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Note

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Gold(I)-Catalyzed Formation of Bicyclo[4.2.0]oct-1-enes

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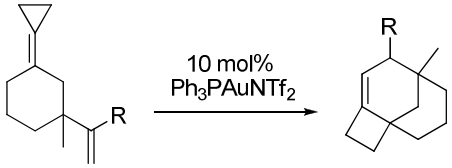


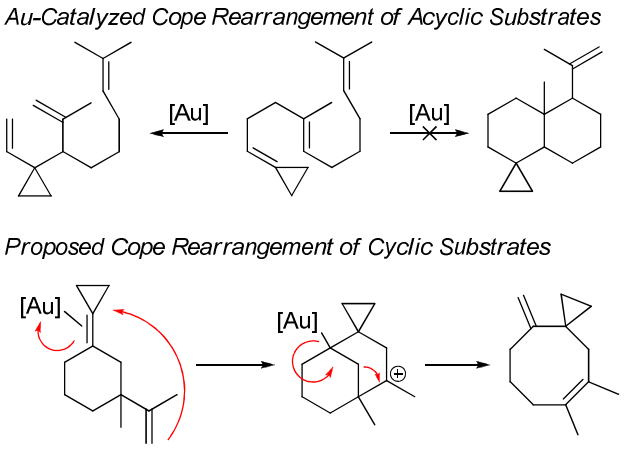
Abstract: Gold(I) catalysts effectively promote the Cope rearrangement of acyclic 1,5-dienes bearing a terminal cyclopropylidene. When this methodology is applied to cyclic substrates an unexpected transformation occurs, resulting in the formation of a tricyclic compound incorporating a bicyclo[4.2.0]oct-1-ene core, a portion of which is found in a number of natural products. Density functional theory calculations (M06 and M06-2X) reveal insight into the mechanism and thermodynamics of this unique transformation.

Transition metal catalysts play a prominent role in promoting the kinetic viability of a variety of synthetic reactions. When used in combination with thermodynamically favorable transformations, like the consumption of C-C unsaturation[1-2] and the release of ring strain,[3-11] numerous useful methodologies have emerged. The construction of complex polycyclic structures from relatively simple starting materials has been the subject of a number of research efforts aimed at accessing biomimetic carbocycles.[12-16]

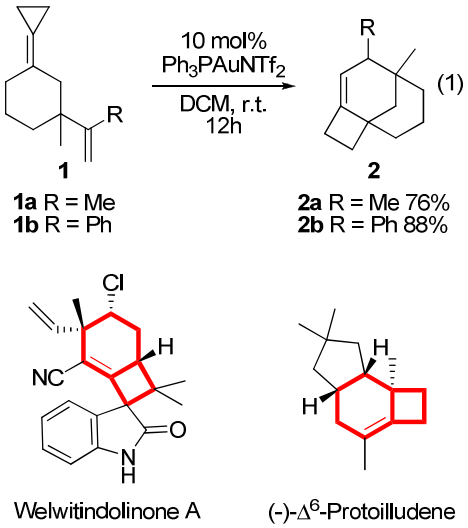
In our own effort to utilize ring strain and unsaturation for biomimetic polycyclization reactions, we discovered that 1,5-dienes with a terminal alkylidene cyclopropane preferentially undergo Cope rearrangements instead of the expected cascade cyclizations under Au(I) catalysis (Scheme 1).[17] This reaction is driven thermodynamically by the relief of ring strain in the cyclopropylidene moiety.[18-19] In this contribution we extend the scope of this rearrangement to cyclic substrates like **1** (R = Me, Ph) with the goal of using alkylidene cyclopropane strain release to access medium sized carbocycles,[20-22] which suffer from their own strain (Scheme 1). To our surprise the Cope rearrangement was seemingly not followed and tricyclic compounds **2**, which feature a bicyclo[4.2.0]oct-1-ene core,

are formed instead (eq 1). This bicyclic skeleton is present in a number of natural products including welwitindolinone A, and the protoilludane class of sesquiterpenes.[23-26]

Scheme 1. Gold Catalyzed Cope Rearrangements



Employing 10 mol% of the Gagosz catalyst,[27] $Ph_3PAuNTf_2$ (Tf = trifluoromethanesulfonyl), allows the reaction to proceed cleanly over 12 hours at room temperature to a single product (**2**). The rearranged **2a** and **2b** are isolable via flash chromatography in good yield (76% and 88% yield, respectively), and were identified by an analysis of the NOESY NMR spectra of **2b**. The assignment of **2a** was made based on similarities in the NMR spectra to **2b**. Key correlations are shown in Figure 1.



The phenyl ring was assigned to the concave face of the molecule through a correlation between H_A (7.35 ppm) and H_B (1.85 ppm), but not between H_A and H_C (1.50 ppm) (Figure 1a), as well as the signal between H_D (3.40 ppm)

and H_E (1.75 ppm) (Figure 1b). The *cis*-ring configuration was assigned by the key interactions between the diaxially oriented H_E (1.75 ppm) and H_F (1.85 ppm), H_G (1.90 ppm) with H_I (3.0 ppm) (Figure 1c), and the supporting resonance between H_A and H_B. A more in-depth discussion of the NOESY data is provided in the Supporting Information.

