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A Convergent Approach to Diverse Spiroethers through Stereoselective Trapping of Rhodium Carbenoids with Gold-Activated Alkynols

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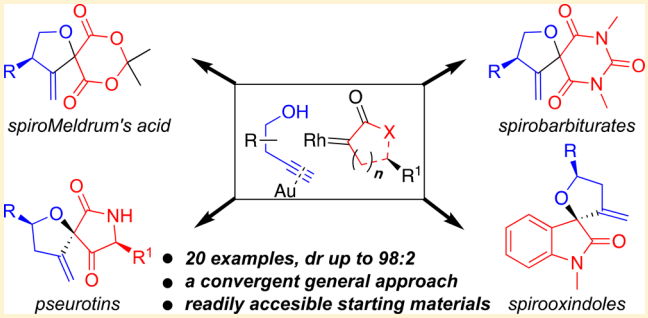
Supporting Information

ABSTRACT: A convergent approach for the stereoselective synthesis of diverse spiroethers is described. The reaction involves stereoselective trapping of diazo-derived rhodium carbenoids with gold-activated alkynols for the installation of spiro cores. The reaction has proven general with a range of readily accessible homopropargylic alcohols and diazo carbonyls to provide functionalized spiroether cores of bioactive scaffolds such as spirobarbiturates, spirooxindoles, and pseurotin natural products.



INTRODUCTION

The spiroether core is found in a wide range of bioactive natural products and drug molecules (Figure 1).[1] Examples include the naturally occurring pseurotins, and spirooxindoles, both natural and synthetic.[2] Griseofulvin, a spiroether drug, is on the World Health Organization list of essential medicines.[3] The importance of this scaffold in drug development can be attributed to the spiro center inducing rigid organization of the overall molecular scaffold, causing the functional groups to be presented to biological targets in well-defined three-dimensional orientations to provide increased binding affinity and bioavailability.[4]

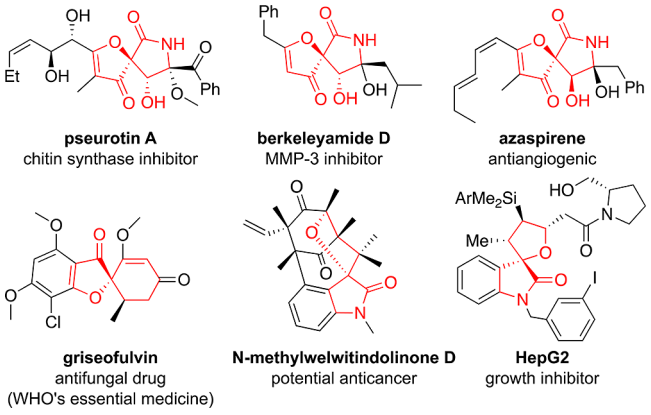


Figure 1. Examples of spiroether natural products and drug molecules.

Due to the biological and therapeutic values, the synthesis of spiroethers remains an area of current interest to the chemical community.[5] The key synthetic challenge is the stereoselective installation of the spiro center. Most methods rely heavily on intramolecular cyclization/rearrangement reactions of an appropriate linear precursor, which requires multiple synthetic steps for preparation (Figure 2a).[6]

To overcome this synthetic challenge, we report a convergent approach for the stereoselective synthesis of diverse

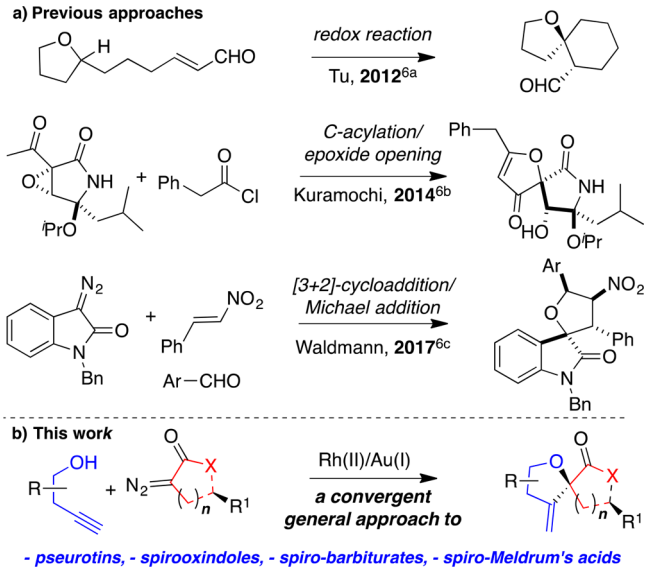


Figure 2. (a) Approaches for spiroether synthesis. (b) This work.

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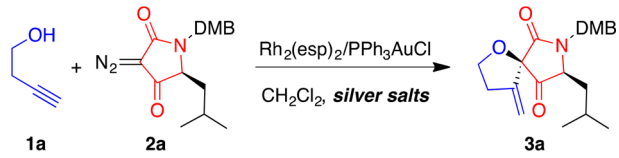
spiroethers through stereoselective trapping of rhodium carbenoids[7] with gold-activated homopropargylic alcohols (Figure 2b). Notably, this approach enables new Conia-ene cyclizations with diester, ketoamide, diamide, and amide functionalities, which were previously problematic to achieve using gold catalysis as described by the Toste group.[8] This limitation of the gold-catalyzed Conia-ene cyclization was also observed in our previous work related to the synthesis of functionalized tetrahydrofurans and γ-butyrolactones.[9]

RESULTS AND DISCUSSION

We initiated our work targeting the densely functionalized spiroether core of berkeleyamide D. First, the diazo compound **2a** was synthesized at gram scale starting from L-leucine methyl ester following the slightly modified literature protocols.[10] For the initial optimization, diazo compound **2a** was subjected to the most efficient $Rh_2(esp)_2$/PPh_3AuCl/AgOTf conditions developed in our lab for diazo-OH insertion/Conia-ene cyclization.[9] Diazo compound **2a** was found to be completely stable and did not decompose at room temperature. When the reaction was refluxed in CH_2Cl_2, diazo **2a** was completely consumed, but the reaction resulted in a very low isolated yield of desired spiroether **3a** (Table 1, entry 1). This is presumably due to the effect of silver triflate, as metal triflates have been known to be a mild source of triflic acid,[11] which could cause decomposition of the desired spiroether product. Therefore, we thought of screening the effect of silver salts with varying counteranions for in situ generation of active cationic gold species. To our delight, $AgSbF_6$ promoted the Conia-ene cyclization in 100% conversion without any decomposition of the spiroether product **3a**, which was isolated as a single diastereomer (entry 7). Also, the reaction was found to be significantly faster and cleaner at higher concentration (entry 8).

Table 1. Effect of Silver(I) Salts on Diazo O−H Insertion/Conia-ene Cyclization[a]



1a 2a 3a

entry	silver salts	T (°C), time	3 conversion %[b] (isolated yield %)[c]
1	AgOTf	rt, 12 h	NR
2	AgOTf	reflux, 3 h	100 (19)
3	AgOAc	reflux, 12 h	NR
4	AgTFA	reflux, 12 h	7
5	$AgBF_4$	reflux, 12 h	40
6	$AgPF_6$	reflux, 12 h	70
7	$AgSbF_6$	reflux, 3 h	100 (66)
8	$AgSbF_6$	reflux, 1 h	100 (68)[d]

[a]All reactions were performed by mixing diazo compound **2a** (1 equiv), **1a** (1.2 equiv), $Rh_2(esp)_2$ (1 mol %), and $AgSbF_6$/PPh_3AuCl (10 mol %) in 0.1 M CH_2Cl_2 with 4 Å molecular sieves (MS). NR = no reaction. [b]Conversion (%) was determined from the crude ^1H NMR spectrum. [c]Isolated yield (%) after flash chromatography. [d]Reaction concentration = 0.3 M.

The relative configuration of the stereocenters in spiroether **3a** was determined based on the nuclear Overhauser effect (NOE) correlations and was further confirmed by the single crystal structure of **3a** using X-ray crystallography (Figure 3).[12] As expected, the resulting spiro junction had the resulting alkene functionality opposite to the bulk of alkyl side chain on the diazo compound.

