Article

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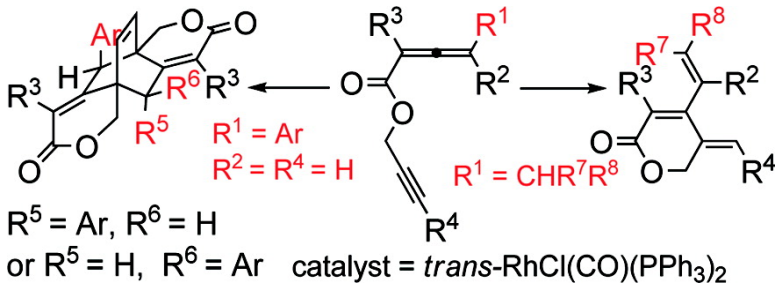

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trans-RhCl(CO)(PPh_3)$_2$-Catalyzed Monomeric and Dimeric Cycloisomerization of Propargylic 2,3-Dienoates. Establishment of α,β-Unsaturated δ-Lactone Rings by Cyclometallation

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Abstract: Cyclometallation of two unsaturated carbon−carbon bonds usually requires the application of low-valent metal catalysts, which could cleave the propargylic ester linkage. Thus, it is desirable to identify a catalyst which could undergo cyclometallation without cleaving the propargylic ester linkage. In this paper, we used *trans*-RhCl(CO)(PPh_3)$_2$ to realize the cyclometallation of propargylic 2,3-dienoates. The substituents at the 4-position of allenoate moiety nicely control the reaction pathway: when the 4-position of propargylic 2,3-dienoate **1** was monosubstituted with an aryl group, the bicyclic intermediate **7** formed by the cyclometallation could highly selectively undergo carbometalation with the alkyne moiety in the second molecule of propargylic 2,3-dienoate **1** to afford metallabicyclic intermediates **8a** or **8b**. Subsequent reductive elimination would afford **9**, which could undergo an intramolecular Diels−Alder reaction resulting in the formation of polycyclic bis(δ-lactone)-containing structures **2**. The intermediate could be trapped by adding 3-methoxyprop-1-yne affording cyclization−aromatization product **4p** highly selectively. If the substituent at the 4-positon of the 2,3-allenoate moiety has a β-H atom, sequential unimolecular cyclometallation/β-H elimination/reductive elimination occurs to afford cross-conjugated 5(*Z*)-alkylidene-4-alkenyl-5,6-dihydropyran-2-ones. The *Z*-stereochemistry of the exo double bond was determined by the cyclometallation. Some of the α,β-unsaturated δ-lactones could be easily converted to other synthetically useful compounds via reduction reaction, hydrogenation, and iodination/coupling protocol.

Introduction

Cyclometallation involving two unsaturated carbon−carbon bonds has been one of the hottest topics in organometallic chemistry.[1] Recently, we observed a bimolecular cyclization of unsubstituted 1,5-bisallenes leading to the formation of 18,19-norsteroid derivatives with the help of a catalytic amount of *trans*-RhCl(CO)(PPh_3)$_2$;[2] under the catalysis of Pd(0), two internal C═C bonds in unsubstituted 1,5-bisallenes could undergo cyclometallation[3] (Scheme 1).

Brummond[4] and Shibata[5] have pioneered the cyclization of allene-ynes for the synthesis of six-membered carbocycles, heterocycles, and δ,ϵ-lactams. However, the synthesis of lactones[6] has rarely been reported probably due to the possible cleavage of the ester linkage. In this paper, we wish to report our own observation that propargylic 2,3-dienoates could undergo a bimolecular cyclization[2] or cyclometalation/β-H elimination/reductive elimination sequence[4,5] to afford α,β-unsaturated δ-lactones depending on the substituents on the 4-position of allene moieties (Scheme 2).

Results and Discussion

Bimolecular Cyclization of Propargyl 4-Aryl-2,3-alkadienoates 1a−1e.[7] The reaction of compound **1a** under the catalysis of 5 mol % *trans*-RhCl(CO)(PPh_3)$_2$ in toluene[2] afforded a pair of diastereoisomers **2a** and *epi*-**2a**, which could be easily separated by flash chromatography on silica gel. The structures of these dimeric cyclization products were unambiguously established by the X-ray diffraction study (Figure 1).[8] It should be noted that although there are four stereogenic centers in the products, only two diastereoisomers were formed.

This bimolecular cyclization reaction of propargylic 2,3-dienoates is very sensitive to the concentration of the reaction (Table 1).

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(2) Ma, S.; Lu, P.; Lu, L.; Hou, H.; Wei, J.; He, Q.; Gu, Z.; Jiang, X.; Jin, X. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 5275.
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(4) (a) Brummond, K. M.; Chen, H.; Sill, P. C.; You, L. *J. Am. Chem. Soc.* **2002**, *124*, 15186. (b) Brummond, K. M.; Mitasev, B. *Org. Lett.* **2004**, *6*, 2245. (c) Brummond, K. M.; Painter, T. O.; Probst, D. A.; Mitasev, B. *Org. Lett.* **2007**, *9*, 347.
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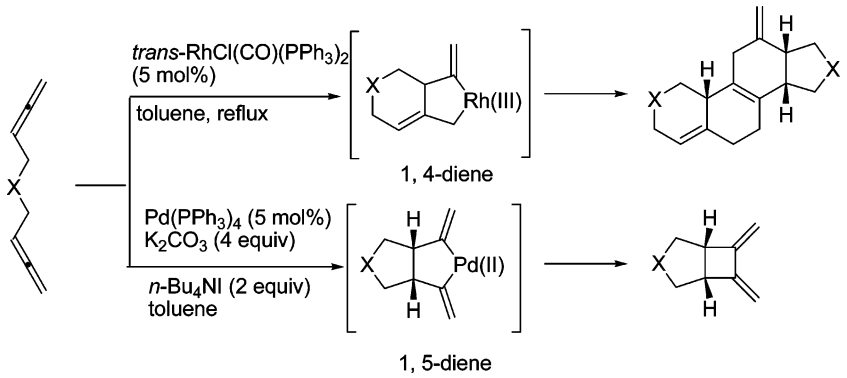
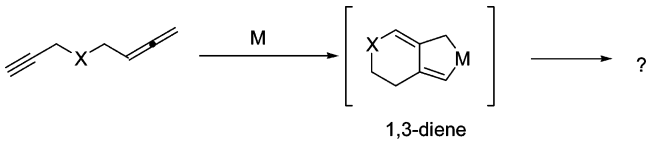
10.1021/ja073582u CCC: $37.00

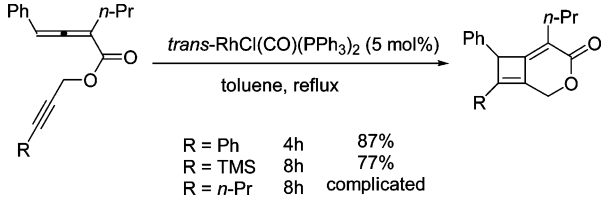
Scheme 1. Cyclometallation of 1,5-Bisallenes