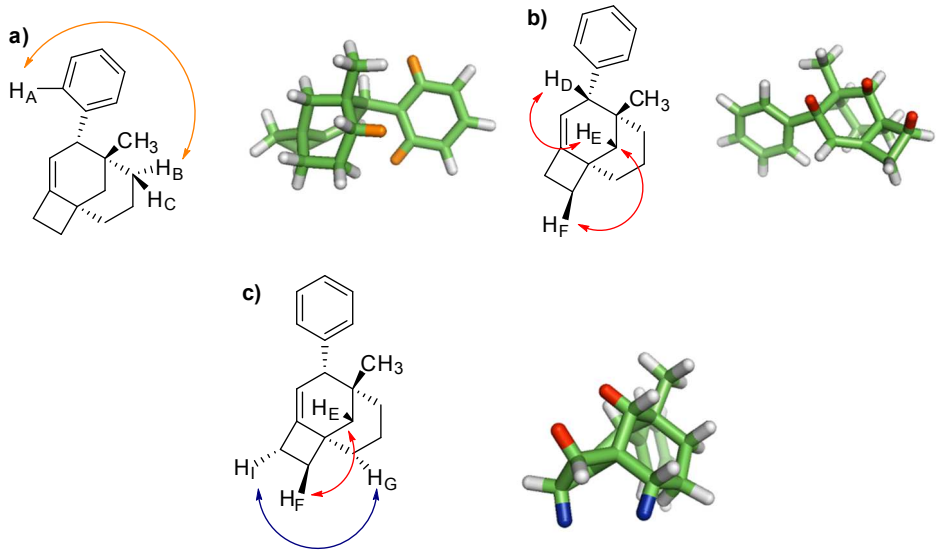
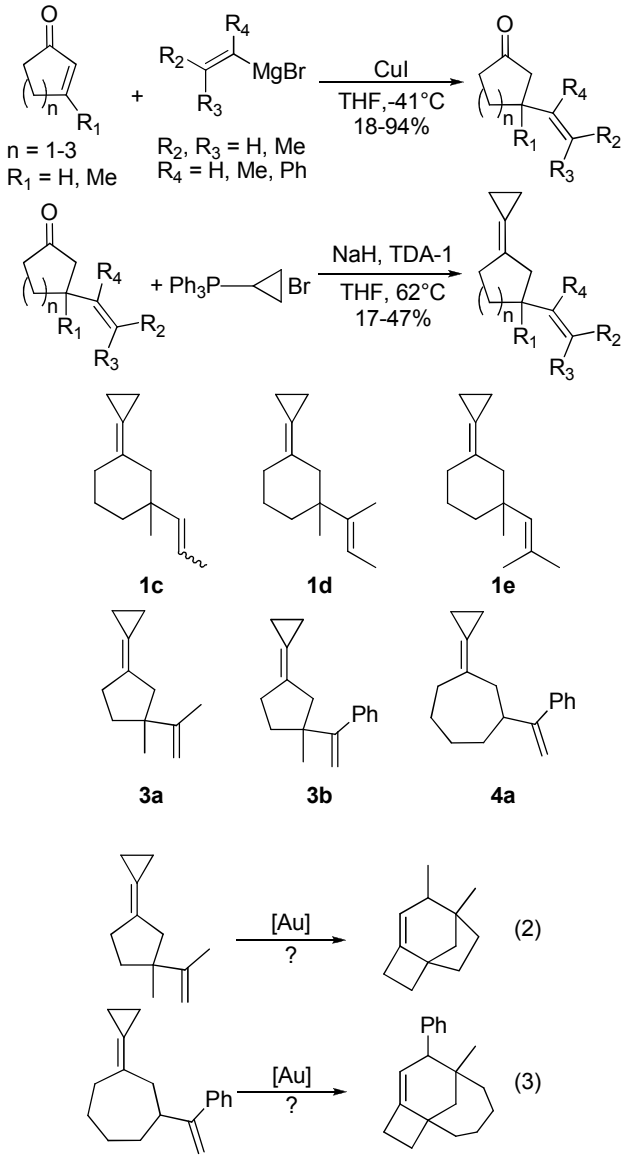


Figure 1. Selected NOESY correlations in NMR spectrum of bicyclo[4.2.0]oct-1-ene **2b**. 3D representations made in PyMOL.[28-32]

To explore the scope of the reaction a series of additional substrates were synthesized, varying in ring size and substitution on the pendant alkene (Scheme 2). These were obtained in two steps from the cyclic enone via a Cu-mediated Michael addition at low temperature, followed by a Wittig reaction. The former reactions were generally high yielding for commercially available Grignard reagents (68-94%), but low yields were obtained from the Grignard reagent prepared from α-bromostyrene (18-58%). The resulting ketone could be transformed, in poor to moderate yield, into the desired substrate with cyclopropyltriphenylphosphonium bromide and NaH, facilitated by the phase transfer catalyst tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1).[33] It was hoped that the cyclopentylidene and cycloheptylidene substrates would provide access to tricyclic compounds that varied in ring structure (eqs 2 and 3, respectively).

Scheme 2. Synthesis of Cyclic Substrates.



Unfortunately, the additional substrates gave neither the tricyclic products nor the analogous originally hypothesized medium ring products. Despite considerable experimentation compounds **1c**-**1e,** and **4a** gave complex, intractable mixtures of compounds. Attempts to optimize via choice of solvent (nitromethane, 1,2-dichloroethane) and catalyst (e.g. (*R*)-BINAP$(AuCl)_2$, (*S*)-xylyl-PHANEPHOS$(AuCl)_2$), or activating agent ($AgBF_4$, $AgSbF_6$, $AgPF_6$), failed to simplify the reaction mixtures. It was observed that in the case of **4a** the identity of the counter-ion affected the ratio of products observed in the GC-MS but not the number of species formed. For compounds **3a** and **3b** two major products were formed along with a number of minor products. Control reactions with $HCl{\cdot}Et_2O$ gave the same products in the same ratios, as did a separate control reaction between **3a** and $AgPF_6$

in DCM, suggesting unproductive, Brønsted Acid catalyzed alkene isomerization pathways. These isomerization reactions removed the ring strain of the methylenecyclopropane by transformation of the exocyclic alkene into an endocyclic olefin (within the cyclopentyl ring, see Supporting Information). Identical control reactions with the 6- and 7- membered ring substrate analogs were sluggish and did not produce the same reaction mixtures observed as when Au(I) complexes were reacted. No tricyclic product was formed when the control reactions were run with **1a** and **1b**, supporting a gold catalyzed transformation for the production of **2**.

