 mL) was added the diazo in hexanes (10 mL) dropwise over 10 min. After 5 min, the mixture was removed from the glovebox and chromatographed directly to obtain the cyclized products **2d** with a little **3d** (0.150 g, 75% yield from **7d**) as a clear oil. TLC: R_f (30% MTBE/PE) = 0.5. ^{1}H NMR, δ: 0.88 (s, 3H), 0.95 (s, 3H), 1.72−1.82 (m, 1H), 1.84−1.94 (m, 1H), 1.97−2.09 (m, 2H), 2.40−2.59 (m, 2H), 7.20−7.23 (m, 2H), 7.27−7.36 (m, 3H). ^{13}C NMR, δ: u 209.6, 134.8, 41.5, 40.8, 40.7, 23.8; d 131.1, 126.9, 126.8, 67.4, 29.8, 17.5. IR (film): 3036, 2948, 2869, 1707, 1486 cm^{-1}. HRMS Calcd $C_{14}H_{18}O$ 202.1358. Found: 202.1359. GC−MS R_t for **2d** was 10.89 min, and for **3d**, the R_t was 10.81 min. Integration of the peaks found a 13.1:1.0 ratio of **2d** versus **3d**. Upon closer inspection of the ^{13}C NMR, we observed a peak at δ 217.5 corresponding to the cyclopentanone.

1-(4-Bromophenyl)oct-7-en-2-ol (10). To a solution of 1,7-octadiene (5.00 g, 45.5 mmol) in CH_2Cl_2 (200 mL) was added *m*CPBA (8.60 g, 49.9 mmol) The mixture was stirred at 0 °C for 2 h. The mixture was quenched with 1 M aqueous NaOH and then partitioned between brine and CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and concentrated. The residue was then chromatographed to yield the mono epoxide **9** (5.15 g, 90% yield) as a clear oil. TLC: R_f (10% MTBE/PE) = 0.58. ^{1}H NMR, δ: 1.41−1.64 (m, 6H), 2.09 (d, J = 6.3 Hz, 2H), 2.49 (dd, J = 5.1, 2.8 Hz, 1H), 2.71−2.81 (m, 1H), 2.93 (dd, J = 3.7, 2.9 Hz, 1H), 4.91−5.09 (m, 2H), 5.83 (ddt, J = 17.0, 10.3, 6.7 Hz, 1H). ^{13}C NMR, δ: u 114.5, 47.1, 33.6, 32.3, 28.6, 25.4; d 138.7, 52.3. IR (film): 3046, 2987, 2918, 2850, 1638 cm^{-1}. The ^{1}H NMR data matches published spectra.[22]

To a solution of 1,4-dibromobenzene (19.29 g, 81.74 mmol) in Et_2O (200 mL) were added Mg turnings (2.45 g, 102.17 mmol). The reaction was initiated with an I_2 chip and brought to reflux. Once the exotherm stopped, the mixture was cooled to −30 °C. A CuBr·Me_2S complex (0.838 g, 4.09 mmol) was added, followed by a solution of the epoxide **9** (5.15 g, 40.87 mmol) in Et_2O (100 mL) added dropwise

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over 5 min. The mixture was allowed to warm to rt and then quenched with saturated aqueous NH_4Cl and then partitioned between Et_2O and, sequentially, 1 M aqueous HCl and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield the alcohol **10** (9.23 g, 72% yield from 1,7-octadiene) as a white solid. Mp = 65−68 °C. TLC: R_f (30% MTBE/PE) = 0.5. ^{1}H NMR, δ: 1.38−1.56 (m, 7H), 2.02−2.14 (m, 2H), 2.64 (dd, J = 13.6, 8.3 Hz, 1H), 2.80 (dd, J = 13.6, 4.3 Hz, 1H), 3.81 (dt, J = 8.0, 3.9 Hz, 1H), 4.91−5.08 (m, 2H), 5.83 (ddt, J = 17.0, 10.3, 6.7 Hz, 1H), 7.12 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.3 Hz, 2H). ^{13}C NMR, δ: u 137.6, 120.3, 114.5, 43.3, 36.6, 33.7, 28.8, 25.1; d 138.3, 131.5, 131.1, 72.3. IR (film): 3344, 3266, 2918, 2866, 2348 cm^{-1}. HRMS Calcd $C_{14}H_{19}BrO$ 282.0619. Found: 282.0621.