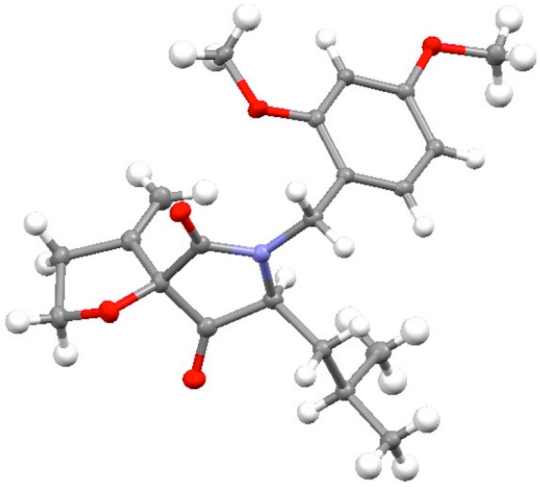


Figure 3. X-ray crystal structure of spiroether **3a**.

With optimized conditions in hand, we then investigated the scope of the reaction. Diazo ketoamide derived from D-leucine methyl ester also proceeded cleanly to afford **3b** as a single diastereomer. The relative stereochemistry of product **3b** was also confirmed by the single crystal structure.[13] As expected, compound **3b** was found to be an enantiomer of **3a** having identical NMR spectra and opposite optical rotation (Figure 4). Diazo ketoamide derived from L-phenylalanine also proceeded in good yield to provide the core structure of the azaspirene natural product (**3c**). Finally, high stereoselectivity was also maintained with the diazo ketoamide derived from L-alanine bearing a small methyl group as side chain (**3d**).

Interestingly, when the cascade reaction was attempted with the *R*-enantiomer of the alcohol having mismatched stereochemistry (steric bulk on the face opposite that of the side chain of diazo), the reaction was found to be sluggish and proceeded with low yield as well as low diastereoselectivity (**3e**). Meanwhile, the secondary alcohol (*S*-enantiomer) having matched stereochemistry (steric bulk on the same face as the side chain of diazo) proceeded in good yield with high diastereoselectivity (**3f**). A similar trend was also observed in another mismatched alcohol example having a benzyl side chain (**3g**).

To further explore the generality of this transformation, other stable acceptor/acceptor diazo compounds were also examined. The diazo derivative of Meldrum's acid was prepared and subjected to the optimized conditions to provide the Conia-ene cyclization product **3h** in moderate yield. This diazo diester was also compatible with substituted primary and secondary alkynols (entries **3i,j**). The moderate yields observed with spiro-Meldrum's acid substrates can be attributed to molecular instability due to the high level of entropic driving force for fragmentation in the presence of Lewis acids.[14] Next, the chemistry was applied to access the spirobarbiturates, which are medicinally relevant molecules with diverse biological activities.[15] As expected, the diazo barbituric acid bearing a diamide functionality also accommodated primary as well as secondary (entries **3k−m**) alcohol substituents.

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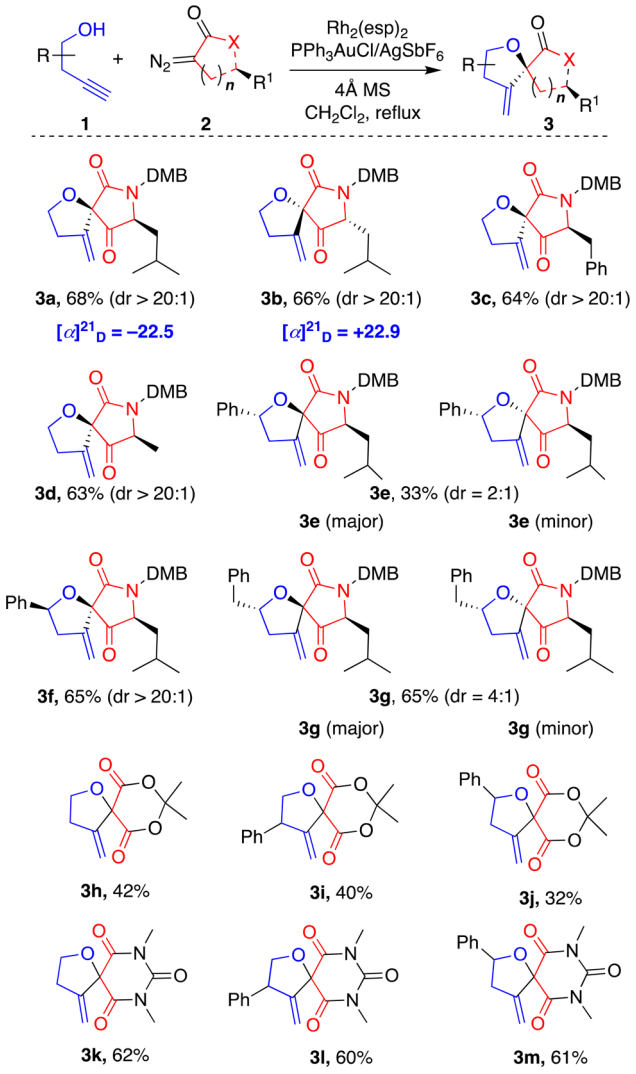


Figure 4. Substrate scope of the synergistic Rh/Au-catalyzed diazo-OH insertion/Conia-ene cyclization. All reactions were performed by mixing diazo compounds (1 equiv) with a solution of **1a–f** (1.2 equiv), $Rh_2(esp)_2$ (1 mol %), and $AgSbF_6/PPh_3AuCl$ (10 mol %) in 0.3 M CH_2Cl_2 with 4 Å MS.

In hopes of extending the methodology to donor/acceptor cyclic diazos, isatin diazo **2g** was synthesized and subjected to the most efficient $Rh_2(esp)_2/PPh_3AuOTf$ conditions developed in our lab for stereoselective O–H insertion/Conia-ene cyclization.[9] This condition proved to be low yielding, providing a majority of insertion product **4b**. After further optimization, a combination of $Rh_2(TFA)_4/PPh_3AuOTf$ at 0 °C provided the desired product **3n** in good yield (Figure 5). These conditions accommodated primary and secondary alcohols and both electronically donating and withdrawing substituents on the isatin diazo (entries **3o–t**). The stereochemistry of compound **3p** was confirmed by NOE and was influenced by the steric bulk of the alkynol substrate.

To probe the reaction mechanism, deuterium labeling experiments were carried out with both the acceptor/acceptor and donor/acceptor diazo compounds (Scheme 1). In both cases, no deuterium scrambling was observed, and the deuterium was found to be syn to the carbonyl functionality as observed by the Toste group.[8] These results suggest a mechanism involving the trapping of enol intermediate with a

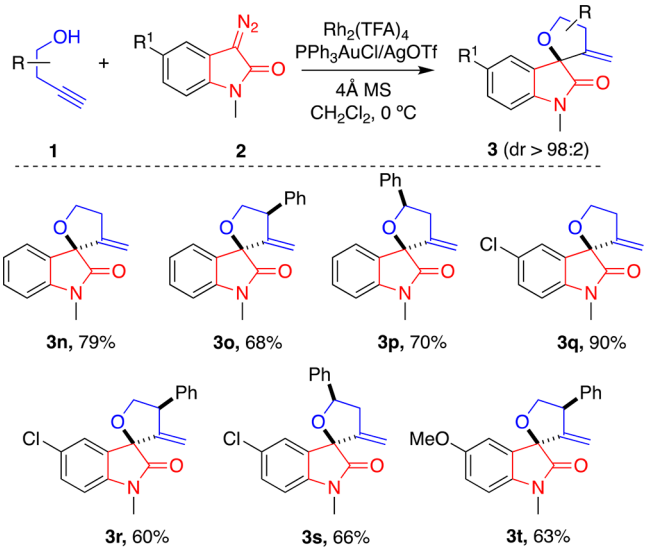
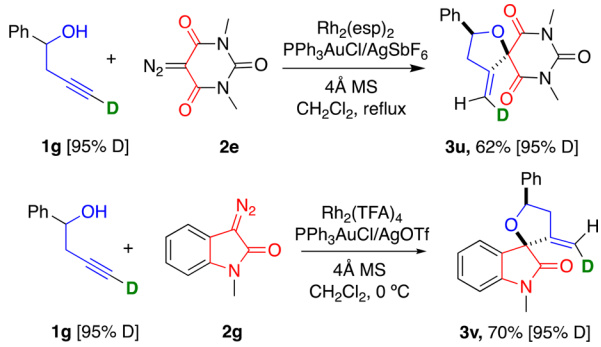


Figure 5. All reactions were performed by syringe pump addition of a solution of diazo compounds **2g–i** (1.2 equiv) and alkynols (1.0 equiv) in 0.1 M in CH_2Cl_2 to a premixed stirred solution of $Rh_2(TFA)_4$ (1 mol %), and AgOTf/PPh_3AuCl (5 mol %) in 0.2 M CH_2Cl_2 with activated 4 Å MS at 0 °C.