Insight into the reaction's mechanism and limitations was achieved through density functional theory (DFT) calculations using the M06/6-31G(d) method with the SDD basis set for Au and a DCE solvent continuum (CPCM), as implemented in GAUSSIAN09.[34-37] Two potential pathways for the rearrangement were examined, the first proceeding through the originally envisioned Cope rearrangement/ring expansion, which initiates by Au(I) activation of the alkylidene cyclopropane (**A**, Figure 2). Cyclization initiated by complexation at this point of unsaturation is predicted to proceed with a barrier of 22 kcal/mol (relative to **B**), passing through tertiary carbocation **A1** to give the cyclooctenes **A2**/**A3**, in a stepwise formal [3s,3s] sigmatropic rearrangement that is exergonic by ~3-5 kcal/mol (see the Supporting Information for additional details). From this point a second electrophilic cyclization is initated at the endocyclic alkene to give **A4** (via **A3-TS**)[38]. Unexpectedly, no transition state structure could be found to enable the direct ring expansion of the cyclopropane in **A4**. Instead a conformational change is needed (via **A4-TS**) to orient the bonds and associated orbitals for facile ring expansion (see **A5**). Expansion of the cyclopropane to the tetracyclic 6-5-4-3 intermediate **C** proceeds through **A5-TS**, the highest energy transition state structure in the predicted pathway. Deprotonation followed by protodemetallation provides the complexed product **2a**, with the overall process being exergonic by more than 25 kcal/mol.

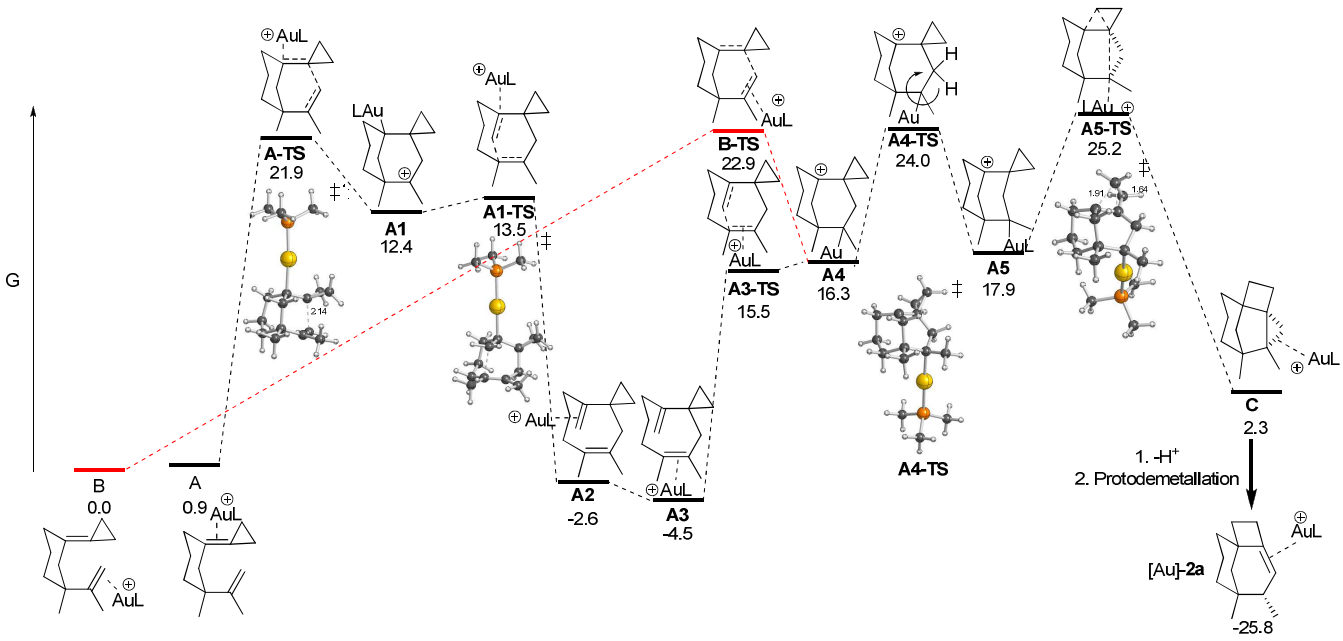
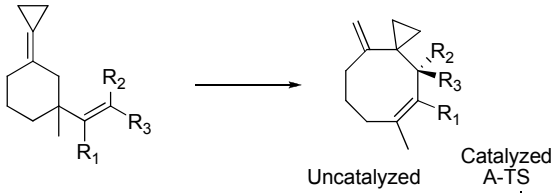


Figure 2. Computed relative free energies (kcal/mol) for species involved in potential rearrangements of **1a**.

An alternative pathway, which avoids formation of a cyclooctene intermediate but converges with pathway **A** at structure **A4**, involves initiation of the Cope rearrangement at the pendant alkene instead of the cyclopropylidene moiety. In this pathway, cyclization of **B** to **A4** proceeds directly through a transition state structure (**B-TS**, 22.9 kcal/mol) that is only slightly higher energy than **A-TS**.

The failure of substrates **1c**-**1e** were also probed computationally and the results are summarized in Table 1. First, each of these reactions was found to be at least slightly endergonic, with each pathway suffering some additional defficiency. Substitution at R_2 creates steric interactions with the cyclohexyl ring and increases the relative energy of **A-TS**. In these cases ((*Z*)-**1c** and **1e**), a transition state structure leading from the starting material to the ring expanded product could not be located. In addition, compound (*E*)-**1c**, rearranges through a secondary carbocation rather than a tertiary carbocation (c.f. Figure 2). While substrate **1d** demonstrated an achievable ring expansion barrier the analogous **A5-TS** was too high in energy (31 kcal/mol) for conversion to **C**. The source of this high barrier appears to result from a steric clash between methyl groups. .