7-(4-Bromophenyl)-6-hydroxyheptanal (11). To a solution of the alcohol **10** (1.00 g, 3.53 mmol) in CH_2Cl_2:MeOH (6:1, 20 mL) at −78 °C was sparged O_3. Once the solution turned a blue color, the mixture was quenched with PPh_3 (0.92 g, 3.53 mmol). The residue was chromatographed directly to yield the aldehyde **11** (0.99 g, 99% yield) as a white solid. Mp = 72−75 °C. TLC: R_f (60% MTBE/PE) = 0.36. ^{1}H NMR, δ: 1.39−1.76 (m, 6H), 2.48 (td, J = 7.2, 1.5 Hz, 2H), 2.57−2.70 (m, 1H), 2.73−2.85 (m, 1H), 3.82 (d, J = 3.8 Hz, 1H), 7.11 (d, J = 8.3 Hz, 2 H), 7.46 (d, J = 8.3 Hz, 2H), 9.80 (s, 1H). ^{13}C NMR, δ: u 137.4, 120.4, 43.8, 43.4, 36.4, 25.2, 21.9; d 202.6, 131.0, 131.2, 72.1. IR (film): 3341 (broad), 2916, 2850, 2722, 1707, 1481 cm^{-1}. HRMS Calcd $C_{13}H_{17}BrO_2$ 284.0412. Found: 284.0418.

1-(4-Bromophenyl)-8-methylnon-7-en-2-ol (12). To a solution of the alcohol **11** (0.40 g, 1.40 mmol) in THF (5.0 mL) at 0 °C was added potassium *tert*-butoxide (KO-*t*-Bu) (0.63 g, 5.60 mmol). The solution was stirred for 10 min, and isopropyltriphenylphosphonium bromide (1.21 g, 2.80 mmol) was added. After being allowed to warm to rt, the mixture was quenched with 1 M aqueous HCl and then partitioned between Et_2O and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield the alkene **12** (0.231 g, 53% yield) as a white solid. Mp = 50−53 °C. TLC: R_f (60% MTBE/PE) = 0.7. ^{1}H NMR, δ: 1.37 (dd, J = 3.5, 1.5 Hz, 3H), 1.44−1.54 (m, 4H), 1.61 (s, 3H), 1.71 (s, 3H), 2.00 (d, J = 6.8 Hz, 2H), 2.63 (dd, J = 13.6, 8.3 Hz, 1H), 2.79 (dd, J = 13.6, 4.3 Hz, 1H), 3.80 (bs, 1H), 5.07−5.20 (m, 1H), 7.12 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2 H). ^{13}C NMR, δ: u 137.6, 120.3, 43.3, 36.8, 29.8, 27.9, 25.7; d 131.5, 131.1, 124.5, 72.7, 25.3, 17.7. IR (film): 3390 (broad), 2927, 2856, 1687, 1487 cm^{-1}. HRMS Calcd $C_{16}H_{23}BrO$ 310.0923. Found: 310.0926.

1-(4-Bromophenyl)-8-methylnon-7-en-2-one (13). To a solution of the alcohol **12** (0.230 g, 0.79 mmol) in CH_3CN (3.0 mL) was added PCC (0.003 g, 0.014 mmol) followed by H_5IO_6 (0.18 g, 0.81 mmol). After 30 min, the mixture was filtered through a short pad of Celite eluting with Et_2O. The filtrate was concentrated, and the residue was chromatographed to yield the ketone **13** (0.219 g, 95% yield) as a yellow oil. TLC: R_f (30% MTBE/PE) = 0.69. ^{1}H NMR, δ: 1.17−1.40 (m, 3H), 1.69 (s, 3H), 1.69 (s, 3H), 1.96 (q, J = 7.3 Hz, 2H), 2.47 (t, J = 7.3 Hz, 2H), 3.66 (s, 2H), 5.08 (tt, J = 7.2, 1.3 Hz, 1H), 7.09 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.6 Hz, 2H). ^{13}C NMR, δ: u 207.8, 133.2, 121.0, 49.2, 42.1, 29.2, 27.7, 23.3; d 131.7, 131.1, 23.5, 17.7. IR (film): 2926, 2850, 1712, 1487, 1447 cm^{-1}. HRMS Calcd $C_{16}H_{21}BrO$ 308.0776. Found: 308.0764.