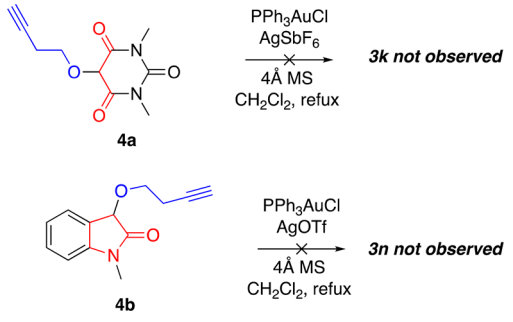
Scheme 1. Deuterium Labeling Experiments



gold-alkyne π-coordinated complex, ruling out the formation of gold-acetylide.[16]

For further insight, the insertion products were synthesized with the acceptor/acceptor and donor/acceptor diazo compounds using rhodium as a catalyst. When the insertion compounds were subjected to the gold-catalyzed Conia-ene cyclization,[8] we did not observe any cyclized product even after 12 h in refluxing dichloromethane (Scheme 2).

Scheme 2. Control Experiments



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We also attempted the cascade reaction with chiral rhodium salts Rh_2(*S*-DOSP) and Rh_2(*S*-PTAD) with diazo **2g**. Notably, no enantiomeric excess (ee) was observed using chiral Rh(II)-salts, which was in accordance with the literature reports of inducing negligible enantioselectivity with chiral rhodium catalysts involving trapping of electrophiles with oxonium and ammonium ylides that are formed in situ from the carbene–heteroatom insertion.[17]

These findings allow us to propose the reaction mechanism depicted in Figure 6. When added in a stepwise fashion, Rh/Au

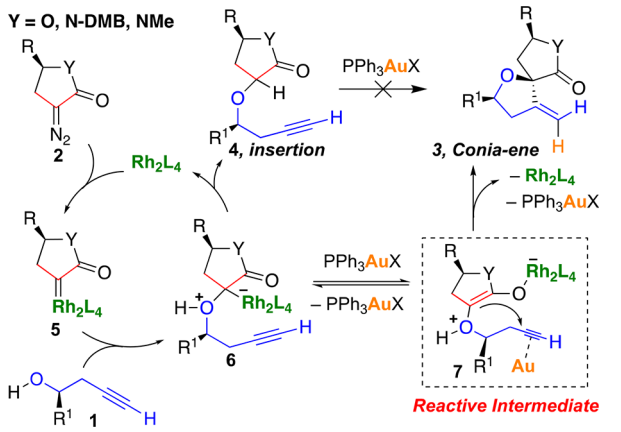

Figure 6. Plausible reaction mechanism.

work independently without exerting any synergistic effect on each other. Specifically, Rh(II) decomposes the diazo compounds **2** to form a Rh-carbenoid **5** that undergoes oxygen insertion to provide a zwitterionic intermediate **6**, which undergoes a keto–enol tautomerism to provide reactive intermediate **7**. The reactive enol form in interemdiate **7** enables Conia-ene cyclization with the monocarbonyl compounds as well as with diesters, ketoamides, and diamides. The enol intermediate **7** also explains the lack of enantioinduction with chiral rhodium salts. The stereochemistry of the Conia-ene cyclization is influenced by the steric bulk of the diazo as well as alkynol substrate, where the enol form approaches the gold-activated alkyne from the opposite face of the steric bulk.

CONCLUSION

The reported synergistic Rh/Au-catalysis conditions are mild, selective, and provide a general convergent route to diverse spiroethers including the asymmetric synthesis of the pseurotin natural product spiroether core. An important feature of this transformation is its high stereoselectivity and the enabling of new Conia-ene cyclizations with diesters, ketoamides, and diamides that would otherwise be difficult to access. Further mechanistic analyses and application to the synthesis of spiroether natural products are ongoing and will be reported in due course.

MATERIALS AND METHODS

All reactions were performed in flame-dried glassware under positive N_2 pressure with magnetic stirring unless otherwise noted. Reagents and solvents were obtained from Sigma-Aldrich, Chem-Impex, VWR International, and Acros Organics and used without further purification unless otherwise indicated. Dichloromethane and acetonitrile were distilled over CaH under N_2 unless otherwise indicated. Tetrahydrofuran was distilled over Na under N_2 with benzophenone indicator. Thin layer chromatography (TLC) was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by staining with potassium permanganate ($KMnO_4$), cerium ammonium molybdate (CAM), phosphomolybdic acid (PMA), and ninhydrin. Silica flash chromatography was performed on Sorbtech 230–400 mesh silica gel 60. Syringe pump addition reactions were conducted using a Harvard Apparatus (model: 55-1111) or a New Era Pump Systems, Inc. (model: NE-300) syringe pump. Sonication was performed using a Bransonic ultrasonic cleaner (model: M5800H). NMR spectra were recorded on a Varian VNMRS 300, 400, and 500 MHz NMR spectrometer at 20 °C in $CDCl_3$ unless otherwise indicated. Chemical shifts are expressed in ppm relative to solvent signals: $CDCl_3$ ((^{1}H, 7.26 ppm, ^{13}C, 77.0 ppm); coupling constants are expressed in hertz (Hz). IR spectra were recorded on a Cary 760 FTIR spectrometer with peaks reported in cm^{-1}. Optical rotations were recorded using an Autopol III automatic polarimeter by Rudolph Research Analytical. Mass spectra were obtained at the OU Analytical Core Facility on an Agilent 6538 high-mass-resolution QTOF mass spectrometer attached to an Agilent 1290 UPLC. X-ray crystallography analysis was carried out at the University of Oklahoma using a Bruker APEX ccd area detector (1) and graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) source. Crystal structures were visualized using CCDC Mercury software (http://www.ccdc.cam.ac.uk/products/mercury/).

Procedure for the Synthesis of Deuterated Alkynol. *1-Phenylbut-3-yn-4-d-1-ol (**1g**).* To a 20 mL round-bottom flask was dissolved 1-phenylbut-3-yn-1-ol (236 mg, 1.63 mmol, 1.0 equiv) in dichloromethane (4 mL), and then TBS-Cl (294 mg, 1.95 mmol, 1.2 equiv) was added, followed by the addition of imidazole (318 mg, 4.68 mmol, 2.4 equiv). The reaction was stirred at room temperature for 30 min. Once complete, the reaction was filtered over Celite/silica gel and concentrated. The crude product was then dissolved in a 2:2:1 mixture of THF, D_2O, and Et_3N (15 mL total) and stirred at reflux (70 °C) for 92 h. The reaction was then extracted with ether (3 × 20 mL), dried over sodium sulfate, and concentrated. The crude compound (278 mg) was then dissolved in dry THF and cooled to −78 °C. Hydrogen fluoride pyridine (5.85 μL) and pyridine (5.85 μL) were then added, and the reaction was stirred overnight. The reaction mixture was quenched via addition of methoxytrimethylsilane (5.90 μL). Solvent was removed, and the crude product was analyzed by ^{1}H NMR. The crude compound was loaded to a silica gel column and purified with 20% EtOAc in hexanes to give the desired alkynol as a yellow oil (278 mg, 75%). TLC: R_f 0.4 (30% EtOAc in hexanes). IR (NaCl): 2958, 2931, 2858, 2362, 2333. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.30 (m, 5H), 4.88 (t, J = 6.4 Hz, 1H), 2.66 (d, J = 6.3 Hz, 2H), 2.50 (s, 1H), 2.09 (t, J = 2.6 Hz, 0.05H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.4, 128.4 (2C), 128.0, 125.7 (2C), 80.3–80.1 (t, J = 7.6 Hz, 1C), 72.3, 71.0–70.4 (t, J = 3.8 Hz, 1C), 29.4. HRMS (ESI) m/z calcd for $C_{10}H_9DO$ ($[M]^+$) 147.0794; found 147.0770.

General Procedure for the Synthesis of Diazo Compounds. To a flame-dried round-bottom flask equipped with a magnetic stir bar was added a prepared solution of lactam precursor in acetonitrile (0.2 M, 1.0 equiv) and *p*-acetamidobenzenesulfonyl azide (1.2 equiv). The reaction mixture was cooled to 0 °C, and triethylamine (3.0 equiv) was added dropwise by hand. The reaction mixture was monitored via TLC until complete lactam consumption was observed. The reaction mixture was then diluted with ethyl acetate and washed with a saturated solution of ammonium chloride. The aqueous layer was extracted with additional ethyl acetate, and combined organics were dried over sodium sulfate, filtered, and concentrated. The crude mixture was then purified via flash silica gel chromatography to furnish diazo compounds. The diazo compounds were stored in benzene at −20 °C.