Scheme 2. Cyclometallation of 1,5-Allenynes



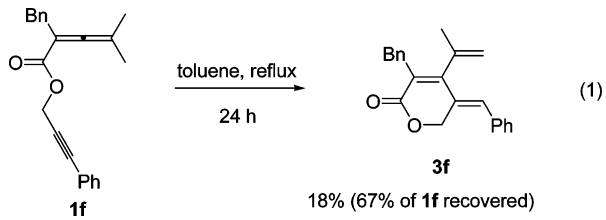
Scheme 3. *trans*-RhCl(CO)(PPh$_3$)$_2$-Catalyzed Reaction of 4-Aryl-2,3-dienoates Bearing an Internal Carbon−Carbon Triple Bond



We obtained the highest yields of product **2a** when the reaction was carried out in xylene (0.042 M) at 140 °C in a reaction tube with a screw cap. The high temperature is believed to be required by the Diels−Alder reaction. With the optimized conditions in hand, we studied the scope of this reaction (Table 2). Preliminary results showed that Ar can be a Ph- (Table 2, entries 1−4) and *p*-MeO-substituted phenyl group (Table 2, entry 5); R could be a benzyl group (Table 2, entry 1) and a primary or secondary alkyl group (Table 2, entries 2−5). The low-yielding nature observed in some cases could be caused by the high reaction temperature applied, which could lead to the polymerization of the starting materials. It should be noted that 4-aryl-2,3-dienoates possessing an internal alkyne moiety with phenyl or TMS underwent an intramolecular [2 + 2]-cycloaddition reaction instead of dimeric cyclization probably due to both the steric and electronic effects.[9] With R being *n*-propyl, the reaction is complicated (Scheme 3).

Unimolecular Cyclization of Propargyl 4-Alkyl-2,3-alkadienoates 1f−1o. However, it is interesting to observe when two methyl groups were installed at the 4-position of the allene moiety, i.e., **1f**, (*Z*)-3-benzyl-5-benzylidene-4-(prop-1-en-2-yl)-5,6-dihydropyran-2-one **3f** (Figure 2)[11] was formed.

The control reaction shows that the ene reaction could also occur under thermal conditions, but with a lower yield and longer reaction time (eq 1).



(1)

Thus, this sequential unimolecular cyclometallation/β-H elimination/reductive elimination of propargylic 2,3-dienoates **1f−1n** was studied (Table 3). This is the first example of an Alder-ene type reaction of an ester-tethered substrate to form a six-membered lactone ring.[4,5,12] In this study, it was observed that the application of $[Rh(CO)_2Cl]_2$ used by the Brummond group for the cyclization of amides and ethers[4] led to the decomposition of the starting propargylic 2,3-dienoates due to the cleavage of the propargylic ester linkage.[4,13] The reaction

(8) Crystal data for compound **2a**: $C_{40}H_{32}O_4$, MW = 576.66, orthorhombic, space group *Pbca*, final *R* indices [$I > 2\sigma(I)$], R1 = 0.0506, wR2 = 0.1099, *R* indices (all data), R1 = 0.0999, wR2 = 0.1265, *a* = 24.367 (2) Å, *b* = 8.1958 (7) Å, *c* = 30.325 (3) Å, α = 90°, *β* = 90°, *γ* = 90°, *V* = 6056.2-(9) Å^3, *T* = 293 (2) K, *Z* = 8, reflections collected/unique: 33 787/6614 (*R*(int) = 0.1050). Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC: 632768. Crystal data for compound *epi*-**2a**: $C_{40}H_{32}O_4$, MW = 576.66, monoclinic, space group *P*2(1)/*c*, final *R* indices [$I > 2\sigma(I)$], R1 = 0.0854, wR2 = 0.1591, *R* indices (all data), R1 = 0.2057, wR2 = 0.2011, *a* = 11.4483 (13) Å, *b* = 30.370 (3) Å, *c* = 8.4474 (10) Å, α = 90°, *β* = 98.854(3)°, *γ* = 90°, *V* = 2902.0(6) Å^3, *T* = 293 (2) K, *Z* = 4, reflections collected/unique: 15 200/5383 (*R*(int) = 0.1430). Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC: 632770.

(9) Jiang, X.; Ma, S. *Tetrahedron* **2007**, *63*, 7589.

(10) Crystal data for compound **2d**: $C_{34}H_{36}O_4$, MW = 508.63, triclinic, space group *P*1, final *R* indices [$I > 2\sigma(I)$], R1 = 0.0900, wR2 = 0.2104, *R* indices (all data), R1 = 0.2184, wR2 = 0.2722, *a* = 8.6809 (14) Å, *b* = 15.504 (2) Å, *c* = 21.838 (3) Å, α = 93.347°, *β* = 92.725°, *γ* = 94.441°, *V* = 2921.4(8) Å^3, *T* = 293 (2) K, *Z* = 4, reflections collected/unique: 15 521/10707 (*R*(int) = 0.1336). Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC: 647587. Crystal data for compound *epi*-**2d**: $C_{34}H_{36}O_4$, MW = 508.63, orthorhombic, space group *Pca*2(1), final *R* indices [$I > 2\sigma(I)$], R1 = 0.0765, wR2 = 0.1711, *R* indices (all data), R1 = 0.1616, wR2 = 0.2112, *a* = 28.980 (8) Å, *b* = 9.097 (2) Å, *c* = 21.175 (5) Å, α = 90°, *β* = 90°, *γ* = 90°, *V* = 5582(3) Å^3, *T* = 293 (2) K, *Z* = 8, reflections collected/unique: 29 213/5646 (*R*(int) = 0.1745). Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC: 647588.

(11) Crystal data for compound **3f**: $C_{22}H_{20}O_2$, MW = 316.38, orthorhombic, space group *P*2(1)2(1)2(1), final *R* indices [$I > 2\sigma(I)$], R1 = 0.0592, wR2 = 0.1473, *R* indices (all data), R1 = 0.0629, wR2 = 0.1500, *a* = 6.0205 (7) Å, *b* = 16.6705 (18) Å, *c* = 17.5656 (19) Å, α = 90°, *β* = 90°, *γ* = 90°, *V* = 1763.0(3) Å^3, *T* = 293 (2) K, *Z* = 4, reflections collected/unique: 10 498/2238 (*R*(int) = 0.1078). Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC: 632769.

(12) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021. Dubac, J.; Laporterie, A. *Chem. Rev.* **1987**, *87*, 319. Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426.

(13) For Rh(I)-catalyzed cleaving C−O bond of allylic esters, see: Evans, P. A. *Modern Rhodium-Catalyzed Organic Reactions*; Wiley-VCH: 2005; pp 191−214. For Pd(0)-catalyzed cleaving C−O bond of propargyl carbonates, see: Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, 2004; pp 543−563.