2-(4-Bromophenyl)-3-(2-methylprop-1-enyl)cyclohexanone (2e). To a solution of the ketone **13** (0.120 g, 0.38 mmol) in toluene (2.0 mL) was added DBU (0.09 g, 0.59 mmol) followed by TIBSA (0.19 g, 0.61 mmol). The mixture was kept in the dark for 30 min. The mixture was then chromatographed directly to yield the diazo ketone **1e** (0.063 g, 50% yield) as orange crystals. TLC: R_f (30% MTBE/PE) = 0.76. ^{1}H NMR, δ: 1.41 (q, J = 7.5 Hz, 2H), 1.60 (s, 3H), 1.68 (s, 3H), 2.03 (q, J = 7.3 Hz, 2H), 2.38 (s, 1H), 2.61 (t, J = 7.5 Hz, 2H), 5.12 (ddd, J = 7.1, 5.8, 1.3 Hz, 1H), 7.43 (d, J = 8.8 Hz, 2H), 7.50−7.58 (d, J = 8.8 Hz, 2H). ^{13}C NMR, δ: u 131.9, 124.0, 39.1, 29.4, 27.8, 24.2; d 132.1, 124.0, 25.8, 17.7. The diazo ketone **1e** (0.069 g, 0.188 mmol) was then taken into a glovebox. To a slurry of $Rh_2(esp)_2$ (0.008 g, 0.010 mmol) in hexanes (10 mL) was added the diazo ketone **1e** in hexanes (10 mL) dropwise over 10 min. After 5 min, the mixture was removed from the glovebox and chromatographed directly to obtain the cyclized products **2e** with a little **3e** as a colorless oil (0.051 g, 43% yield from **13**). TLC: R_f (30% MTBE/PE) = 0.66. ^{1}H NMR, δ: 1.34 (s, 3H), 1.51 (s, 3H), 1.62−1.74 (m, 1H), 1.79−2.01 (m, 2H), 2.09−2.25 (m, 1H), 2.43−2.63 (m, 2H), 2.78−2.93 (m, 1H), 3.33 (d, J = 11.6 Hz, 1H), 4.84 (dt, J = 9.4, 1.26 Hz, 1H), 6.92 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.3 Hz, 2H). ^{13}C NMR, δ: u 209.3, 136.5, 132.2, 120.5, 41.3, 32.8, 23.3; d 131.2, 130.7, 128.4, 62.3, 45.2, 25.5, 17.5. IR (film): 2928, 2859, 1707, 1486, 1447 cm^{-1}. HRMS Calcd $C_{16}H_{19}BrO$ 306.0619. Found: 306.0625. GC−MS R_t for **2e** was 12.93 min, and for **3e**, the R_t was 13.10 min. Integration of the peaks showed a 11.5:1.0 ratio of **2e** to **3e**. Upon closer inspection of the ^{13}C NMR, we observed a peak at δ 217.4 corresponding to the cyclopentanone.

1-(4-Bromophenyl)-6-(4-methoxyphenyl)hexan-2-one (16). To a stirred solution of 3-(4-methoxyphenyl)propan-1-ol **14** (2.00 g, 13.15 mmol) in Et_2O (50 mL) was added PBr_3 (1.33 g, 4.98 mmol) at 0 °C. The mixture was heated to reflux for 2.5 h and then quenched with water and partitioned between Et_2O and aqueous $NaHCO_3$. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford the bromide **15** (1.77 g, 63% yield) as a colorless oil. TLC: R_f (MTBE/petroleum ether = 30%) = 0.77. ^{1}H NMR, δ: 2.15 (m, 2H), 2.72 (t, J = 6.8 Hz, 2H), 3.38 (t, J = 6.8 Hz, 2H), 3.79 (s, 3H), 6.82−6.91 (m, 2H), 7.10−7.26 (m, 2H). ^{13}C NMR, δ: u 158.0, 132.6, 34.4, 33.1, 33.0; d 129.5 113.9, 55.3. The ^{1}H NMR data matches published spectra.[23]