Table 1. Energetics of Ring Expansion for Cyclohexyl Substrates



Substrate	R_1	R_2	R_3	Uncatalyzed ΔH^a	Uncatalyzed ΔG	Catalyzed A-TS $\Delta G^{\ddagger}$
1a	Me	H	H	-1.8	-2.6	21.9
(*Z*)-**1c**	H	Me	H	4.7	6.1	N/A
(*E*)-**1c**	H	H	Me	-1.2	0.1	27.7
1d	Me	H	Me	-0.3	1.1	22.4
1e	H	Me	Me	4.4	5.9	N/A

[a] Calculated enthalpies and Gibbs free energies for formation of **A2**, along with computed relative energies for **A**-TS, in kcal/mol. [b] M06-2X/6-31G(d) (gas phase) calculations employed for uncatalyzed reaction and M06/SDD-6-31G(d) (DCE) for catalyzed.

In summary, we have described a Au(I)-catalyzed Cope rearrangement of cyclic cyclopropylidenes into unique tricyclic compounds with a bicyclo[4.2.0]oct-1-ene core, a structural motif present in several classes of natural products. The reaction proceeds efficiently at room temperature to provide the products in good yields. Quantum chemical calculations provide insight into the mechanism and thermodynamics of the reaction.

Experimental Section

All reagents were purchased from commercial sources and used as received unless otherwise noted. All glassware was flame-dried under vacuum unless otherwise indicated. Anhydrous CH_2Cl_2, diethyl ether, and pentanes were passed through a column of alumina. Column chromatography was performed using SilaFlash P60 40-63 μm (230-400 mesh). All NMR spectra were recorded on either a 600 MHz or 400 MHz spectrometer at STP. ^1H, and ^{13}C chemical shifts are reported in parts per million (ppm) relative to residual solvent resonances ($CDCl_3$ or CD_2Cl_2). High resolution mass spectra (EI/HRMS) were obtained on a double-focusing magnetic sector spectrometer .

General Procedure A for Michael Addition Reactions. (For the preparation of *3-methyl-3-(prop-1-en-2-yl)cyclohexanone*) To a flame-dried 100 mL round-bottom flask under N_2 was added CuI (3.45 g, 18.2 mmol, 2.00 eq.) then THF (18 mL). The reaction vessel was cooled to -41°C before the addition of the Grignard reagent, isopropenylmagnesium bromide (0.5 M THF, 36.3 mL, 18.2 mmol, 2.00 eq.) over 30 min. The reaction was stirred at -41°C for 30 min before transferring in 3-methyl-2-cyclohexen-1-one (1.03 mL, 9.08 mmol, 1.00 eq.) dissolved in THF (9 mL) via cannula. The reaction was then stirred 1.5 h at -41°C before quenching with saturated aqueous NH_4Cl (50 mL). The aqueous layer was separated and the organic layer was washed 2 additional times with saturated aqueous NH_4Cl. The combined aqueous washes were then extracted with Et_2O (2x). The combined

organic layers were washed with brine until the aqueous layer was no longer blue-tinted. The organic layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (15% EtOAc/Petroleum Ether) provided the product compound as a yellow oil (1.30 g, 94% yield).

General Procedure B for Wittig cyclopropylidination. (For preparation of *3-cyclopropylidene-1-methyl-1-(prop-1-en-2-yl)cyclohexane* (**1a**)) To a Schlenk flask loaded with a suspension of dry NaH (0.102 g, 4.26 mmol, 1.30 eq.) in THF (25 mL) under N_2 atmosphere was added cyclopropyltriphenylphosphonium bromide (1.63 g, 4.26 mmol, 1.30 eq.) at rt. The reaction flask was then equipped with a condenser and heated to 62°C for 18 h. To the resulting orange suspension was then added the ketone (3-methyl-3-(prop-1-en-2-yl)cyclohexanone, 0.500 g, 3.28 mmol, 1.00 eq.) and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) (0.105 mL, 0.328 mmol, 0.10 eq.) in THF (6 mL). The reaction was stirred for 5 h at 62°C before cooling to rt and quenching with saturated aqueous $NaHCO_3$. The reaction was diluted with deionized H_2O and Et_2O before separating the layers. The aqueous layer was extracted with Et_2O (2x) and the combined organic layers were then washed with brine (2x). The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (Hexanes) provided the product compound as a colorless oil (0.269 g, 47%). A small amount of CH_2Cl_2 was used to load the material onto the column.

General procedure C for preparation and use of (1-phenylvinyl)magnesium bromide: (For preparation of *3-methyl-3-(1-phenylvinyl)cyclohexanone*) To a flame-dried 100-mL 3-neck RBF equipped with a condenser under N_2 atmosphere was added Mg (0.467 g, 19.2 mmol, 2.12 eq) and THF (32.3 mL) and a few small crystals of I_2. Alpha-bromo-styrene (2.35 mL, 18.1 mmol, 2.00 eq) was dissolved in THF (4 mL) then added to the reaction mixture. The solution was heated to 70°C for 5-15 minutes until the consumption of Mg appeared to have stopped. After cooling to room temperature the Grignard solution (~0.5 M) was transferred via cannula to a suspension of CuI (3.45 g, 18.1 mmol, 1.00 eq) in THF (36 mL) at -41°C. The reaction was stirred at -41°C for 30 min before transferring in a solution of 3-methyl-2-cyclohexen-1-one (1.03 mL, 9.07 mmol, 1.00 eq.) dissolved in THF (9 mL) via cannula. The reaction was then stirred 1.5 h at -41°C before quenching with saturated aqueous NH_4Cl (50 mL). The aqueous layer was separated and the organic layer was washed 2 additional times with saturated aqueous NH_4Cl. The combined aqueous washes were then extracted with EtOAc (2x). The combined organic layers were washed with brine until the aqueous layer was no longer blue-tinted, and finally dried over $MgSO_4$, filtered, and concentrated *in*

vacuo. Purification by silica gel chromatography (15% EtOAc/Petroleum Ether) provided the product compound as a yellow oil as a mixture with styrene (1.32 g total, 0.971 g product, 50% yield).