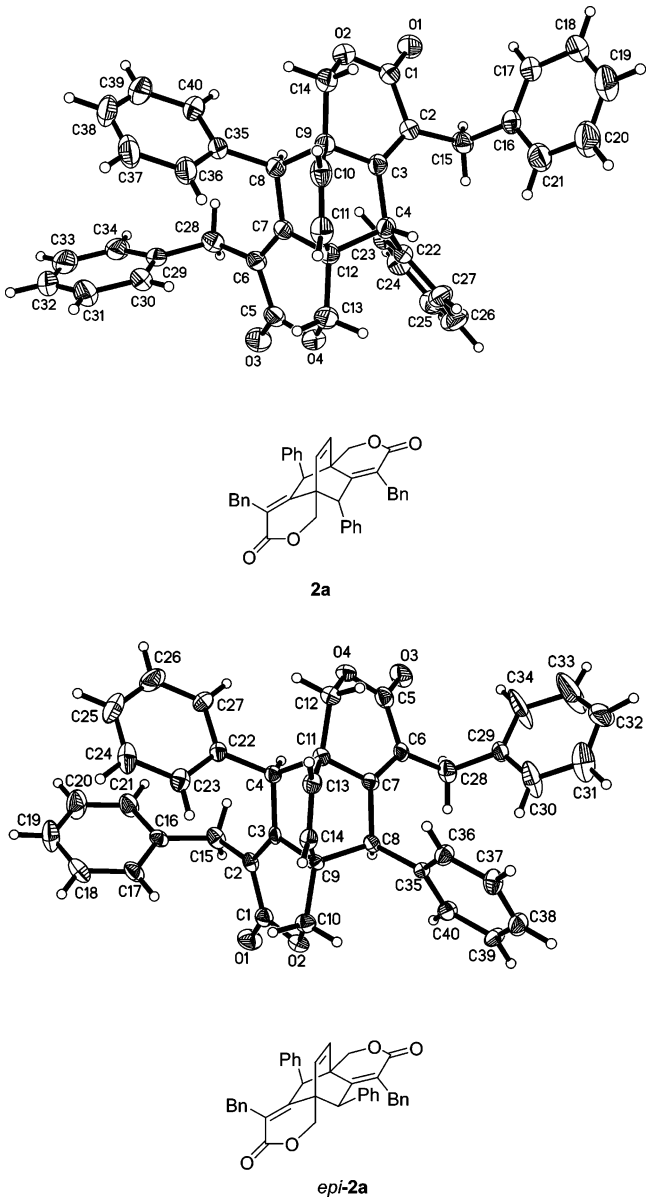
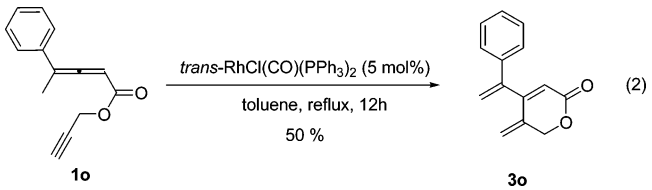


Figure 1. ORTEP representation of **2a** and *epi*-**2a** with thermal ellipsoids at the 30% probability level.

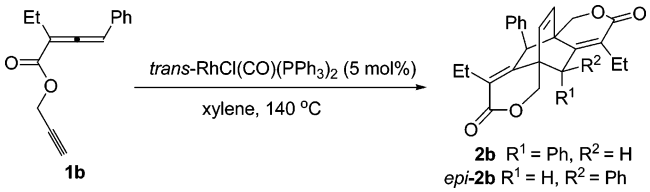
tolerates different substituents at the alkyne moiety (Ph, TMS, Bu, H, Table 3, entries 1−9) and alkyl substiuents at the allene, which could afford the α,β-unsaturated δ-lactones **3** in moderate to good yields. The exo C═C bond in **3** is in a *Z*-configuration.

When both phenyl and methyl groups were introduced at the 4-position of the allene moiety, i.e., **1o**, 5-methylene-4-(1-phenylvinyl)-5,6-dihydropyran-2-one **3o** was formed, implying that the β-hydride elimination is still favored even with only one alkyl group bearing hydrogens to be eliminated (eq 2).



Mechanistic Study. In order to trap any intermediate formed in this reacion, the cyclization of **1p** (an equivalent of **1c**) was conducted in the presence of 3-methoxyprop-1-yne. The reaction afforded 5-(4-bromophenyl)-6-(methoxymethyl)-4-propylisochroman-3-one **4p** in 50% yield (Scheme 4). The structure of **4p**

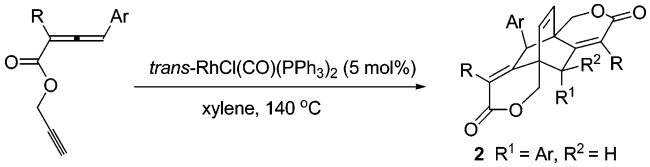
Table 1. Effect of Concentration of **1b** in Xylene on the *trans*-RhCl(CO)$(PPh_3)_2$-Catalyzed Dimeric Cyclization of Propargyl 2-Ethyl-4-phenylbuta-2,3-dienoate **1b**[a]



entry	concentration of **1b** (M)	isolated yield of **2b** (%)	isolated yield of *epi*-**2b** (%)
1	0.0833	30	18
2	0.0417	52	23
3	0.0278	38	22

[a] The reaction was conducted at 140 °C in a Schlenk tube with a screw cap.

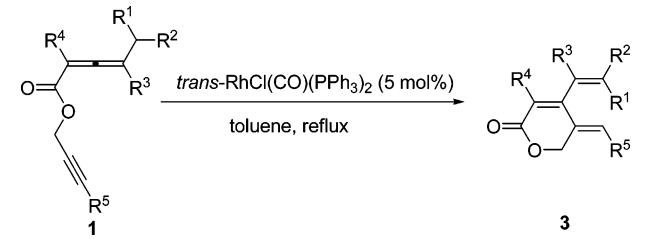
Table 2. Dimeric Cyclization of Propargyl 2,3-Dienoates[a]



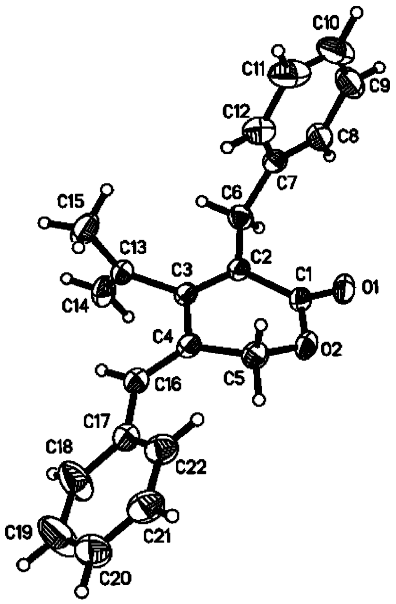
	1					
entry	Ar	R		time (h)	isolated yield of **2** (%)	isolated yield of *epi*-**2** (%)
1	Ph	Bn	**(1a)**	10	27 (**2a**)[8]	13 (*epi*-**2a**)[8]
2	Ph	Et	**(1b)**	12	52 (**2b**)	23 (*epi*-**2b**)
3	Ph	*n*-Pr	**(1c)**	10	45 (**2c**)	21 (*epi*-**2c**)
4	Ph	*i*-Bu	**(1d)**	10	38 (**2d**)[10]	28 (*epi*-**2d**)[10]
5	*p*-$MeOC_6H_4$	*n*-Bu	**(1e)**	10	45 (**2e**)	25 (*epi*-**2e**)

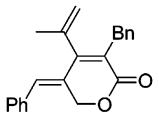
[a] The reaction was conducted at 140 °C in a Schlenk tube with a screw cap using 5 mol % *trans*-RhCl(CO)$(PPh_3)_2$ at a concentration of 0.042 M in xylene.