*(S)-3-Diazo-1-(2,4-dimethoxybenzyl)-5-isobutylpyrrolidine-2,4-dione (**2a**).* Prepared using (*S*)-1-(2,4-dimethoxybenzyl)-5-isobutylpyrrolidine-2,4-dione. Bright yellow oil (600 mg, 77%). $[\alpha]^{21}_D$ −85.5 (c = 0.023, $CHCl_3$). TLC: R_f 0.51 (40% ethyl acetate in hexanes). IR (NaCl): 2999, 2957, 2872, 2839, 2360, 2335, 2123, 1762, 1689, 1612. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, J = 8.1 Hz, 1H), 6.48–6.42 (m, 2H), 4.99 (d, J = 14.8 Hz, 1H), 4.13 (d, J = 14.8 Hz, 1H), 3.80 (d, J = 1.0 Hz, 6H), 3.76 (dd, J = 7.5, 3.9 Hz, 1H), 1.94–1.87 (m,1H),

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1.78−1.65 (m, 2H), 0.92 (d, J = 6.7 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.3, 161.6, 160.9, 158.4, 131.6 (2C), 116.3, 104.4, 98.5, 62.7, 55.4 (2C), 38.9, 38.1, 23.9, 23.6, 22.5. HRMS (ESI) m/z calcd for $C_{17}H_{21}N_3O_4Na$ ($[M + Na]^+$) 354.1430; found 354.1420.

*(R)-3-Diazo-1-(2,4-dimethoxybenzyl)-5-isobutylpyrrolidine-2,4-dione (**2b**).* Prepared using (*R*)-1-(2,4-dimethoxybenzyl)-5-isobutylpyrrolidine-2,4-dione. Bright yellow oil (255 mg, 71%). $[\alpha]^{21}_D$ +85.3 (c = 0.017, $CHCl_3$). TLC: R_f 0.51 (40% ethyl acetate in hexanes). IR (NaCl): 2957, 2870, 2396, 2388, 2123, 1683, 1614. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, J = 8.1 Hz, 1H), 6.52−6.41 (m, 2H), 5.00 (d, J = 14.8 Hz, 1H), 4.14 (d, J = 14.8 Hz, 1H), 3.81 (s, 6H), 3.77 (dd, J = 7.6, 3.9 Hz, 1H), 1.96−1.84 (m, 1H), 1.78−1.65 (m, 2H), 0.93 (d, J = 6.7 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.2, 161.6, 160.8, 158.3, 131.5 (2C), 116.1, 104.3, 98.3, 62.6, 55.3 (2C), 38.8, 38.0, 23.8, 23.6, 22.4. HRMS (ESI) m/z calcd for $C_{17}H_{21}N_3O_4Na$ ($[M + Na]^+$) 354.1430; found 354.1425.

*(S)-5-Benzyl-3-diazo-1-(2,4-dimethoxybenzyl)pyrrolidine-2,4-dione (**2c**).* Prepared using (*S*)-5-benzyl-1-(2,4-dimethoxybenzyl)-pyrrolidine-2,4-dione. Bright yellow oil (126 mg, 47%). $[\alpha]^{21}_D$ −40.2 (c = 0.024, $CHCl_3$). TLC: R_f 0.62 (50% ethyl acetate in hexanes). IR (NaCl): 3028, 3001, 2935, 2937, 2360, 2335, 1768, 1695, 1612. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 2H), 7.31−7.22 (m, 3H), 7.17 (d, J = 9.0 Hz, 1H), 7.12−7.10 (m, 2H), 6.49−6.42 (m, 2H), 5.03 (d, J = 14.6 Hz, 1H), 4.24 (d, J = 14.6 Hz, 1H), 4.02 (t, J = 4.4 Hz, 1H), 3.81 (d, J = 5.7 Hz, 6H), 3.19 (t, J = 4.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.3, 161.8, 161.0, 158.5, 134.5, 131.8 (2C), 129.7 (2C), 128.5 (2C), 127.2 (2C), 116.1, 104.5, 98.5, 64.6, 55.4, 39.4, 34.8. HRMS (ESI) m/z calcd for $C_{20}H_{19}N_3O_4Na$ ($[M + Na]^+$) 388.1273; found 388.1262.

*(S)-3-Diazo-1-(2,4-dimethoxybenzyl)-5-methylpyrrolidine-2,4-dione (**2d**).* Prepared using (*S*)-1-(2,4-dimethoxybenzyl)-5-methylpyrrolidine-2,4-dione. Faint yellow oil (499 mg, 93%). $[\alpha]^{21}_D$ −162.2 (c = 0.024, $CHCl_3$). TLC: R_f 0.63 (50% ethyl acetate in hexanes). IR (NaCl): 2939, 2837, 2360, 2335, 2214, 1664, 1612. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.15 (m, 1H), 6.42 (d, J = 6.8 Hz, 2H), 4.92 (d, J = 14.8 Hz, 1H), 4.15 (d, J = 14.8 Hz, 1H), 3.77 (d, J = 7.4 Hz, 6H), 3.73 (q, J = 6.9 Hz, 1H), 1.36 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.2, 161.0, 160.9, 158.4, 131.4, 116.3, 104.5, 98.4, 60.1, 55.4, 55.4, 43.5, 38.6, 15.3. HRMS (ESI) m/z calcd for $C_{14}H_{15}N_3O_4Na$ ($[M + Na]^+$) 312.0960; found 312.0963.

General Procedure for Rh/Au-Catalyzed Alkynol Trapping with Acceptor/Acceptor Diazos. To a 4.0 mL vial equipped with a magnetic stir bar was added powdered 4 Å molecular sieves (70 mg/mL solvent). The molecular sieves were activated via heat and allowed to cool to room temperature under vacuum. $Rh_2(esp)_2$ (1 mol %), PPh_3AuCl (10 mol %), and $AgSbF_6$ (10 mol %) were then measured directly into the reaction vessel. A solution of alkynol (1.2 equiv) and diazo (1.0 equiv) in dichloromethane (0.3M) was added, and the mixture was sonicated for 30 s. The reaction vessel was sealed and heated to 60 °C. The reaction was monitored by TLC until complete consumption of diazo was observed (between 30 min and 5 h). The crude reaction mixture was then cooled to room temperature, filtered through a pad of Celite, concentrated, and analyzed via ^{1}H NMR. The crude mixture was then purified via flash chromatography to furnish spirocyclic compounds.

*(5R,8S)-7-(2,4-Dimethoxybenzyl)-8-isobutyl-4-methylene-1-oxa-7-azaspiro[4.4]nonane-6,9-dione (**3a**).* Prepared from (*S*)-3-diazo-1-(2,4-dimethoxybenzyl)-5-isobutylpyrrolidine-2,4-dione and but-3-yn-1-ol (conversion of diazo observed in 1 h). Yellow-orange crystalline solid (38 mg, 68%): mp 128−136 °C. $[\alpha]^{21}_D$ −22.5 (c = 0.006, $CHCl_3$). TLC: R_f 0.30 (40% ethyl acetate in hexanes). IR (NaCl): 2956, 2929, 2973, 2360, 2335, 1772, 1702, 1612. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.27 (m, 1H), 6.47−6.45 (m, 2H), 5.19 (d, J = 14.3 Hz, 1H), 5.10 (s, 1H), 4.59 (s, 1H), 4.33 (t, J = 7.1 Hz, 2H), 4.11 (d, J = 14.4 Hz, 1H), 3.88 (t, J = 5.3 Hz, 1H), 3.81 (d, J = 3.3 Hz, 6H), 2.83−2.72 (m, 2H), 1.90−1.72 (m, 3H), 0.95 (d, J = 6.3 Hz, 3H), 0.80 (d, J = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.0, 170.1, 161.0, 158.5, 148.0, 132.2, 116.0, 107.9, 104.4, 98.5, 83.2, 70.1, 61.1, 55.4, 55.3, 38.7, 37.1, 33.2, 24.3, 23.6, 22.5. HRMS (ESI) m/z calcd for $C_{21}H_{27}NO_5Na$ ($[M + Na]^+$) 396.1787; found 396.1783.