General Procedure D for Au(I) Catalyzed Rearrangement: (For preparation of *6,7-dimethyltricyclo[5.3.1.0]undec-4-ene (**2a**))* To a 1-dram vial equipped with a stirbar was added $Ph_3PAuNTf_2$ (0.011 g, 0.0142 mmol, 0.10 eq) followed by DCM (0.5 mL). The reaction was stirred briefly before addition of **1a** (0.025g, 0.142 mmol, 1.00 eq). The reaction was then stirred for 12 h before concentrating *in vacuo*. A pipette column was then used for purification by silica gel chromatography (Hexanes) to provide the product compound as a colorless oil (0.019 g, 76%). A small amount of DCM was used to add the material to the column.

*3-methyl-3-(prop-1-en-2-yl)cyclohexanone***:** Yellow oil (1.30 g, 94% yield). ^{1}H NMR: (600 MHz, $CDCl_3$) δ 4.80 (s, 1H), 4.71 (s, 1H), 2.58 (d, *J* = 14.4 Hz, 1H), 2.28 (dt, *J* = 15.0, 5.7 Hz, 1H), 2.22-2.18 (m, 1H), 2.17 (d, *J* = 14.4 Hz, 1H), 1.91-1.87 (m, 1H), 1.84-1.77 (m, 1H), 1.71-1.67 (m, 1H), 1.69 (s, 3H), 1.56 (ddd, *J* = 13.2, 9.6, 3.6 Hz, 1H), 1.06 (s, 3H); ^{13}C-NMR: (150 MHz, $CDCl_3$) δ 211.9, 150.0, 112.0, 52.7, 43.9, 41.0, 35.0, 27.0, 22.0, 19.3. HRMS (EI+) calculated for $C_{10}H_{16}O$ 152.12012, found 152.12093.

3-cyclopropylidene-1-methyl-1-(prop-1-en-2-yl)cyclohexane **(1a):** Colorless oil (0.269 g, 47% yield). ^{1}H NMR: (600 MHz, $CDCl_3$) δ 4.74 (s, 1H), 4.73 (s, 1H), 2.41 (d, *J* = 13.2 Hz, 1H), 2.26-2.22 (m, 1H), 2.17-2.14 (m, 1H), 2.13 (d, *J* = 13.2 Hz, 1H), 1.71 (s, 3H), 1.71-1.68 (m, 1H), 1.55-1.50 (m, 2H), 1.47-1.44 (m, 1H), 0.99-0.96 (m, 4H), 0.94 (s, 3H); ^{13}C-NMR: (150 MHz, $CDCl_3$) δ 152.9, 126.1, 113.9, 109.4, 43.8, 41.0, 36.5, 33.2, 25.9, 23.4, 19.8, 2.13, 2.10. HRMS (EI+) calculated for $C_{13}H_{20}$ 176.15650, found 176.15722.

3-methyl-3-(1-phenylvinyl)cyclohexanone: Characterization data matched that previously reported.[39]

(1-(3-cyclopropylidene-1-methylcyclohexyl)vinyl)benzene **(1b)**: Synthesized following general procedure **B** using 3-methyl-3-(1-phenyvinyl)cyclohexanone. Stirred 5 h at 62°C after addition of ketone in THF. Purified by silica gel chromatography (Hexanes) to give a colorless oil (0.281g, 36% yield). ^{1}H NMR: (400 MHz, CD_2Cl_2) δ 7.30-7.22 (m, 3H), 7.16-7.13 (m, 2H), 5.23 (d, *J* = 1.6 Hz, 1H), 4.82 (d, *J* = 1.6 Hz, 1H), 2.46 (d, *J* = 13.2 Hz, 1H), 2.31 (dt, *J* = 13.2, 5.2 Hz, 1H), 2.23 (d, *J* = 12.8 Hz, 1H), 2.15-2.09 (m, 1H), 1.75-1.69 (m, 1H), 1.68-1.60 (m, 1H), 1.59-1.46 (m, 2H), 1.06 (s, 3H), 1.02-0.89 (m, 4H); ^{13}C-NMR: (100 MHz, CD_2Cl_2) δ 159.6, 144.0, 129.7, 127.8, 126.8, 126.1, 114.5, 113.5, 44.5, 41.5, 37.2, 33.4, 25.9, 23.7, 2.21. HRMS (EI+) calculated for $C_{18}H_{22}$ 238.17215, found 238.17139.

3-methyl-3-(prop-1-enyl)cyclohexanone: Synthesized following general procedure **A** using 1-propenylmagnesium bromide solution (0.5 M THF). Purified by silica gel chromatography (15% EtOAc/Petroleum Ether) to give a yellow oil as a 1:1 inseperable mixture of *E*/*Z* isomers (0.981 g, 71% yield). Spectroscopic data reported is of the mixture of isomers. ^{1}H NMR: (600 MHz, CD_2Cl_2) δ 5.39 (ddt *J* = 12.0, 7.8, 7.2 Hz, 1H), 5.36-5.29 (m, 2H), 5.20 (dq, *J* = 11.7, 1.8 Hz, 1H), 2.45 (d, *J* = 13.2 Hz, 1H), 2.34 (dt, *J* = 13.8, 1.8 Hz, 1H), 2.22-2.16 (m, 5H), 2.10 (d, *J* = 13.8 Hz, 1H), 1.95-1.91 (m, 1H), 1.88-1.76 (m, 4H), 1.69 (dd, *J* = 7.2, 1.8 Hz, 3H), 1.64-1.55 (m, 3H), 1.62 (d, *J* = 4.8 Hz, 3H), 1.16 (s, 3H), 1.00 (s, 3H); ^{13}C-NMR: (150 MHz, CD_2Cl_2) δ 211.6, 211.5, 139.4, 137.0, 125.6, 123.4, 55.1, 52.8, 41.7, 41.4, 41.3, 38.1, 37.5, 28.2, 27.6, 23.1, 22.7, 18.4, 14.8. HRMS (EI+) calculated for $C_{10}H_{16}O$ 152.12012, found 152.12048.