Table 3. Unimolecular Cyclization of Propargylic 2,3-Alkadienoates **1f**−**1n**



	1							
entry	R^1	R^2	R^3	R^4	R^5		time (h)	isolated yield of **3** (%)
1	H	H	Me	Bn	Ph	**(1f)**	15	67 (**3f**)
2	−$(CH_2)_5$−		H	H	TMS	**(1g)**	8	78 (**3g**)
3	H	H	Me	Bn	TMS	**(1h)**	34	66 (**3h**)
4	H	H	Me	Bn	*n*-Bu	**(1i)**	48	84 (**3i**)
5	−$(CH_2)_5$−		H	H	*n*-Bu	**(1j)**	27	63 (**3j**)
6	H	H	Me	Me	*n*-Bu	**(1k)**	34	58 (**3k**)
7	H	H	Me	Me	H	**(1l)**	17	75 (**3l**)
8	H	H	Me	Me	TMS	**(1m)**	24	53(**3m**)
9	H	H	Me	H	Ph	**(1n)**	14	63(**3n**)

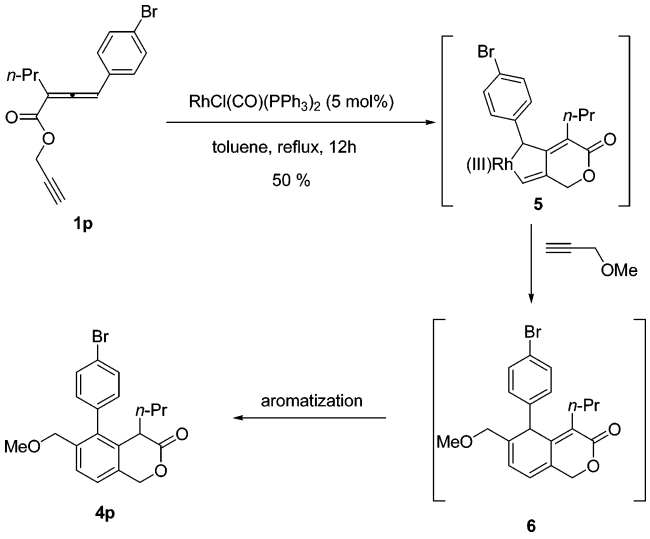




3f

Figure 2. ORTEP representation of **3f** with thermal ellipsoids at the 30% probability level.

Scheme 4. Cyclization of Propargyl 2,3-Alkadienoate **1p** in the Presence of 3-Methoxyprop-1-yne



was confirmed via an X-ray diffraction study (Figure 3).[14] With the unequivocal structural information of compound **4p**, it was reasoned that this compound was formed via the aromatization of **6**, which, in turn, was produced by the insertion of the triple bond in progargyl methyl ether to the C−Rh bond in bicyclic

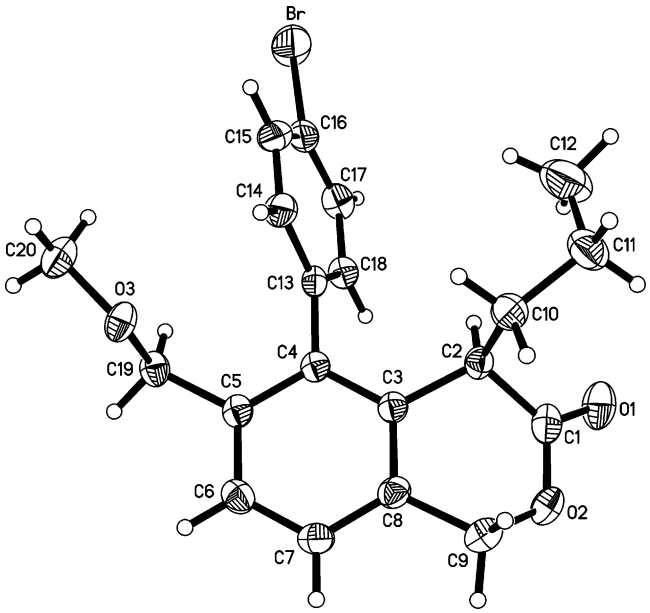


Figure 3. ORTEP representation of **4p** with thermal ellipsoids at the 30% probability level.

intermediate **5** and subsequent reductive elimination. This provided strong evidence for the mechanism of this reaction.

Based on the above results, a possible mechanistic rationale was proposed for the conversion of **1** to **2**/*epi*-**2** and **3** (Scheme 5). The reaction could proceed via the cyclometallation[2,4,5,15] of the carbon−carbon triple bond and the remote double bond of the tethered allene in **1** affording metallabicyclic intermediate **7**; if the substituent at the 4-positon of the dienoate moiety has a β-H atom, the β-H elimination occurs to form rhodium hydride intermediate **10**. Subsequent reductive elimination afforded 5,6-dihydropyran-2-one product **3**. The *Z*-stereochemistry of the exo double bond was determined by the cyclometallation and stereoselective reductive elimination. If there is no hydrogen available for β-hydride elimination by replacing an alkyl group with an aryl group, this bicyclic intermediate could highly selectively undergo carbometallation with the alkyne moiety in the second molecule of propargylic 2,3-dienoate **1** to afford metallabicyclic intermediates **8a** or **8b**. Subsequent reductive elimination would afford **9**, which could undergo an intramolecular Diels−Alder reaction[2,15a,16,17] to form the bridged polycyclic product **2** and its epimer *epi*-**2** (Scheme 5).

Derivatization of α,β-Unsaturated δ-Lactone. α,β-Unsaturated δ-lactones are widely distributed in both plants and fungi and possess a diverse range of biological activity. They have

(14) Crystal data for compound **4p**: $C_{20}H_{21}BrO_3$, MW = 389.28, monoclinic, space group *P*2(1)/*c*, final *R* indices [$I > 2\sigma(I)$], R1 = 0.0581, wR2 = 0.1345, *R* indices (all data), R1 = 0.1034, wR2 = 0.1637, *a* = 15.432 (2) Å, *b* = 14.140 (2) Å, *c* = 8.4535 (12) Å, α = 90°, β = 102.317(3)°, γ = 90°, *V* = 1802.1(4) Å^3, *T* = 293 (2) K, *Z* = 4, reflections collected/unique: 10 456/3915 (*R*(int) = 0.1458). Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC: 647589.

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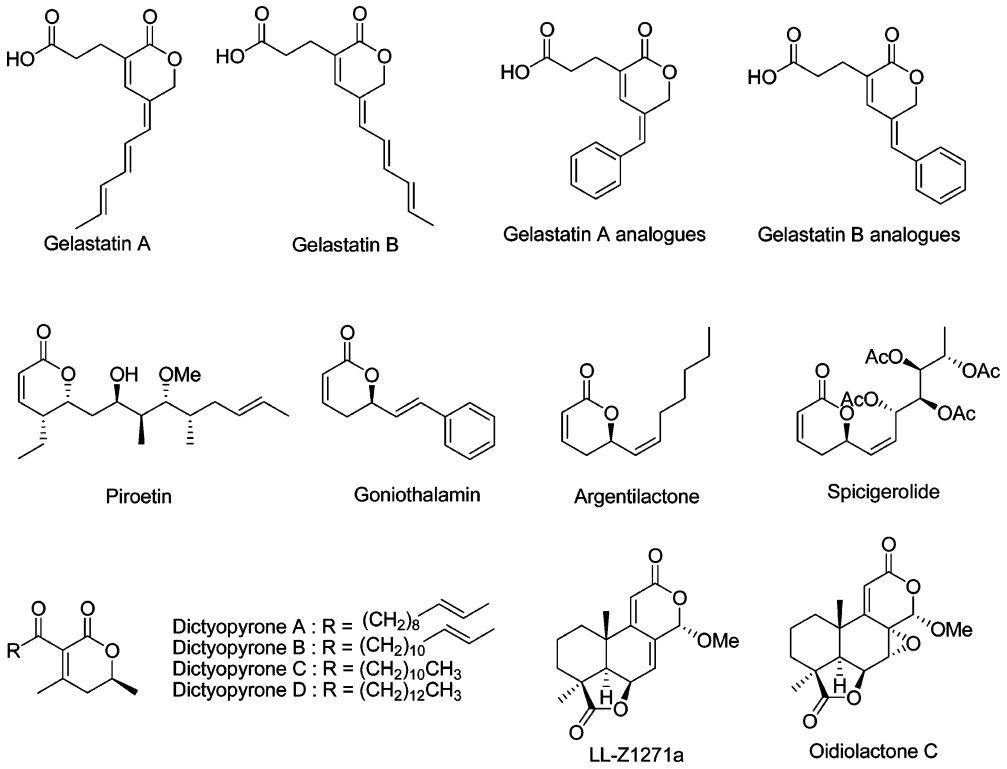