*(5S,8R)-7-(2,4-Dimethoxybenzyl)-8-isobutyl-4-methylene-1-oxa-7-azaspiro[4.4]nonane-6,9-dione (**3b**).* Prepared from (*R*)-3-diazo-1-(2,4-dimethoxybenzyl)-5-isobutylpyrrolidine-2,4-dione and but-3-yn-1-ol (conversion of diazo observed in 1 h). Yellow crystalline solid (37 mg, 66%): mp 127−139 °C. $[\alpha]^{21}_D$ +22.9 (c = 0.011, $CHCl_3$). TLC: R_f 0.30 (40% ethyl acetate in hexanes). IR (NaCl): 2956, 2875, 2841, 2360, 2335, 1772, 1703, 1612. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.27 (m, 1H), 6.49−6.45 (m, 2H), 5.19 (d, J = 14.4 Hz, 1H), 5.10 (s, 1H), 4.58 (s, 1H), 4.33 (t, J = 7.8, 2H), 4.11 (d, J = 14.4 Hz, 1H), 3.88 (t, J = 5.3 Hz, 1H), 3.81 (d, J = 3.2 Hz, 6H), 2.86−2.73 (m, 2H), 1.89−1.72 (m, 3H), 0.95 (d, J = 6.3 Hz, 3H), 0.79 (d, J = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.0, 170.1, 161.0, 158.5, 148.0, 132.2, 116.0, 107.9, 104.4, 98.4, 83.2, 70.1, 61.3, 55.4, 55.3, 38.7, 37.1, 33.2, 24.3, 23.6, 22.5. HRMS (ESI) m/z calcd for $C_{21}H_{27}NO_5Na$ ($[M + Na]^+$) 396.1787; found 396.1787.

*(5R,8S)-8-Benzyl-7-(2,4-dimethoxybenzyl)-4-methylene-1-oxa-7-azaspiro[4.4]nonane-6,9-dione (**3c**).* Prepared from (*S*)-5-benzyl-3-diazo-1-(2,4-dimethoxybenzyl)pyrrolidine-2,4-dione and but-3-yn-1-ol (conversion of diazo observed in 30 min). Vibrant yellow oil (23 mg, 64%). $[\alpha]^{21}_D$ −37.8 (c = 0.017, $CHCl_3$). TLC: R_f 0.33 (50% ethyl acetate in hexanes). IR (NaCl): 3294, 3076, 2958, 2872, 2841, 2360, 2335, 1772, 1703, 1612. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.18 (m, 4H), 7.13−7.09 (m, 2H), 6.51−6.43 (m, 2H), 5.14 (d, J = 14.4 Hz, 1H), 5.06 (s, 1H), 4.54 (s, 1H), 4.28−4.23 (m, 2H), 4.21−4.15 (m, 2H), 3.81 (d, J = 2.1 Hz, 6H), 3.30 (dd, J = 14.7, 3.4 Hz, 1H), 3.17 (dd, J = 14.7, 6.4 Hz, 1H), 2.74−2.71 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.2, 170.0, 161.0, 158.5, 147.9, 135.1, 132.3, 129.5 (2C), 128.6 (2C), 127.1, 115.9, 108.0, 104.5, 98.5, 83.2, 70.0, 63.2, 55.4, 55.4, 39.1, 34.5, 33.1. HRMS (ESI) m/z calcd for $C_{24}H_{25}NO_5Na$ ($[M + Na]^+$) 430.1630; found 430.1635.

*(5R,8S)-7-(2,4-Dimethoxybenzyl)-8-methyl-4-methylene-1-oxa-7-azaspiro[4.4]nonane-6,9-dione (**3d**).* Prepared from (*S*)-3-diazo-1-(2,4-dimethoxybenzyl)-5-methylpyrrolidine-2,4-dione and but-3-yn-1-ol (conversion of diazo observed in 1 h). Faint yellow oil (32 mg, 63%). $[\alpha]^{21}_D$ −68.0 (c = 0.011, $CHCl_3$). TLC: R_f 0.28 (50% ethyl acetate in hexanes). IR (NaCl): 2956, 2873, 2841, 2360, 2335, 2125, 2096, 1772, 1701, 1612. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.25 (m, 1H), 6.47−6.46 (m, 2H), 5.20 (d, J = 14.5 Hz, 1H), 5.12 (s, 1H), 4.63 (s, 1H), 4.34 (t, J = 7.0 Hz, 2H), 4.11 (d, J = 14.5 Hz, 1H), 3.90 (q, J = 6.8 Hz, 1H), 3.82 (s, 6H), 2.84−2.73 (m, 2H), 1.41 (d, J = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.2, 169.4, 161.0, 158.5, 147.5, 132.1, 116.0, 108.0, 104.5, 98.5, 83.6, 70.0, 58.1, 55.4, 55.4, 38.3, 33.0, 14.3. HRMS (ESI) m/z calcd for $C_{18}H_{21}NO_5Na$ ($[M + Na]^+$) 354.1317; found 354.1299.

*(2R,5R,8S)-7-(2,4-Dimethoxybenzyl)-8-isobutyl-4-methylene-2-phenyl-1-oxa-7-azaspiro[4.4]nonane-6,9-dione (**3e** major).* In this mismatch diazo/alcohol case, the reaction became sluggish after 5 h and full consumption of alcohol compound was not observed. Prepared from (*S*)-3-diazo-1-(2,4-dimethoxybenzyl)-5-isobutylpyrrolidine-2,4-dione and (*R*)-1-phenylbut-3-yn-1-ol (partial conversion of diazo observed in 5 h). Vibrant yellow oil (14 mg, 22%) $[\alpha]^{21}_D$ −38.1 (c = 0.008, $CHCl_3$). TLC: R_f 0.46 (30% ethyl acetate in hexanes). IR (NaCl): 3001, 2956, 2931, 2872, 2841, 2123, 1772, 1703, 1612. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60−7.56 (m, 2H), 7.40−7.33 (m, 2H), 7.32−7.28 (m, 2H), 6.48−6.46 (m, 2H), 5.47 (dd, J = 9.1, 6.6 Hz, 1H), 5.23 (d, J = 14.3 Hz, 1H), 5.11 (s, 1H), 4.62 (s, 1H), 4.14 (d, J = 14.4 Hz, 1H), 3.90−3.86 (m, 1H), 3.82 (d, J = 2.8 Hz, 6H), 3.13−3.07 (m, 1H), 2.88−2.82 (m, 1H), 1.92−1.80 (m, 1H), 1.81−1.73 (m, 2H), 0.94 (d, J = 6.6 Hz, 3H), 0.81 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.2, 169.4, 160.95, 158.5, 148.0, 140.8, 132.1, 128.4 (2C), 128.1, 126.5 (2C), 115.8, 108.0, 104.4, 98.4, 82.7, 61.3, 55.4, 55.3, 42.1, 38.8, 37.4, 29.7, 24.3, 23.7, 22.4. HRMS (ESI) m/z calcd for $C_{27}H_{31}NO_5Na$ ($[M + Na]^+$) 472.2100; found 472.2107.

*(2R,5S,8S)-7-(2,4-Dimethoxybenzyl)-8-isobutyl-4-methylene-2-phenyl-1-oxa-7-azaspiro[4.4]nonane-6,9-dione (**3e** minor).* Prepared from (*S*)-3-diazo-1-(2,4-dimethoxybenzyl)-5-isobutylpyrrolidine-2,4-dione and (*R*)-1-phenylpent-3-yn-1-ol (conversion of diazo observed in 4 h). Yellow oil (7 mg, 11%). TLC: R_f 0.31 (30% ethyl

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acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.48 (m, 2H), 7.40−7.28 (m, 5H), 6.47 (d, J = 2.2 Hz, 1H), 5.45 (dd, J = 10.6, 5.6 Hz, 1H), 5.19 (d, J = 14.4 Hz, 1H), 5.09 (d, J = 2.6 Hz, 1H), 4.61 (d, J = 2.9 Hz, 1H), 4.13 (d, J = 14.4 Hz, 1H), 3.96 (t, J = 5.5 Hz, 1H), 3.82 (d, J = 2.5 Hz, 6H), 3.01 (dd, J = 15.1, 5.4 Hz, 1H), 2.82−2.67 (m, 1H), 1.92−1.74 (m, 3H), 0.94 (d, J = 6.5 Hz, 2H), 0.81 (d, J = 6.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.8, 170.4, 160.9, 158.4, 147.6, 140.4, 132.3, 128.4, 128.0 (2C), 126.5, 125.6, 116.1, 108.0, 104.4, 98.4, 84.0, 82.8, 60.9, 55.2, 42.1, 38.6, 37.2, 29.6, 24.3, 23.6, 22.3. HRMS (ESI) m/z calcd for $C_{27}H_{32}NO_5$ ([M + H]$^+$) ; 450.2280; found 450.2281.