3-cyclopropylidene-1-methyl-1-(prop-1-enyl)cyclohexane **(1c)**: Synthesized following general procedure **B** using 3-methyl-3-(prop-1-enyl)cyclohexanone. Stirred 2.5 h at 62°C after addition of ketone in THF. Purified by silica gel chromatography (Hexanes) to give a colorless oil as a 1:1 inseparable mixture of *E*/*Z* isomers (0.185 g, 32% yield). Spectroscopic data reported is of the mixture of isomers. ^{1}H NMR: (600 MHz, CD_2Cl_2) δ 5.43-5.36 (m, 1H), 5.35-5.29 (m, 2H), 5.23 (dq, *J* = 12.0, 1.8 Hz, 1H), 2.39 (d, *J* = 12.6 Hz, 1H), 2.29-2.23 (m, 1H), 2.21 (d, *J* = 13.2 Hz, 1H), 2.17-2.10 (m, 2H), 2.06 (d, *J* = 19.5 Hz, 1H), 2.04 (d, *J* = 19.8, 1H), 1.86-1.82 (m, 1H), 1.71 (dd, *J* = 7.2, 1.8 Hz, 3H), 1.63 (dd, *J* = 4.8, 1.2 Hz, 3H), 1.61-1.46 (m, 6H), 1.44-1.38 (m, 2H), 1.11 (s, 3H), 1.03-0.95 (m, 8H), 0.91 (s, 3H); ^{13}C-NMR: (150 MHz, CD_2Cl_2) δ 141.9, 139.3, 126.4, 126.2, 123.9, 121.1, 114.2, 114.0, 47.7, 45.4, 39.3, 39.0, 38.9, 38.3, 33.5, 33.4, 27.2, 26.5, 24.2, 23.7, 18.6, 15.0, 2.21, 2.17, 2.11. HRMS (EI+) calculated for $C_{13}H_{20}$ 176.15650, found 176.15742.

(E)-3-(but-2-en-2-yl)-3-methylcyclohexanone: Synthesized following general procedure **A** using 1-methyl-1-propenylmagnesium bromide solution (0.5 M THF). Stirred 2 h at -41°C after addition of ene-one. Purified by silica gel chromatography (15% EtOAc/Petroleum Ether) to give a yellow oil; 3:1 ratio of inseperable diastereomers (1.13 g, 75% yield). Spectroscopic data reported is of the mixture of isomers. ^{1}H NMR: (600 MHz, CD_2Cl_2) δ 5.31 (q, *J* = 7.8 Hz, 1H), 5.24 (q, *J* = 6.6 Hz, (1/3) = 1H, minor isomer), 2.69 (d, *J* = 13.8 Hz, 1H), 2.54 (d, *J* = 14.4 Hz, (1/3) = 1H, minor isomer), 2.29-2.20 (m, 2H), 2.18-2.12 (m, 2H), 1.93-1.74 (m, 2H), 1.70-1.67 (m, 6H), 1.56-1.55 (m, 1H), 1.14 (s, 3H), 1.03 (s, (1) = 3H, minor isomer); ^{13}C-NMR: (150 MHz, CD_2Cl_2) δ 211.9, 211.8, 140.9, 140.8, 121.7, 119.4, 54.1, 53.0, 44.7, 44.3, 41.4, 41.3, 36.3, 35.3, 27.2, 26.2, 24.2, 22.8, 22.4, 15.9, 14.0, 12.4. HRMS (EI+) calculated for $C_{11}H_{18}O$ 166.13577, found 166.13636.

(E)-1-(but-2-en-2-yl)-3-cyclopropylidene-1-methylcyclohexane **(1d)**: Synthesized following general procedure **B** using (*E*)-3-(but-2-en-2-yl)-3-methylcyclohexanone. Stirred 4.5 h at 62°C after addition of ketone in THF. Purified by silica gel chromatography (Hexanes) to give a colorless oil as an inseperable 3:1 ratio of diastereomers (0.106 g, 17% yield). Spectroscopic data reported is of the mixture of isomers. ^{1}H NMR: (600 MHz, CD_2Cl_2) δ 5.33-5.30 (m, (1/3) = 1H, minor isomer), 5.26-5.23 (m, 1H), 2.54 (d, *J* = 13.2 Hz, 1H), 2.37 (d, *J* = 12.6 Hz, (1/3) = 1H, minor isomer), 2.28-2.24 (m, 1H), 2.20-2.16 (m, 1H), 2.13 (d, *J* = 13.2 Hz, 1H), 2.01-1.97 (m, 1H), 1.69 (bs, 6H), 1.60-1.50 (m, 3H), 1.06 (s, 3H), 0.99 (bs, 4H), 0.91 (s, (1) = 3H, minor isomer); ^{13}C-NMR: (150 MHz, CD_2Cl_2) δ 143.23, 143.16, 126.9, 126.7, 120.3, 116.7, 114.1, 113.8, 45.4, 44.1, 41.64, 41.58, 37.6, 36.8, 33.6, 33.5, 25.5, 25.3, 24.03, 23.99, 23.7, 16.1, 14.0, 12.6, 2.4, 2.21, 2.19, 2.1. HRMS (EI+) calculated for $C_{14}H_{22}$ 190.17215, found 190.17239.

3-methyl-3-(2-methylprop-1-enyl)cyclohexanone: Synthesized following general procedure **A** using 2-methyl-1-propenylmagnesium bromide solution (0.5 M THF). Stirred 1.5 h at -41°C after addition of ene-one. Purified by silica gel chromatography (15% EtOAc/Petroleum Ether) to give a yellow oil (1.02 g, 68% yield). ^{1}H NMR: (600 MHz, CD_2Cl_2) δ 5.03 (s, 1H), 2.41 (d, *J* = 12.6 Hz, 1H), 2.21 (d, *J* = 4.8 Hz, 2H), 2.17 (d, *J* = 13.2 Hz, 1H), 1.93 (bs, 1H), 1.83 (bs, 2H), 1.71 (s, 3H), 1.67 (s, 3H), 1.60 (bs, 1H), 1.15 (s, 3H); ^{13}C-NMR: (150 MHz, CD_2Cl_2) δ 211.7, 133.6, 131.0, 55.6, 41.4, 40.9, 38.3, 28.3, 27.6, 23.1, 19.5. HRMS (EI+) calculated for $C_{11}H_{18}O$ 166.13577, found 166.13609.