To a stirred solution of the bromide **15** (1.77 g, 8.27 mmol) in THF (50 mL) were added Mg turnings (0.396 g, 16.54 mmol) and an I_2 chip at rt. The reaction mixture was heated to reflux for 1 h, and then CuBr·Me_2S (0.016 g, 0.82 mmol) powder was added at −30 °C. The reaction mixture was stirred for 5 min at this temperature, and the cooling bath was removed. After 10 min, the cooling bath was replaced, and a solution of the epoxide **6a** (1.75 g, 8.27 mmol) in THF (5.0 mL) was added to the mixture during 1 min. The reaction mixture was stirred for 20 min at −30 to −20 °C. The reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous NH_4Cl. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford the alcohol as a colorless oil. To a stirred solution of the alcohol was added Dess−Martin periodinane (3.74 g, 8.80 mmol) at 0 °C. After an additional 3 h at rt, the reaction mixture was filtered through a pad of silica gel and washed with Et_2O. The filtrate was concentrated, and the residue was chromatographed to afford the ketone **16** (2.04 g, 43% yield from **14**) as a colorless oil. TLC: R_f (MTBE/petroleum ether = 10%) = 0.38. ^{1}H NMR, δ: 1.51−1.61 (m, 4H), 2.45 (t, J = 7.2 Hz, 2H), 2.52 (t, J = 7.2 Hz, 2H), 3.61 (s, 2H), 3.78 (s, 3H), 6.80−6.83 (m, 2H), 7.03−7.06 (m, 4H), 7.42−7.46 (m, 2H). ^{13}C NMR, δ: u 207.6, 157.8, 134.2, 133.2, 121.0, 49.3, 42.0, 34.7, 31.0, 23.3; d 131.8, 131.1, 129.2, 113.8, 55.3. IR (film): 3429, 2934, 1712, 1643, 1512 cm^{-1}. HRMS Calcd $C_{19}H_{22}BrO_2$ [M + H] 361.0803. Found: 361.0816.

***cis*-2-(4-Bromophenyl)-3-(4-methoxyphenyl)cyclohexanone (2f).** To a stirred solution of the ketone (0.250 g, 0.692 mmol) in toluene (8.0 mL) was added TIBSA (0.26 g, 0.84 mmol) at rt. DBU (0.32 g, 2.10 mmol) was added dropwise over 1 min. The reaction mixture was stirred for 20 min at rt and then chromatographed to afford the diazo ketone **1f** (0.220 g, 83% yield) as a yellow oil. TLC: R_f (MTBE/petroleum ether = 10%) = 0.34. ^{1}H NMR, δ: 1.63−1.78 (m, 4H), 2.57−2.61 (m, 4H), 3.78 (s, 3H), 6.80−6.83 (m, 2H), 7.06−7.09 (m, 2H), 7.38 (d, J = 7.6 Hz, 2H), 7.50−7.53 (m, 2 H). ^{13}C NMR, δ: u 192.3, 157.8, 134.1, 124.7, 120.5, 39.0, 34.7, 31.1, 24.1; d 134.1, 129.3, 127.0, 113.8, 55.3. The diazo ketone **1f** (0.220 g, 0.57 mmol) was then taken into a glovebox. To a slurry of $Rh_2(esp)_2$ (0.021 g, 0.028 mmol) in hexanes (10 mL) was added the diazo ketone **1f** in hexanes (10 mL) dropwise over 10 min. After 5 min, the mixture was removed from the glovebox and chromatographed directly to obtain the cyclized product **2f** (0.186 g, 60% yield from **16**) as a colorless oil. TLC: R_f (MTBE/petroleum ether = 20%) = 0.29. ^{1}H NMR, δ: 1.92−1.96 (m, 1H), 2.10−2.21 (m, 3H), 2.57−2.70 (m, 2H), 3.57−3.61 (m, 1H), 3.74 (s, 3H), 3.98 (d, J = 5.6 Hz, 1H), 6.73−6.76 (m, 2H), 6.85−6.92 (m, 4H), 7.23−7.26 (m, 2H). ^{13}C NMR, δ: u 210.1, 158.2, 135.4, 133.2, 120.8, 40.8, 29.6, 23.2; d 131.4, 131.0, 129.2, 113.7, 60.5, 55.2, 47.9. IR (film): 2934, 1706, 1609, 1512, 1248, 808 cm^{-1}. HRMS [M + Na]

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Calcd $C_{19}H_{19}BrO_2Na$ 381.0466. Found: 381.0461. Further elution gave the trans cyclohexanone as a colorless oil (3 mg, 4% yield). TLC: R_f (MTBE/petroleum ether = 20%) = 0.26. GC−MS analysis showed only the cyclohexanone product.