(2S,5R,8S)-2-Benzyl-7-(2,4-dimethoxybenzyl)-8-isobutyl-4-methylene-1-oxa-7-azaspiro[4.4]nonane-6,9-dione (**3f**). Prepared from (*S*)-3-diazo-1-(2,4-dimethoxybenzyl)-5-isobutylpyrrolidine-2,4-dione and (*S*)-1-phenylbut-3-yn-1-ol using general procedure F (conversion of diazo observed in 45 min). Vibrant yellow oil (16 mg, 65%). $[\alpha]^{21}_D$ −72.4 (c = 0.006, $CHCl_3$). TLC: R_f 0.61 (40% ethyl acetate in hexanes). IR (NaCl): 3001, 2958, 2933, 2870, 2358, 2341, 2123, 1770, 1699, 1614. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54−7.51 (m, 2H), 7.39−7.28 (m, 4H), 6.50−6.45 (m, 2H), 5.45 (dd, J = 10.6, 5.6 Hz, 1H), 5.19 (d, J = 14.4 Hz, 1H), 5.09 (s, 1H), 4.62 (s, 1H), 4.14 (d, J = 14.4 Hz, 1H), 3.96 (t, J = 7.2 Hz, 1H), 3.82 (d, J = 3.1 Hz, 6H), 3.03−3.01 (m, 1H), 2.78−2.75 (m, 1H), 1.94−1.83 (m, 1H), 1.82−1.77 (m, 2H), 0.95 (d, J = 6.6 Hz, 3H), 0.81 (d, J = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.9, 170.5, 161.0, 158.4, 147.7, 140.5, 132.4, 128.4 (2C), 128.1, 126.6, 116.1, 108.1, 104.5, 98.5, 84.0, 82.9, 61.0, 55.4, 55.3, 42.1, 38.7, 37.3, 24.3, 23.7, 22.4, 20.8. HRMS (ESI) m/z calcd for $C_{27}H_{31}NO_5Na$ ([M + Na]$^+$) 472.2100; found 472.2099.

(2S,5R,8S)-7-(2,4-Dimethoxybenzyl)-8-isobutyl-4-methylene-2-phenyl-1-oxa-7-azaspiro[4.4]nonane-6,9-dione (**3g** *major*). Prepared from (*S*)-3-diazo-1-(2,4-dimethoxybenzyl)-5-isobutylpyrrolidine-2,4-dione and (*S*)-1-phenylbut-3-yn-1-ol (partial conversion of diazo observed in 45 min). Vibrant yellow oil (41 mg, 52%). $[\alpha]^{21}_D$ −63.5 (c = 0.012, $CHCl_3$). TLC: R_f 0.37 (30% ethyl acetate in hexanes). IR (NaCl): 3032, 3001, 2956, 2926, 2870, 2362, 2335, 2121, 1772, 1699, 1612. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.27 (m, 2H), 7.26−7.18 (m, 4H), 6.45−6.44 (m, 2H), 5.16 (d, J = 14.4 Hz, 1H), 5.01 (s, 1H), 4.78−4.68 (m, 1H), 4.53 (s, 1H), 4.10 (d, J = 14.4 Hz, 1H), 3.89−3.86 (m, 1H), 3.80 (d, J = 3.2 Hz, 6H), 3.23 (dd, J = 13.6, 6.0 Hz, 1H), 2.84 (dd, J = 13.6, 7.7 Hz, 1H), 2.69−2.67 (m, 1H), 2.52−2.44 (m, 1H), 1.84−1.82 (m, 1H), 1.79−1.77 (m, 2H), 0.95 (d, J = 6.5 Hz, 3H), 0.80 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.2, 170.4, 160.9, 158.4, 147.9, 137.7, 132.2 (2C), 129.3, 128.4, 126.4, 116.0, 108.1, 104.4, 98.4, 84.1, 82.2, 61.0, 55.4, 55.3, 41.8, 38.6, 37.2, 29.7, 24.3, 23.7, 22.4, 14.1. HRMS (ESI) m/z calcd for $C_{28}H_{33}NO_5Na$ ([M + Na]$^+$]) 486.2256; found 486.2264.

(2S,5S,8S)-7-(3,4-Dimethylbenzyl)-8-isobutyl-4-methylene-2-phenyl-1-oxa-7-azaspiro[4.4]nonane-6,9-dione (**3g** *minor*). Prepared from (*S*)-3-diazo-1-(2,4-dimethoxybenzyl)-5-isobutylpyrrolidine-2,4-dione and (*R*)-1-phenylbut-3-yn-1-ol (partial conversion of diazo observed in 5 h). Yellow oil (10 mg, 13%). TLC: R_f 0.39 (30% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.28 (m, 4H), 7.25−7.14 (m, 3H), 6.48 (d, J = 7.9 Hz, 2H), 5.21 (d, J = 14.4 Hz, 1H), 5.05 (d, J = 2.2 Hz, 1H), 4.72 (p, J = 6.8 Hz, 1H), 4.58 (d, J = 2.5 Hz, 1H), 4.14 (d, J = 14.4 Hz, 1H), 3.87 (t, J = 5.5 Hz, 1H), 3.82 (d, J = 4.1 Hz, 6H), 3.26 (dd, J = 13.6, 6.4 Hz, 1H), 2.86 (dd, J = 13.6, 7.7 Hz, 1H), 2.78−2.70 (m, 1H), 2.61−2.54 (m, 1H), 1.89−1.81 (m, 1H), 1.77 (dd, J = 7.5, 5.3 Hz, 2H), 0.95 (d, J = 6.6 Hz, 3H), 0.80 (d, J = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.9, 171.0, 158.4, 147.7, 132.2 (2C), 129.3 (2C), 128.3 (2C), 126.3 (2C), 116.0, 108.2, 104.4, 98.4, 82.0, 60.9, 55.4, 41.8, 38.7, 38.2, 37.2, 30.9, 29.7, 24.2, 23.6, 22.3. HRMS (ESI) m/z calcd for $C_{28}H_{33}NO_5$ ([M + H]$^+$]) 464.2437 ; found 464.2427.

8,8-Dimethyl-4-methylene-1,7,9-trioxaspiro[4.5]decane-6,10-dione (**3h**). Prepared from 5-diazo-2,2-dimethyl-1,3-dioxane-4,6-dione and but-3-yn-1-ol (conversion of diazo observed in 30 min). Clear oil (20 mg, 42%). TLC: R_f 0.6 (20% EtOAc in hexanes). IR (NaCl): 2957, 2918, 2850, 2359, 2340, 1732, 1714, 1633, 1608. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36 (q, J = 2.0 Hz, 1H), 5.26 (q, J = 2.1 Hz, 1H), 4.42 (t, J = 7.1 Hz, 2H), 2.90 (tt, J = 7.1, 2.2 Hz, 2H), 1.82 (d, J = 4.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3 (2C), 149.5, 109.9, 106.0, 71.4, 32.6, 30.5, 27.3 (2C). HRMS (ESI) m/z calcd for $C_{10}H_{12}O_5Na$ ([M + Na]$^+$) 235.0582; found 235.0578.

8,8-Dimethyl-4-methylene-3-phenyl-1,7,9-trioxaspiro[4.5]decane-6,10-dione (**3i**). Prepared from 5-diazo-2,2-dimethyl-1,3-dioxane-4,6-dione and 2-phenylbut-3-yn-1-ol (conversion of diazo observed in 30 min). Clear oil (12 mg, 40%). TLC: R_f 0.75 (20% EtOAc in hexanes). IR (NaCl): 3004, 2980, 2918, 2950, 2359, 2341, 1791, 1761, 1683. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.30 (m, 5H), 5.35 (ddd, J = 3.1, 1.9, 0.6 Hz, 1H), 4.95 (dd, J = 2.8, 1.9 Hz, 1H), 4.75 (td, J = 8.3, 0.5 Hz, 1H), 4.42 (dd, J = 10.4, 8.2 Hz, 1H), 4.24 (ddt, J = 10.6, 8.5, 2.9 Hz, 1H), 1.87−1.85 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.6, 166.9, 154.2, 129.1 (2C), 128.9 (2C), 127.7 (2C), 111.4, 106.2, 78.2, 50.4, 30.6, 27.3 (2C). HRMS (ESI) m/z calcd for $C_{16}H_{16}O_5Na$ ([M + Na]$^+$) 311.0895; found 311.0894.