3-cyclopropylidene-1-methyl-1-(2-methylprop-1-enyl)cyclohexane **(1e)**: Synthesized following general procedure **B** using 3-methyl-3-(2-methylprop-1-enyl)cyclohexanone. Stirred 3 h at 62°C after addition of ketone in THF. Purified by silica gel chromatography (Hexanes) to give a colorless oil (0.206 g, 33% yield). ^{1}H NMR: (600 MHz, CD_2Cl_2) δ 5.04 (s, 1H), 2.35 (d, *J* = 13.2 Hz, 1H), 2.26-2.24 (m, 1H), 2.12 (bs, 1H), 2.02 (d, *J* = 12.6 Hz, 1H) 1.82-1.79 (m, 1H), 1.70 (s, 3H), 1.64 (s, 3H) 1.57-1.54 (m, 1H), 1.51-1.45 (m, 1H), 1.42-1.38 (m, 1H), 1.08 (s, 3H), 1.03-0.98 (m, 4H); ^{13}C-NMR: (150 MHz, CD_2Cl_2) δ 133.5, 131.4, 126.6, 114.1, 48.0, 39.5, 38.0, 33.5, 28.3, 27.1, 24.2, 19.5, 2.2, 2.1. HRMS (EI+) calculated for $C_{14}H_{22}$ 190.17215, found 190.17146.

3-methyl-3-(prop-1-en-2-yl)cyclopentanone: Synthesized following general procedure **A** using isopropenylmagnesium bromide (0.5 M THF) and 3-methylcyclopent-2-enone. Stirred 1.5 h at -41°C after addition of ene-one. This material was sufficiently pure to be taken on without further purification as a yellow oil (0.991 g, 79% yield). ^{1}H NMR: (600 MHz, CD_2Cl_2) δ 4.78 (t, *J* = 1.8 Hz, 1H), 4.71 (s, 1H), 2.38 (d, *J* = 17.4 Hz, 1H), 2.28-2.24 (m, 2H), 2.09 (d, *J* = 17.4 Hz, 1H), 2.07-2.02 (m, 1H), 1.88-1.84 (m, 1H), 1.79 (s, 3H), 1.17 (s, 3H); ^{13}C-NMR:

(150 MHz, CD_2Cl_2) δ 218.9, 151.6, 109.5, 51.6, 45.3, 37.1, 34.3, 25.9, 19.8. HRMS (EI+) calculated for $C_9H_{14}O$ 138.10447, found 138.10502.

3-cyclopropylidene-1-methyl-1-(prop-1-en-2-yl)cyclopentane **(3a)**: Synthesized following general procedure **B** using 3-methyl-3-(prop-1-en-2-yl)cyclopentanone. Stirred 5 h at 62°C after addition of ketone in THF. Purified by silica gel chromatography (Hexanes) to give a colorless oil (0.096g, 18% yield). ^{1}H NMR: (600 MHz, $CDCl_3$) δ 4.70 (s, 1H), 4.68 (s, 1H), 2.47-2.41 (m, 3H), 2.23 (d, *J* = 15.0 Hz, 1H), 1.82-1.77 (m, 1H), 1.76 (s, 3H), 1.63-1.58 (m, 1H), 1.04 (s, 3H), 0.97-0.95 (m, 4H); ^{13}C-NMR: (150 MHz, $CDCl_3$) δ 153.1, 130.6, 111.4, 108.2, 47.7, 44.7, 37.2, 30.0, 25.4, 20.3, 2.5, 2.4. HRMS (EI+) calculated for $C_{12}H_{19}$ (M+1) 163.14868, found 163.14901.

3-methyl-3-(1-phenylvinyl)cyclopentanone: Synthesized following general procedure **C** using 3-methylcyclopent-2-enone. Stirred 4 h at -41°C after addition of ene-one. Purification by gradient silica gel chromatography (Petroleum Ether to 95:5 Pet. Ether:Et_2O to 90:5:5 Pet. Ether:Et_2O:EtOAc) provided the product compound as a yellow oil (0.327g, 18% yield) ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.31-7.26 (m, 3H), 7.15-7.14 (m, 2H), 5.17 (s, 1H), 4.96 (s, 1H), 2.50 (d, *J* = 17.4 Hz, 1H), 2.31-2.28 (m, 2H), 2.20-2.14 (m, 1H), 2.15 (dd, *J* = 17.4, 1.8 Hz, 1H), 1.86 (ddt, *J* = 9.6, 6.6, 1.8 Hz, 1H), 1.25 (s, 3H); ^{13}C-NMR: (150 MHz, $CDCl_3$) δ 218.8, 156.4, 142.3, 128.8, 128.0, 127.2, 113.8, 51.9, 45.2, 36.7, 34.5, 26.6. HRMS (EI+) calculated for $C_{14}H_{16}O$ 200.12012, found 200.11936.