***trans*-2-(4-Bromophenyl)-3-(4-methoxyphenyl)cyclohexanone (2f′).** To a stirred solution of **2f** (0.020 g, 0.057 mmol) in CH_2Cl_2 (0.5 mL) was added a few drops of DBU at rt. After 1 h, silica gel was added, the mixture was concentrated, and the residue was chromatographed to afford the cyclohexanone **2f′** as a colorless oil (0.012 g, 63% yield). TLC: R_f (MTBE/petroleum ether = 20%) = 0.26. ^{1}H NMR, δ: 1.84−2.13 (m, 3H), 2.20−2.25 (m, 1H), 2.57−2.63 (m, 2H), 3.11 (td, J = 11.6 Hz, 4.0 Hz, 1H), 3.71−3.78 (m, 4H), 6.67−6.69 (m, 2H), 6.78−6.81 (m, 2H), 6.92−6.94 (m, 2H), 7.25−7.28 (m, 2H). ^{13}C NMR, δ: u 208.4, 158.0, 135.9, 134.8, 120.5, 42.0, 34.8, 26.1; d 131.2, 131.1, 128.1, 113.8, 63.4, 55.1, 51.6. IR (film): 2931, 1706, 1611, 1512, 1248, 802 cm^{-1}. HRMS [M + Na] Calcd $C_{19}H_{19}BrO_2Na$ 381.0466. Found: 381.0461.

4-(Benzyloxy)-1-(4-bromophenyl)butan-2-one (19). To a slurry of NaH (4.40 g, 38.3 mmol) in THF (100 mL) and TBAI (0.51 g, 1.38 mmol) was added homoallylic alcohol **17** (2.00 g, 27.7 mmol). Benzyl bromide (9.49 g, 55.5 mmol) was added neat dropwise over 1 min. The solution was refluxed for 3 h, quenched with 1 M aqueous HCl, and then partitioned between Et_2O and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was dissolved into CH_2Cl_2 (100 mL) at 0 °C, and *m*CPBA (1.40 g, 8.14 mmol) was added. The mixture was stirred at 0 °C for 3 h, quenched with 1 M aqueous NaOH, and then partitioned between CH_2Cl_2 and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography to yield the epoxide **18** (3.89 g, 79% yield) as a clear oil. TLC: R_f (MTBE/petroleum ether = 30%) = 0.26. ^{1}H NMR, δ: 1.82−1.75 (m, 1H), 1.96−1.90 (m, 1H), 2.54 (dd, J = 5.0, 2.8 Hz, 1H), 2.80 (t, J = 4.3 Hz, 1H), 3.11−3.07 (m, 1H), 3.67−3.60 (m, 2H), 4.54 (s, 2H), 7.23−7.19 (m, 5H). ^{13}C NMR, δ: 138.2, 128.4, 127.6, 73.1, 67.0, 50.1, 47.1, 32.9. The ^{1}H NMR data matches published spectra.[24]

To a stirred solution of 1,4-dibromobenzene (3.92 g, 16.62 mmol) in THF (60 mL) were added Mg turnings (0.797 g, 33.24 mmol) and I_2 at rt. The reaction mixture was heated to reflux for 1 h and CuBr·Me_2S (0.332 g, 1.62 mmol) powder was added at −30 °C. The reaction mixture was stirred for 5 min at this temperature, and the cooling bath was removed. After 10 min, the cooling bath was replaced, and a solution of the epoxide **18** (3.89 g, 16.62 mmol) in THF (30 mL) was added during 1 min. The reaction mixture was stirred for 20 min at −30 °C. The reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous NH_4Cl. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford the alcohol as a colorless oil. To a stirred solution of the alcohol was added Dess−Martin periodinane (4.11 g, 17.00 mmol) at 0 °C. After an additional 3 h at rt, the reaction mixture was filtered through a pad of silica gel and washed with Et_2O. The filtrate was concentrated, and the residue was chromatographed to afford the ketone **19** (3.93 g, 44% yield) as a clear oil. TLC: R_f (MTBE/petroleum ether = 20%) = 0.37. ^{1}H NMR, δ: 2.71−2.77 (m, 2H), 3.67−3.77 (m, 4H), 4.49 (s, 2H), 7.03−7.07 (m, 2H), 7.26−7.36 (m, 5H), 7.42−7.45 (m, 2H). ^{13}C NMR, δ: u 206.0, 138.0, 132.9, 121.1, 73.3, 65.3, 49.8, 42.3; d 131.8, 131.3, 128.4, 127.7. IR (film): 2859, 1713, 1101, 736 cm^{-1}. HRMS [M + Na] Calcd $C_{17}H_{17}BrO_2Na$ 355.0310. Found: 355.0301.