Figure 4. Some examples of natural α,β-unsaturated δ-lactones.

been reported as plant growth inhibitors, insect antifeedants, and antifungal/antitumor agents.[18] For example, gelastatin A, B and their analogues appear to be a viable lead in searching for therapeutically useful MMP inhibitors;[19] pironetin has been found to inhibit the cell cycle progression in the M phase;[20] goniothalamin has been shown to induce the apoptotic process;[21] argentilactone is an anticancer agent;[22] spicigerolide exhibits cytotoxic activity;[23] α-Pyronoids (dictyopyrones A−D) have been utilized as *anti*-leukemic agents;[24] LL-Z1271α and oidiolactone C demonstrate cytotoxic and antimicrobial activity.[25] These compounds indicate the importance of this methodology.

On the other hand, this type of products may also be used as important intermediates in organic synthesis. The carbonyl group in β-vinyl-γ-benzylidene-α,β-unsaturated δ-lactone **3f** could be reduced to a hydroxy group affording hemiacetal **11f** upon its treatment with DIBAL-H; The relatively electron-rich vinylic and exocyclic C=C bonds in **3f** could be easily hydrogenated with high regioselectivity to afford α,β-unsaturated δ-lactone **12f** (Scheme 6).

The vinylic silane moiety in product **3l** could be converted to vinylic iodide **13m** in 88% yield by its treatment with NIS. This compound could be used for subsequent Suzuki coupling and Sonogashira coupling reaction to afford **14m**, **15m**, and **16m** (Scheme 7).

Conclusion

In conclusion, both monomeric and dimeric cyclization of propargylic 2,3-dienoates were demonstrated for the highly selective synthesis of δ-lactones. The substituents at the 4-position of 2,3-alkadienoate moiety cleanly control the reaction pathway: when the 4-position was substituted with an aryl group, bimolecular cyclization occurred resulting in the formation of polycyclic bis(δ-lactone)-containing structures; with an alkyl substitutent at this position, unimolecular cyclization occurred, leading to cross-conjugated 5(*Z*)-alkylidene-4-alkenyl-5,6-dihydropyran-2-ones. It should be noted that the propargylic 2,3-allenoic acid ester linkage survived under the current protocol. Due to the importance of α,β-unsaturated δ-lactone,[26] this method could be potentially useful in organic synthesis and medicinal chemistry. Further studies in this area are being pursued in our laboratory.

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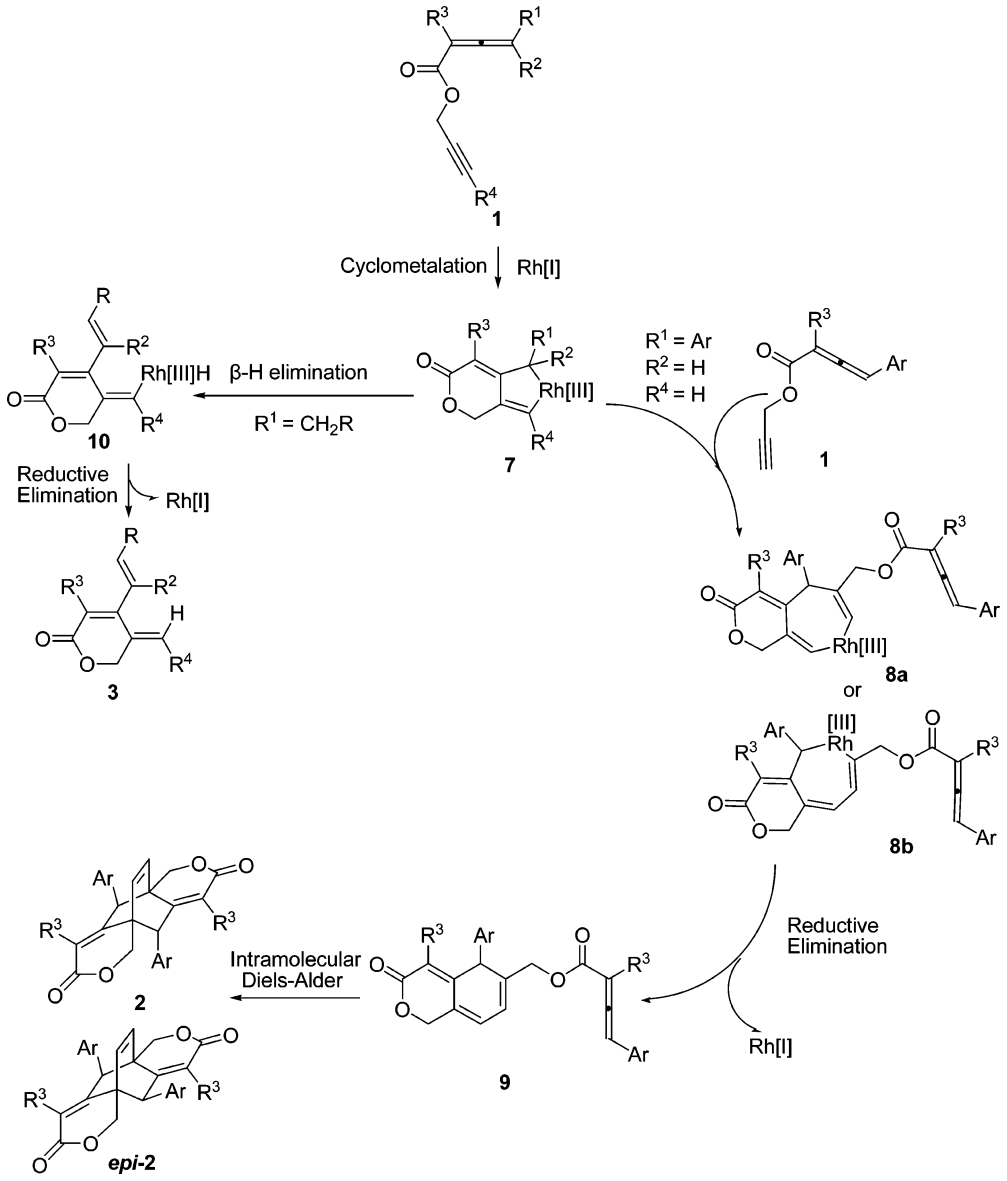
Scheme 5. Proposed Mechanism for the Mono- or Dimeric Cyclizations of Propargylic 2,3-Alkadienoates Catalyzed by *trans*-RhCl(CO)(PPh_3)$_2$



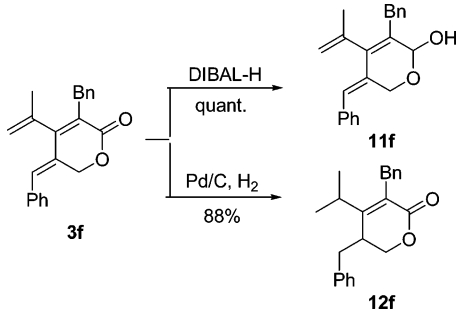
Experimental Section

General Procedure I. A solution of 2,3-dienoate acid,[7] propargylic bromide, and K_2CO_3 in acetone was stirred at room temperature. After the reaction was complete as monitored by TLC (petroleum ether/ethyl acetate = 10:1), filtration, rotary evaporation, and flash chromatography on silica gel (eluent: petroleum ether/ethyl ether = 30:1) afforded **1a**−**p**.