(1-(3-cyclopropylidene-1-methylcyclopentyl)vinyl)benzene **(3b)**: Synthesized following general procedure **B** using 3-methyl-3-(1-phenylvinyl)cyclopentanone. Stirred 8.5 h at 62°C after addition of ketone in THF. Purified by silica gel chromatography (Hexanes) to give a colorless oil (0.221 g, 30% yield). ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.29-7.24 (m, 3H), 7.20-7.18 (m, 2H), 5.17 (d, *J* = 1.2 Hz, 1H), 4.87 (d, *J* = 1.2 Hz, 1H), 2.57 (d, *J* = 15.6 Hz, 1H), 2.44 (bs, 2H), 2.26 (d, *J* = 15.6 Hz, 1H), 1.97-1.92 (m, 1H), 1.66-1.62 (m, 1H), 1.13 (s, 3H), 0.96-0.94 (m, 4H); ^{13}C-NMR: (150 MHz, $CDCl_3$) δ 158.4, 143.7, 130.3, 128.8, 127.7, 126.7, 112.6, 111.7, 47.8, 45.4, 37.8, 29.8, 26.2, 2.5, 2.4. HRMS (EI+) calculated for $C_{17}H_{20}$ 224.15650, found 224.15584.

3-(1-phenylvinyl)cycloheptanone: Synthesized following general procedure **C** using 2-cyclohepten-1-one. Stirred 1.5 h at -41°C after addition of ene-one. Purification by gradient silica gel chromatography (Petroleum Ether to 95:5 Pet. Ether:Et_2O to 90:5:5 Pet. Ether:Et_2O:EtOAc) provided the product compound as a pale yellow oil (1.13 g, 58% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.32-7.31 (m, 4H), 7.29-7.26 (m, 1H), 5.19 (s, 1H), 5.02 (s, 1H), 2.82 (t, *J* = 10.4 Hz, 1H), 2.70-2.61 (m, 1H), 2.69 (t, *J* = 14.4 Hz, 1H), 2.55-2.51 (m, 2H), 2.07-2.03 (m, 1H), 1.99-1.90 (m,

2H), 1.69-1.59 (m, 1H), 1.52-1.35 (m, 2H); ^{13}C-NMR: (100 MHz, $CDCl_3$) δ 214.1, 154.0, 142.0, 128.6, 127.7, 126.8, 111.7, 49.7, 44.2, 41.0, 37.3, 29.3, 24.4. HRMS (EI+) calculated for $C_{15}H_{18}O$ 214.13577, found 214.13519.

1-cyclopropylidene-3-(1-phenylvinyl)cycloheptane **(4a)**: Synthesized following general procedure **B** using 3-(1-phenylvinyl)cycloheptanone. Stirred 3.5 h at 62°C after addition of ketone in THF. Purified by silica gel chromatography (Hexanes) to give a colorless oil (0.367 g, 47% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.39-7.37 (m, 2H), 7.33-7.29 (m, 2H), 7.27- 7.25 (m, 1H), 5.19 (s, 1H), 5.06 (s, 1H), 2.71 (d, *J* = 14.0 Hz, 1H), 2.64 (t, *J* = 10.4 Hz, 1H), 2.52 (d, *J* = 14.8 Hz, 1H), 2.42-2.36 (m, 1H), 2.28 (t, *J* = 12.4 Hz, 1H), 1.94-1.91 (m, 1H), 1.85-1.79 (m, 2H), 1.56-1.49 (m, 1H), 1.44-1.30 (m, 2H), 0.99-0.93 (m, 4H); ^{13}C-NMR: (100 MHz, $CDCl_3$) δ 155.7, 143.0, 128.9, 128.4, 127.3, 126.8, 116.8, 110.6, 44.9, 41.0, 36.7, 34.6, 28.5, 27.8, 2.35. HRMS (EI+) calculated for $C_{18}H_{22}$ 238.17215, found 238.17115.

6,7-dimethyltricyclo[5.3.1.0]undec-4-ene (**2a**): Colorless oil (0.019 g, 76%). ^{1}H NMR: (600 MHz, $CDCl_3$) δ.5.17 (s, 1H), 2.82-2.75 (m, 1H), 2.50-2.46 (m, 1H), 2.01 (bs, 1H), 1.74-1.70 (m, 3H), 1.63 (dd, *J* = 13.8, 2.4 Hz, 1H), 1.50-1.40 (m, 3H), 1.32 (dt, *J* = 12.3, 4.2 Hz, 1H), 1.26 (d, *J* = 11.4 Hz, 1H), 0.94 (d, *J* = 7.2 Hz, 3H), 0.87 (dt, *J* = 13.8, 5.4 Hz, 1H), 0.84 (s, 3H); ^{13}C-NMR: (150 MHz, $CDCl_3$) δ 143.1, 121.7, 48.9, 46.5, 42.2, 35.8, 34.9, 33.4, 32.5, 30.8, 28.9, 22.2, 14.7. HRMS (EI+) calculated for $C_{13}H_{20}$ 176.15650, found 176.15578.

7-methyl-6-phenyltricyclo[5.3.1.0]undec-4-ene (**2b**): Synthesized following general procedure **D** using compound **1b**. Purified by silica gel chromatography (Hexanes) to give a colorless oil (0.022 g, 88% yield). ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.31-7.26 (m, 4H), 7.22-7.20 (m, 1H), 5.37 (s, 1H), 3.35 (s, 1H), 2.95-2.88 (m, 1H), 2.59 (dt, *J* = 13.8, 5.4 Hz, 1H), 1.91-1.88 (m, 1H), 1.84-1.76 (m, 3H), 1.70 (d, *J* = 10.8 Hz, 1H), 1.45-1.41 (m, 3H), 1.07-1.04 (m, 1H), 0.97 (s, 3H), 0.79 (dt, *J* = 13.8 5.4 Hz, 1H); ^{13}C-NMR: (150 MHz, $CDCl_3$) δ 145.2, 142.7, 130.0, 127.8, 126.2, 119.4, 55.4, 49.7, 46.4, 36.3, 35.4, 33.7, 32.6, 31.4, 29.3, 22.5. HRMS (EI+) calculated for $C_{18}H_{22}$ 238.17215, found 238.17229.

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Supporting Information: ^{1}H and ^{13}C NMR spectroscopic data for all new compounds and discussion of 2D NMR spectroscopic data for compound **2b**, as well as coordinates and energies for all computed structures and complete ref. 34 is provided. This information is available free of charge via the Internet at http://pubs.acs.org.

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