8,8-Dimethyl-4-methylene-2-phenyl-1,7,9-trioxaspiro[4.5]decane-6,10-dione (**3j**). Prepared from 5-diazo-2,2-dimethyl-1,3-dioxane-4,6-dione and 1-phenylbut-3-yn-1-ol (conversion of diazo observed in 30 min). Clear oil (24 mg, 32%). TLC: R_f 0.80 (20% EtOAc in hexanes). IR (NaCl): 3052, 2920, 2850, 2358, 2341, 1791, 1759, 1683. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57−7.55 (m, 2H), 7.42−7.33 (m, 3H), 5.53 (dd, J = 10.5, 5.8 Hz, 1H), 5.37 (dt, J = 2.9, 1.5 Hz, 1H), 5.29 (dt, J = 3.1, 1.5 Hz, 1H), 3.15 (ddt, J = 15.5, 5.7, 1.4 Hz, 1H), 2.95 (ddt, J = 15.4, 10.5, 2.9 Hz, 1H), 1.84 (d, J = 9.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 167.0, 149.5, 139.3, 128.6 (2C), 128.6, 126.7, 109.9, 109.9, 106.1, 84.6, 82.1, 41.5, 30.6, 27.4. HRMS (ESI) m/z calcd for $C_{16}H_{16}O_5Na$ ([M + Na]$^+$) 311.0895; found 311.0895.

7,9-Dimethyl-4-methylene-1-oxa-7,9-diazaspiro[4.5]decane-6,8,10-trione (**3k**). Prepared from 5-diazo-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione and 3-butyn-1-ol (conversion of diazo observed in 40 min). Cloudy oil (40 mg, 62%). TLC: R_f 0.43 (30% EtOAc in hexanes). IR (NaCl): 2858.5, 2358.9, 2339.7, 1670.6. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (q, J = 2.1, 1.5 Hz, 1H), 5.00 (q, J = 2.2 Hz, 1H), 4.45 (td, J = 7.1, 1.2 Hz, 2H), 3.45 (d, J = 1.0 Hz, 6H), 2.84 (tdd, J = 6.9, 2.5, 1.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 159.4, 155.0, 149.0, 108.3, 78.9, 70.9, 32.4, 31.5, 29.4. HRMS (ESI) m/z calcd for $C_{10}H_{12}N_2O_4Na$ ([M + Na]$^+$) 247.0695; found 247.0698.

7,9-Dimethyl-4-methylene-3-phenyl-1-oxa-7,9-diazaspiro[4.5]decane-6,8,10-trione (**3l**). Prepared from 5-diazo-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione and 2-phenylbut-3-yn-1-ol (conversion of diazo observed in 40 min). Cloudy oil (75 mg, 60%). TLC: R_f 0.63 (30% EtOAc in hexanes). IR (NaCl): 3061, 3030, 2958, 2899, 2852, 2361, 2342, 1759, 1693, 1681, 1602. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.17 (m, 5H), 5.11 (ddd, J = 2.9, 2.1, 0.5 Hz, 1H), 4.85 (dd, J = 2.8, 2.1 Hz, 1H), 4.80 (t, J = 8.4 Hz, 1H), 4.49 (dd, J = 10.3, 8.2 Hz, 1H), 4.21−4.16 (m, 1H), 3.39 (s 3H), 3.37 (s 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 167.4, 153.8, 150.9, 137.1, 128.9 (2C), 128.3, 127.6, 109.7, 84.2, 77.7, 72.6, 67.5, 50.2, 29.4. HRMS (ESI) m/z calcd for $C_{16}H_{16}N_2O_4Na$ ([M + Na]$^+$) 323.1008; found 323.1013.

7,9-Dimethyl-4-methylene-2-phenyl-1-oxa-7,9-diazaspiro[4.5]decane-6,8,10-trione (**3m**). Prepared from 5-diazo-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione and (*S*)-1-phenylbut-3-yn-1-ol (conversion of diazo observed in 1 h). Faint yellow oil (21 mg, 61%). TLC: R_f 0.73 (50% ethyl acetate in hexanes). IR (NaCl): 3056, 2920, 2850, 2360, 2330, 1732, 1693, 1681. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65−7.61 (m, 2H), 7.42−7.31 (m, 3H), 5.57 (dd, J = 10.5, 5.7 Hz, 1H), 5.26−5.25 (m, 1H), 5.02−5.01 (m, 1H), 3.38 (d, J = 2.7 Hz, 6H), 3.12−3.05 (m, 1H), 2.88 (ddt, J = 15.4, 10.5, 2.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.7, 149.3 (2C), 139.9, 128.6 (2C), 128.4 (2C), 126.6, 108.3, 83.9, 41.5, 29.4, 29.2 (2C). HRMS (ESI) m/z calcd for $C_{16}H_{16}N_2O_4Na$ ([M + Na]$^+$) 323.1008; found 323.1014.

General Procedure for the Alkynol Trapping with *N*-Methylisatin Diazos. In a 15 mL round-bottom flask were activated powdered 4 Å molecular sieves (100 mg/mmol of diazo) via heat and cooled to room temperature under vacuum. $Rh_2(TFA)_4$ (1 mol %), AgOTf (5 mol %), and PPh_3AuCl (5 mol %) were added and dissolved in a solution of dry dichloromethane (0.2 M). The flask was sealed and cooled to 0 °C in an ice−water bath. In a separate 4 mL

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vial, alkynol (1 equiv) and *N*-methylisatin diazo (1.2 equiv) were dissolved together in dry dichloromethane (0.1 M) and taken into a syringe. The diazo/alkynol solution was then added to the catalytic mixture dropwise via syringe pump at a rate of 1 mL/h. Once addition was complete, the reaction was diluted with dichloromethane (20 mL) and quenched with a saturated solution of sodium bicarbonate. The aqueous layer was extracted, and combined organics were dried over sodium sulfate, filtered, and concentrated. NMR spectra of the crude product were analyzed, and the mixture was purified by flash chromatography with the designated solvent system as listed below.

1′-Methyl-3-methylene-4,5-dihydro-3H-spiro[furan-2,3′-indolin]-2′-one (**3n**). Prepared from 3-diazo-1-methylindolin-2-one and but-3-yn-1-ol. Orange oil (30 mg, 79%). TLC: R_f 0.38 (20% EtOAc in hexanes). IR (NaCl): 3059, 2922, 2362, 2339, 1724, 1614. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (td, J = 7.7, 1.3 Hz, 1H), 7.19 (dd, J = 7.5, 1.3 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 5.10 (t, J = 2.2 Hz, 1H), 4.57 (t, J = 2.4 Hz, 1H), 4.51 (td, J = 8.1, 6.7 Hz, 1H), 4.25(td, J = 7.9, 5.9 Hz, 1H), 3.16 (s, 3H), 3.13−3.07 (m, 1H), 2.93−2.85 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 149.4, 144.6, 129.9, 129.5, 125.3, 124.8, 123.2, 123.0, 108.6, 108.2, 68.1, 32.9 HRMS (ESI) m/z calcd for $C_{13}H_{13}NO_2Na$ ([M + Na]$^+$) 238.0844; found 238.0835.

1′-Methyl-3-methylene-4-phenyl-4,5-dihydro-3H-spiro[furan-2,3′-indolin]-2′-one (**3o**). Prepared from 3-diazo-1-methylindolin-2-one and 2-phenylbut-3-yn-1-ol. Orange oil (25 mg, 68%). TLC: R_f 0.41 (20% EtOAc in hexanes). IR (NaCl): 3057, 3028, 2920, 2893, 2850, 2360, 2343, 1722, 1614. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.30 (m, 7H), 7.10 (td, J = 7.5, 1.0 Hz, 1H), 6.84 (dt, J = 7.7, 0.7 Hz, 1H), 4.85 (t, J = 8.4 Hz, 1H), 4.76 (d, J = 2.5 Hz, 1H), 4.65 (d, J = 2.8 Hz, 1H), 4.49 (tt, J = 8.2, 2.7 Hz, 1H), 4.26 (t, J = 8.1 Hz, 1H), 3.19 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 153.7, 144.6, 140.0, 130.1, 128.8, 128.6 (2C), 127.9 (2C) 127.1, 125.2, 123.3, 110.6, 108.3, 77.3, 75.4, 49.9, 26.3. HRMS (ESI) m/z calcd for $C_{19}H_{17}NO_2Na$ ([M + Na]$^+$) 314.1157; found 314.1152.