Preparation of Prop-2′-ynyl 2-Benzyl-4-phenylbuta-2,3-dienoate (1a). A solution of 2-benzyl-4-phenylbuta-2,3-dienoic acid (1.003 g, 4 mmol), propargyl bromide (1.6 g, 13 mmol), and K_2CO_3 (704 mg, 5 mmol) in acetone (40 mL) was stirred at room temperature for 12 h to afford 859 mg (74%) of **1a**: Liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.15 (m, 10 H), 6.55 (t, J = 2.4 Hz, 1 H), 4.77 (dd, J = 15.9, 2.7 Hz, 1 H), 4.68 (dd, J = 15.9, 2.7 Hz, 1 H), 3.74 (dd, J = 14.7, 2.1 Hz, 1 H), 3.68 (dd, J = 14.7, 2.1 Hz, 1 H), 2.43 (t, J = 2.1 Hz, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 213.5, 165.6, 138.7, 131.8, 128.9, 128.8, 128.3, 127.9, 127.4, 126.5, 103.6, 99.0, 77.6, 74.9, 52.6, 35.5; MS (EI) *m*/*z* (%) 288 (M^+, 1.02), 91 (100); IR (neat) 3288, 3030, 2120, 1944, 1718, 1600, 1496, 1454, 1260, 1086, 1063 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{16}O_2$ (M^+) 288.1150. Found 288.1134.

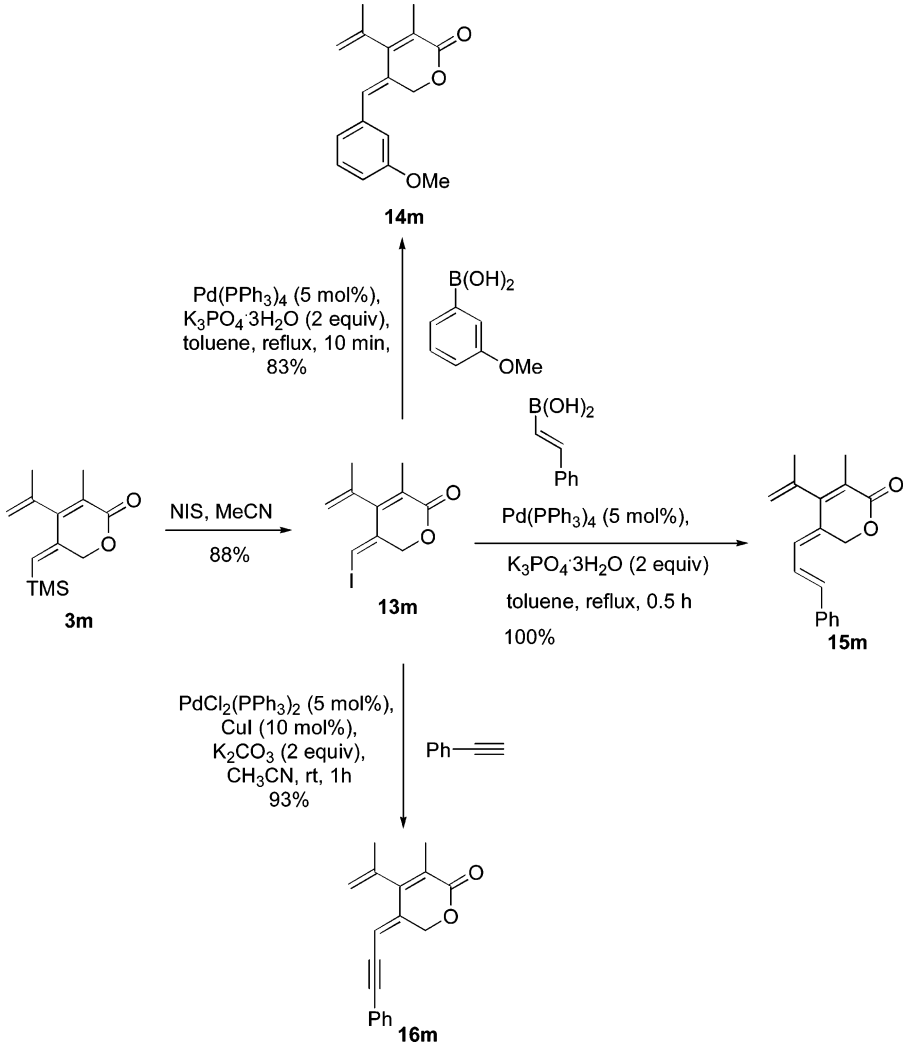
General Procedure II. A solution of propargylic 2,3-dienoate **1a**−**1e** and **1p** (0.25 mmol) and *trans*-RhCl(CO)(PPh_3)$_2$ (8 mg, 0.0125 mmol) in 6 mL of dry xylene was heated at 140 °C in a Schlenk tube with a screw cap. After the reaction was complete as monitored by TLC (petroleum ether/ethyl acetate = 3:1), rotary evaporation, and flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 5:1) afforded **2a**−**e** and **2p** (more polar) and *epi*-**2a**−**e** and *epi*-**2p** (less polar).

Scheme 6. Derivatization of α,β-Unsaturated δ-Lactone **3f**



Preparation of Products 2a and *epi*-2a. A solution of prop-2′-ynyl 2-benzyl-4-phenylbuta-2,3-dienoate **1a** (70 mg, 0.25 mmol) and *trans*-RhCl(CO)(PPh_3)$_2$ (9 mg, 0.0125 mmol) in 6 mL of dry xylene

Scheme 7. Iodination of Lactone **3m** and the Coupling Reaction of the Iodide **13m**



was heated at 140 °C for 10 h to afford 19 mg (28%) of **2a** (more polar) and 9 mg (13%) of *epi*-**2a** (less polar). **2a**: Solid, mp 259−260 °C (petroleum ether/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.26 (m, 4 H), 7.26−7.00 (m, 10 H), 6.93−6.80 (m, 6 H), 6.41 (d, J = 7.5 Hz, 1 H), 5.82 (d, J = 7.5 Hz, 1 H), 4.70 (d, J = 12.3 Hz, 1 H), 4.61 (d, J = 12.3 Hz, 1 H), 4.45 (d, J = 12.0 Hz, 1 H), 4.24 (s, 1 H), 4.17 (d, J = 12.0 Hz, 1 H), 3.77 (s, 1 H), 3.48 (d, J = 14.1 Hz, 1 H), 3.40 (d, J = 15.0 Hz, 1 H), 2.99 (d, J = 14.1 Hz, 1 H), 2.73 (d, J = 15.0 Hz, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 164.8, 163.0, 156.4, 152.2, 138.6, 137.2, 136.8, 135.54, 135.48, 132.1, 130.4, 129.11, 129.07, 128.8, 128.5, 128.34, 128.32, 128.26, 128.0, 126.3, 126.1, 69.2, 67.0, 57.7, 51.1, 46.8, 46.3, 33.7, 33.4; MS (ESI) *m*/*z* (%) 615 (M + K^+, 30), 577 (M + H^+, 100); IR (neat) 1706, 1701, 1602, 1495, 1465, 1453, 1198, 1151 cm^{-1}; HRMS (ESI) calcd for $C_{40}H_{32}O_4Na$ (M + Na^+) 599.2193. Found 599.2187.