***cis*-3-(4-Bromophenyl)tetrahydro-2-phenylpyran-4-one (2g).** To a stirred solution of the ketone (0.250 g, 0.759 mmol) in toluene (8.0 mL) was added TIBSA (0.26 g, 0.84 mmol) at rt. DBU (0.32 g, 2.10 mmol) was added dropwise over 1 min. The reaction mixture was stirred for 20 min at rt and then chromatographed to afford the diazo ketone **1g** (0.224 g, 83% yield) as a yellow oil. TLC: R_f (MTBE/petroleum ether = 10%) = 0.34. ^{1}H NMR, δ: 2.86 (m, 2H), 3.85 (m, 2H), 4.51 (s, 2H), 7.61 (m, 9H). ^{13}C NMR, δ: u 190.5, 138.0, 124.7, 120.6, 73.4, 66.0, 39.5; d 132.1, 128.4, 127.74, 127.66, 127.4. The diazo ketone **1g** (0.22 g, 0.629 mmol) was then taken into a glovebox. To a slurry of $Rh_2(esp)_2$ (0.021 g, 0.028 mmol) in hexanes (10 mL) was added the diazo ketone **1g** in hexanes (10 mL) dropwise over 10 min. After 5 min, the mixture was removed from the glovebox and chromatographed directly to obtain the cyclized product **2g** (0.120 g 48% yield from **19**). TLC: R_f (MTBE/petroleum ether = 20%) = 0.40. ^{1}H NMR, δ: 2.36−2.40 (m, 1H), 2.99−3.08 (m, 1H), 3.95−4.01 (m, 2H), 4.60−4.64 (m, 1H), 5.08 (d, J = 3.2 Hz, 1H), 7.19−7.32 (m, 9H). ^{13}C NMR, δ: u 205.7, 138.0, 133.6, 121.4, 67.0, 38.5; d 131.5, 131.4, 128.2, 127.3, 125.4, 81.3, 62.3. IR (film): 2970, 2859, 1714, 1486, 1166, 723 cm^{-1}. HRMS Calcd $C_{17}H_{15}BrO_2$ [M+] 330.0255. Found: 330.0249. Upon closer inspection of the ^{13}C NMR, we observed a peak at δ 217.6 corresponding to the cyclopentanone.

***trans*-3-(4-Bromophenyl)tetrahydro-2-phenylpyran-4-one (2g′).** To a stirred solution of cylohexanone **2f** (0.020 g, 0.05 mmol) in CH_2Cl_2 (1 mL) was added a few drops of DBU. After stirring for 2 h at rt, the solution was chromatographed directly to obtain the trans product **2g′** (0.020 g, 100% yield). TLC: R_f (MTBE/petroleum ether = 20%) = 0.32. ^{1}H NMR, δ: 2.66 (dd, J = 14.8 Hz, 1.2 Hz, 1H), 2.95−3.03 (m, 1H), 3.80 (d, J = 10.0 Hz, 1H), 4.03−4.09 (m, 1H), 4.52−4.69 (m, 1H), 4.80 (d, J = 10.0 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 7.10−7.42 (m, 7H). ^{13}C NMR, δ: u 204.9, 138.9, 132.9, 121.3, 67.3, 42.4; d 131.5, 131.4, 128.36, 128.31, 126.7, 86.2, 64.8. IR (film): 2970, 2859, 1714, 1486, 1166, 723 cm^{-1}. HRMS: Calcd $C_{17}H_{16}BrO_2$ [M + H] 331.0334. Found: 331.0324.