epi-**2a**: Solid, mp 274−275 °C (petroleum ether/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.25 (m, 6 H), 7.12−7.00 (m, 10 H), 6.70−6.60 (m, 4 H), 5.86 (s, 2 H), 4.52 (d, J = 12.0 Hz, 2 H), 4.43 (d, J = 12.0 Hz, 2 H), 4.17 (s, 2 H), 3.43 (d, J = 14.4 Hz, 2 H), 3.36 (d, J = 14.4 Hz, 2 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 164.0, 157.6, 137.4, 136.5, 131.0, 130.4, 128.6, 128.2, 128.1, 126.2, 66.5, 52.8, 46.6, 34.0; MS (ESI) *m*/*z* (%) 615 (M + K^+, 25), 599 (M + Na^+, 20), 594 (M + NH_4^+, 40), 577 (M + H^+, 100); IR (neat) 1716, 1601, 1494, 1452, 1310, 1142 cm^{-1}; HRMS (ESI) calcd for $C_{40}H_{33}O_4$ (M + H^+) 577.2373. Found 577.2372.

General Procedure III: A solution of propargylic 2,3-dienoate **1f**−**1o** (0.25 mmol) and *trans*-RhCl(CO)(PPh_3)$_2$ (9 mg, 0.0125 mmol) in 6 mL of dry toluene was refluxed under Ar. After the reaction was complete as monitored by TLC (petroleum ether/ethyl acetate = 10:1), rotary evaporation and flash chromatography on silica gel (eluent: petroleum ether/ethyl ether = 20:1) afforded the product **3f**−**o.**

Synthesis of (*Z*)-3-Benzyl-5-benzylidene-4-(prop-1-en-2-yl)-5,6-dihydropyran-2-one (3f). A solution of 3′-phenylprop-2′-ynyl 2-benzyl-4-methylpenta-2,3-dienoate **1f** (64 mg, 0.20 mmol) and *trans*-RhCl(CO)(PPh_3)$_2$ (7 mg, 0.01 mmol) in 5 mL of dry toluene was refluxed under Ar for 15 h to afford 43 mg (67%) of **3f**. Some starting material remained. Solid, mp 89−90 °C (petroleum ether/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.10 (m, 10 H), 6.89 (s, 1 H), 5.41 (s, 1 H), 5.23 (s, 2 H), 5.00 (s, 1 H), 3.87 (s, 2 H), 1.94 (s, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 164.6, 153.6, 139.7, 139.4, 135.0, 133.2, 129.0, 128.6, 128.5, 128.4, 128.3, 126.0, 124.9, 118.0, 66.5, 34.0, 23.1; MS (EI) *m*/*z* (%) 316 (M^+, 0.57), 91 (100); IR (neat) 1699, 1602, 1494, 1446, 1413, 1344, 1272, 1263, 1185, 1122, 1059 cm^{-1}. Anal. Calcd for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.45; H, 6.26.

Mechanistic Study. Synthesis of 5-(*p*-Bromophenyl)-6-(methoxymethyl)-4-propylisochroman-3-one (4p). A solution of prop-2′-ynyl 2-propyl-4-(*p*-bromophenyl)buta-2,3-dienoate **1p** (46 mg, 0.15 mmol), 3-methoxyprop-1-yne (110 mg, 1.57 mmol), and *trans*-RhCl(CO)(PPh_3)$_2$ (6 mg, 0.0087 mmol) in 3.6 mL of dry toluene was heated at 110 °C in the reaction tube with a screw cap for 10 h to afford 28 mg (50%) of the product **4p**: Solid, mp 71−72 °C (petroleum ether/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61−7.55 (m, 2 H), 7.45 (d, J = 7.8 Hz, 1 H), 7.23 (d, J = 7.8 Hz, 1 H), 7.12−7.07 (m,

1 H), 7.07−6.98 (m, 1 H), 5.57 (d, J = 14.3 Hz, 1 H), 5.23 (d, J = 14.3 Hz, 1 H), 4.06 (s, 2 H), 3.55−3.45 (m, 1 H), 3.24 (s, 3 H), 1.80−1.60 (m, 2 H), 1.45−1.10 (m, 2 H), 0.70 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 172.3, 138.4, 137.1, 135.3, 133.9, 131.9, 131.4, 131.2, 131.0, 130.2, 127.1, 124.5, 122.1, 72.2, 69.5, 58.4, 43.3, 33.5, 20.3, 13.3; MS (EI) m/z (%) 390 (M^+, ^{81}Br, 5.61), 388 (M^+, ^{79}Br, 5.76), 43 (100); IR (neat) 2959, 2929, 1739, 1490, 1465, 1384, 1234, 1194, 1096 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{21}O_3Br$ (M^+) 388.0674. Found 388.0664.

Synthetic Application. 1. Synthesis of (*Z*)-3-Benzyl-5-benzylidene-4-(prop-1-en-2-yl)-5,6-dihydro-2*H*-pyran-2-ol (11f). To a solution of (*Z*)-3-benzyl-5-benzylidene-4-(prop-1-en-2-yl)-5,6-dihydro-pyran-2-one **3f** (50 mg, 0.16 mmol) in 1 mL of dry THF at −78 °C was added DIBAL-H (1 M in toluene, 0.64 mL) for 5 min. After quenching the reaction with saturated NaCl, extraction with ether, drying over Na_2SO_4, filtration, and evaporation, the residue was purified by column chromatography on silica gel to afford 55 mg (100%) of the product **11f**: Liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.12 (m, 10 H), 6.63 (s, 1 H), 5.35 (s, 1 H), 5.19 (d, J = 4.8 Hz, 1 H), 5.04 (s, 1 H), 4.87 (d, J = 13.7 Hz, 1 H), 4.64 (d, J = 13.7 Hz, 1 H), 3.83 (d, J = 15.0 Hz, 1 H), 4.52 (d, J = 15.0 Hz, 1 H), 3.45−3.30 (br, 1 H), 1.96 (s, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 140.9, 139.1 138.8, 136.6, 131.3, 131.1, 129.0, 128.7, 128.4, 128.2, 127.0, 126.1, 116.9, 89.4, 58.2, 36.2, 23.8; MS (EI) m/z (%) 318 (M^+, 18.72), 91 (100); IR (neat) 3395, 3025, 2913, 1642, 1600, 1493, 1451, 1371, 1264 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{22}O_2$ (M^+) 318.1620. Found 318.1616.