(1*S*,2*R*)-2-(3-methoxyphenyl)-3,3-dimethylcyclohexanol (20). To a solution of the ketone (0.260 g, 1.13 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added diisobutylaluminum hydride (DIBAL-H) (20% in toluene) (4.70 mL, 5.65 mmol) dropwise over 5 min. After 30 min, the mixture was quenched with 1 M aqueous HCl and then partitioned between CH_2Cl_2 and 1 M aqueous HCl. The organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to obtain the alcohol **20** (0.186 g, 71% yield) as a clear oil. TLC: R_f (30% MTBE/PE) = 0.66. ^{1}H NMR, δ: 0.92 (s, 3H), 1.02 (s,3 H), 1.29−1.40 (m, 2H), 1.65−1.83 (m, 3H), 1.91 (dt, J = 8.7, 4.2 Hz, 1H), 2.59 (d, J = 3.8 Hz, 1H), 3.83 (s, 3H), 4.04−4.24 (m, 1H), 6.73−6.86 (m, 1H), 6.94−7.07 (m, 2H), 7.15−7.28 (m, 1H). ^{13}C NMR, δ: u 159.1, 142.7, 38.9, 36.7, 22.6; d 129.7, 123.5, 117.1, 111.4, 62.5, 62.5, 60.8, 33.1, 30.9. IR (film): 3467 (broad), 2942, 2866, 1599, 1588 cm^{-1}. HRMS Calcd $C_{15}H_{22}O_2$ 234.1620. Found: 234.1626.

1-Methoxy-3-((1*R*,6*S*)-6-methoxy-2,2-dimethylcyclohexyl)-benzene (21). To a solution of the alcohol **20** (0.18 g, 0.77 mmol) in THF (3.0 mL) was added NaH (60% in mineral oil) (0.13 g, 3.85 mmol) followed by dimethyl sulfate (0.30 g, 2.31 mmol). The mixture was heated to reflux overnight and then quenched with 1 M aqueous HCl and partitioned between Et_2O and brine. The organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to obtain the methyl ether product **21** (0.167 g, 85% yield) as a clear oil. TLC: R_f (10% MTBE/PE) = 0.61. ^{1}H NMR, δ: 0.77 (s, 3H), 1.04 (s, 3H), 1.23−1.41 (m, 2H), 1.49 (dt, J = 13.4, 4.3 Hz, 1H), 1.57−1.66 (m, 1H), 1.77−1.94 (m, 1H), 1.99−2.14 (m, 1H), 2.43 (d, J = 3.0 Hz, 1H), 3.27 (s, 3H), 3.54 (d, J = 4.04 Hz, 1H), 3.83 (s, 3H), 6.73−6.84 (m, 1H), 7.01 (d, J = 7.83 Hz, 1H), 7.12−7.23 (m, 2H). ^{13}C NMR, δ: u 158.7, 143.9, 41.1, 32.0, 17.9; d 128.0, 123.5, 116.6, 111.1, 56.8, 55.0, 34.7. IR (film): 2933, 1599, 1580, 1484, 1456 cm^{-1}. HRMS Calcd $C_{16}H_{24}O_2$ 248.1776. Found: 248.1774

Methyl 3-((1*S*,6*S*)-6-methoxy-2,2-dimethylcyclohexyl)-3-oxopropanoate (22). To a solution of the bis ether (0.150 g, 0.605 mmol) freshly distilled in EtOH (10 mL) at −78 °C was condensed anhydrous NH_3. Pieces of Li metal were added to this solution until a blue color persisted for 5−10 min. The solution was allowed to evaporate overnight, and then the pH was adjusted to between 9 and 8 by 1 M aqueous HCl and then extracted with EtOAc. The organic extracts were dried (Na_2SO_4) and concentrated. The residue was dissolved in CH_2Cl_2 (45 mL) and MeOH (5 mL). At −78 °C, O_3 was sparged until a blue color developed. The mixture was quenched with dimethyl sulfide (1 mL). The solution was chromatographed directly to obtain the β-keto ester product **22** (0.087 g, 60% yield for two steps) as a clear oil. TLC: R_f (30% MTBE/PE) = 0.57. ^{1}H NMR, δ: 0.95 (s, 3H), 0.99 (s, 3H), 1.32−1.45 (m, 2H), 1.53−1.74 (m, 3H), 1.77−1.97 (m, 3H), 3.02 (d, J = 5.3 Hz, 1H), 3.34 (s, 3H), 3.52 (d, J = 1.7 Hz, 2H), 3.56−3.64 (m, 1H), 3.74 (s, 3H). ^{13}C NMR, δ: u 205.2, 167.7, 54.4, 34.8, 33.8, 25.2, 19.8; d 78.6, 59.2, 56.4, 52.0, 28.6, 27.7. IR

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(film): 2948, 1749, 1714, 1456, 1438 cm^{-1}. HRMS Calcd $C_{13}H_{22}O_4$ 242.1518. Found 242.1515.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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