2. Synthesis of 3,5-Dibenzyl-4-isopropyl-5,6-dihydropyran-2-one (12f). A solution of (*Z*)-3-benzyl-5-benzylidene-4-(prop-1-en-2-yl)-5,6-dihydropyran-2-one **3f** (47 mg, 0.15 mmol) and Pd/C (5 mg) in 1 mL of CH_3OH under 1 atm of H_2 atmosphere was stirred at room temperature for 5 h. After evaporation, the residue was purified by column chromatography on silica gel to afford 42 mg (88%) of the product **12f**: Liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.12 (m, 10 H), 4.14 (dd, J = 11.1, 1.2 Hz, 1 H), 4.02 (dd, J = 11.1, 0.9 Hz, 1 H), 3.91 (d, J = 15.0 Hz, 1 H), 3.75 (d, J = 15.0 Hz, 1 H), 3.25−3.10 (m, 1 H), 2.94 (dd, J = 13.2, 3.0 Hz, 1 H), 2.74 (dd, J = 14.1, 12.0 Hz, 1 H), 2.55−2.45 (m, 1 H), 1.25 (d, J = 6.6 Hz, 3 H), 1.10 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 165.8, 162.6, 139.6, 138.6, 129.1, 128.7, 128.5, 128.0, 126.8, 126.0, 124.7, 67.2, 36.2, 36.0, 31.9, 31.2, 21.7, 20.3; MS (EI) m/z (%) 320 (M^+, 28.87), 91 (100); IR (neat) 3061, 3027, 2966, 2935, 1711, 1602, 1494, 1467, 1453, 1130 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{24}O_2$ (M^+) 320.1776. Found 320.1772.

3. Synthesis of (*Z*)-5-(Iodomethylene)-3-methyl-4-(prop-1-en-2-yl)-5,6-dihydropyran-2-one (13m). A solution of 3-methyl-5-methylene-4-(prop-1-en-2-yl)-5,6-dihydropyran-2-one **3m** (118 mg, 0.50 mmol) and *N*-iodosuccinimide (230 mg, 1.02 mmol) in 4 mL of dry CH_3CN was refluxed for 10 h. After evaporation, the residue was purified by column chromatography on silica gel to afford 128 mg (88%) of the product **13m**: Liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (s, 1 H), 5.34 (s, 1 H), 5.01 (s, 2 H), 4.86 (s, 1 H), 1.89 (s, 3 H), 1.87 (s, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 165.1, 149.4, 138.8, 137.0, 121.1, 117.8, 84.4, 72.8, 22.2, 14.3; MS (EI) m/z (%) 290 (M^+, 1.98), 91 (100); IR (neat) 3068, 2919, 1717, 1643, 1600, 1452, 1395, 1255, 1129 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{11}O_2I$ (M^+) 289.9804. Found 298.9809.

4. Synthesis of (*Z*)-5-(*m*-Methoxybenzylidene)-3-methyl-4-(prop-1-en-2-yl)-5,6-dihydropyran-2-one (14m). A mixture of **13m** (44 mg, 0.15 mmol), 3-methoxyphenylboronic acid (45 mg, 0.3 mmol), $Pd(PPh_3)_4$ (9 mg, 5 mol %), and $K_3PO_4\cdot 3H_2O$ (81 mg, 0.3 mmol) in toluene (2 mL) was refluxed under Ar for 10 min. After evaporation, the residue was purified by column chromatography on silica gel to afford **14m** (34 mg, 83%): Liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (t, J = 8.0 Hz, 1 H), 6.86 (d, J = 8.0 Hz, 1 H), 6.77 (s, 1 H), 6.73 (d, J = 8.0 Hz, 1 H), 6.68 (s, 1 H), 5.38 (s, 1 H), 5.22 (s, 2 H), 4.93 (s, 1 H), 3.81 (s, 3 H), 2.00 (s, 3 H), 1.94 (s, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 165.3, 159.5, 152.7, 139.7, 136.4, 132.0, 129.5, 128.5, 121.8, 121.4, 117.5, 114.6, 113.7, 66.8, 55.2, 22.5, 14.7; MS (EI) m/z (%) 270 (M^+, 42.13), 226 (100); IR (neat) 2922, 1713, 1598, 1576, 1489, 1458, 1432, 1261, 1127 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{18}O_3$ (M^+) 270.1256. Found 270.1261.

5. Synthesis of 3-Methyl-5-(*Z*)-(((*E*)-3-phenylvinyl)methylene)-4-(prop-1-en-2-yl)-5,6-dihydropyran-2-one (15m). A solution of **13m** (40 mg, 0.14 mmol), (*E*)-styrylboronic acid (41 mg, 0.28 mmol), $Pd(PPh_3)_4$ (8 mg, 5 mol %), and $K_3PO_4\cdot 3H_2O$ (76 mg, 0.28 mmol) in toluene (2 mL) was refluxed under Ar for 0.5 h. After evaporation, the residue was purified by column chromatography on silica gel to afford **15m** (52 mg, 100%): Liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.40 (m, 2 H), 7.40−7.20 (m, 3 H), 6.94 (dd, J = 15.2, 11.4 Hz, 1 H), 6.78 (d, J = 15.2 Hz, 1 H), 6.45 (d, J = 11.4 Hz, 1 H), 5.39−5.32 (m, 1 H), 5.22−5.18 (m, 2 H), 4.90−4.82 (m, 1 H), 1.98 (s, 3 H), 1.93−1.90 (m, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 165.8, 152.8, 139.5, 138.3, 136.4, 130.6, 128.8, 128.7, 127.0, 126.8, 122.3, 121.2, 117.1, 66.1, 22.6, 14.6; MS (EI) m/z (%) 266 (M^+, 6.70), 84 (100); IR (neat) 3033, 2922, 2855, 1706, 1616, 1582, 1449, 1258, 1128 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{18}O_2$ (M^+) 266.1307. Found 266.1303.

6. Synthesis of (*Z*)-3-Methyl-5-(3-phenylprop-2-ynylidene)-4-(prop-1-en-2-yl)-5,6-dihydropyran-2-one (16m). A mixture of **13m** (39 mg, 0.14 mmol), phenylacetylene (32 mg, 0.3 mmol), $PdCl_2(PPh_3)_2$ (5 mg, 5 mol %), CuI (4 mg, 10 mol %), K_2CO_3 (42 mg, 0.3 mmol), and CH_3CN (2 mL) was stirred at rt under Ar for 1 h. Evaporation and purification by column chromatography on silica gel afforded **16m** (33 mg, 93%): Liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.40 (m, 2 H), 7.40−7.27 (m, 3 H), 5.96 (s, 1 H), 5.35 (s, 1 H), 5.29 (s, 2 H), 4.88 (s, 1 H), 1.98 (s, 3 H), 1.91 (s, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 165.1, 150.7, 138.8, 137.8, 131.5, 129.0, 128.5, 122.6, 122.4, 117.6, 109.6, 102.0, 85.4, 67.9, 22.3, 14.6; MS (EI) m/z (%) 264 (M^+, 46.71), 178 (100); IR (neat) 3080, 2919, 2854, 2187, 1709, 1642, 1598, 1489, 1442, 1256, 1130 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{16}O_2$ (M^+) 264.1150. Found 264.1153.

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Supporting Information Available: All experimental procedures and analytical data for all starting materials and products; copies of ^{1}H/^{13}C NMR spectra of all new compounds; ORTEP drawing of **2d** and *epi*-**2d**; the CIF files of all crystals. This material is available free of charge via the Internet at http://pubs.acs.org.

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