1′-Methyl-3-methylene-5-phenyl-4,5-dihydro-3H-spiro[furan-2,3′-indolin]-2′-one (**3p**). Prepared from 3-diazo-1-methylindolin-2-one and 1-phenylbut-3-yn-1-ol. Orange oil (55 mg, 70%). TLC: R_f 0.59 (20% EtOAc in hexanes). IR (NaCl): 3062, 2953, 2926, 2854, 2594, 2358, 2341, 1728, 1614. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67−7.66 (m, 1H), 7.42−7.35 (m, 2H), 7.11 (t, J = 7.5 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 5.31 (dd, J = 11.0, 5.3 Hz, 1H), 5.14 (d, J = 2.7 Hz, 1H), 4.57 (d, J = 2.9 Hz, 1H), 3.30 (ddt, J = 14.2, 11.0, 2.9 Hz, 1H), 3.21 (s, 3H) 3.10 (dd, J = 14.7, 5.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 145.6, 134.8 (2C), 129.9 (2C), 128.1 (2C), 126.9 (2C), 125.0 (2C), 123.2 (2C), 108.9, 108.1, 82.2, 42.5, 26.4. LRMS (ESI) m/z calcd for $C_{19}H_{17}NO_2Na$ ([M + Na]$^+$) 314.1157; found 314.1151.

5′-Chloro-1′-methyl-3-methylene-4,5-dihydro-3H-spiro[furan-2,3′-indolin]-2′-one (**3q**). Prepared from 5-chloro-3-diazo-1-methylindolin-2-one and 3-butyn-1-ol. Orange oil (27 mg, 90%). TLC: R_f 0.25 (30% EtOAc in hexanes). IR (NaCl): 2958, 2920, 2891, 2358, 2331, 1780, 1610. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, J = 8.3, 2.1 Hz, 1H), 7.19 (dd, J = 2.1, 0.4 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 5.15 (t, J = 2.2 Hz, 1H), 4.60 (t, J = 2.3 Hz, 1H), 4.51 (td, J = 8.1, 6.6 Hz, 1H), 4.26 (td, J = 7.9, 5.9 Hz, 1H), 3.16 (s, 3H), 3.11 (dddt, J = 15.5, 8.3, 6.0, 2.4 Hz, 1H), 2.89 (dddt, J = 15.4, 7.7, 6.6, 2.1 Hz, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3, 134.2, 134.1, 131.1, 129.8, 129.3, 128.5, 125.3, 109.2, 109.0, 68.4, 32.8, 26.3. HRMS (ESI) m/z calcd for $C_{13}H_{12}ClNNaO_2$ ([M + Na]$^+$) 272.0454; found 272.0445.

5′-Chloro-1′-methyl-3-methylene-4-phenyl-4,5-dihydro-3H-spiro[furan-2,3′-indolin]-2′-one (**3r**). Prepared from 5-chloro-3-diazo-1-methylindolin-2-one and 2-phenylbut-3-yn-1-ol. Orange oil (14 mg, 60%). TLC: R_f 0.52 (20% EtOAc in hexanes). IR (NaCl): 2931, 2858, 2362, 2349, 1728. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44−7.30 (m, 5H), 7.25 (d, J = 2.1 Hz, 1H), 6.79 (d, J = 8.3 Hz, 1H), 4.86 (t, J = 8.4 Hz, 1H), 4.80 (d, J = 2.5 Hz, 1H), 4.69 (d, J = 2.8 Hz, 1H), 4.51 (tt, J = 8.3, 2.7 Hz, 1H), 4.25 (t, J = 8.2 Hz, 1H), 3.19 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 153.2, 143.1, 139.4, 130.9, 130.0, 128.8, 128.6 (2C), 128.5, 127.2 (2C), 125.6, 110.9, 109.2, 75.5, 49.8, 29.7, 26.4. HRMS (ESI) m/z calcd for $C_{19}H_{16}ClNO_2Na$ ([M + Na]$^+$) 348.0767; found 348.0753.

5′-Chloro-1′-methyl-3-methylene-5-phenyl-4,5-dihydro-3H-spiro[furan-2,3′-indolin]-2′-one (**3s**). Prepared from 5-chloro-3-diazo-1-methylindolin-2-one and 1-phenylbut-3-yn-1-ol. Orange oil (18 mg, 66%). TLC: R_f 0.71 (30% EtOAc in hexanes). IR (NaCl): 3427, 3298, 3049, 2926, 2353, 1728, 1612. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66−7.63 (m, 2H), 7.42−7.36 (m, 4H), 7.33 (p, J = 1.5 Hz, 3H), 6.77 (d, J = 8.2 Hz, 1H), 5.30 (dd, J = 11.0, 5.3 Hz, 1H), 5.18 (dd, J = 2.9, 1.1 Hz, 1H), 4.60 (dd, J = 3.0, 0.8 Hz, 1H), 3.30 (ddt, J = 14.1, 11.0, 2.9 Hz, 1H), 3.20 (s, 3H), 3.09 (ddt, J = 14.7, 5.4, 1.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 149.1, 143.2, 140.6, 131.3, 129.9, 128.5, 128.3, 128.2, 128.0, 126.9, 125.7, 125.5, 109.9, 82.4, 72.3, 70.9, 42.4, 29.5. HRMS (ESI) m/z calcd for $C_{19}H_{16}ClNO_2Na$ ([M + Na]$^+$) 348.0767; found 348.0753.

5′-Methoxy-1′-methyl-3-methylene-4-phenyl-4,5-dihydro-3H-spiro[furan-2,3′-indolin]-2′-one (**3t**). Prepared from 3-diazo-5-methoxy-1-methylindolin-2-one and 2-phenylbut-3-yn-1-ol. Orange oil (5 mg, 63%). TLC: R_f 0.42 (20% EtOAc in hexanes). IR (NaCl): 3429, 3400, 2922, 2856, 2366, 2341, 1724. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44−7.26 (m, 5H), 6.89−6.87 (m, 2H), 6.79−6.73 (m, 1H), 4.87 (t, J = 8.4 Hz, 1H), 4.79 (d, J = 2.5 Hz, 1H), 4.69 (d, J = 2.8 Hz, 1H), 4.52 (tt, J = 8.3, 2.7 Hz, 1H), 4.26 (t, J = 8.0 Hz, 1H), 3.81 (s, 3H), 3.18 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 156.4 (2C), 139.8 (2C), 134.0 (2C), 114.3 (2C), 112.3 (2C), 109.9, 108.6, 75.3, 65.8, 55.8, 49.8, 29.7, 26.3, 15.2. HRMS (ESI) m/z calcd for $C_{20}H_{19}NO_3Na$ ([M + Na]$^+$) 344.1263; found 344.1246.

Deuterium Labeled Control Experiments. *7,9-Dimethyl-4-(methylene-d)-2-phenyl-1-oxa-7,9-diazaspiro[4.5]decane-6,8,10-trione* (**3u**). Prepared from 5-diazo-1,3-dimethylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione and 1-phenylbut-3-yn-4-*d*-1-ol. Cloudy oil (75 mg, 62%). TLC: R_f 0.63 (30% EtOAc in hexanes). IR (NaCl): 2926, 2854, 2366, 1693. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67−7.61 (m, 2H), 7.45−7.37 (m, 2H), 7.38−7.31 (m, 1H), 5.60 (dd, J = 10.5, 5.8 Hz, 1H), 5.26 (dd, J = 2.8, 1.3 Hz, 1H), 5.04 (dt, J = 3.2, 1.5 Hz, 0.11H), 3.39 (d, J = 2.7 Hz, 6H), 3.10 (ddd, J = 15.4, 5.8, 1.4 Hz, 1H), 2.90 (ddd, J = 15.4, 10.5, 2.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.7, 167.7 (2C), 150.9 (2C), 149.1, 139.9 (2C), 108.2−107.0 (t, J = 24 Hz, 1C), 83.9, 41.4 (2C), 29.7 (2C), 29.3 (2C). HRMS (ESI) m/z calcd for $C_{16}H_{15}DN_2O_4Na$ ([M + Na]$^+$) 324.1071; found 324.1071.

1′-Methyl-3-(methylene-d)-5-phenyl-4,5-dihydro-3H-spiro[furan-2,3′-indolin]-2′-one (**3v**). Prepared from 3-diazo-1-methylindolin-2-one and 1-phenylbut-3-yn-4-*d*-1-ol. Orange oil (14 mg, 70%). TLC: R_f 0.59 (20% EtOAc in hexanes). IR (NaCl): 3057, 3028, 2924, 2981, 2854, 2358, 2339, 1722, 1614. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67−7.66 (m, 1H), 7.42−7.35 (m, 2H), 7.11 (t, J = 7.5 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 5.31 (dd, J = 11.0, 5.3 Hz, 1H), 5.15 (d, J = 2.7 Hz, 1H), 4.58 (d, J = 2.9 Hz, 0.06 H), 3.30 (ddt, J = 14.2, 11.0, 2.9 Hz, 1H), 3.21 (s) 3.10 (dd, J = 14.7, 5.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 145.6 (2C), 134.8 (2C), 129.9 (2C), 128.1 (2C), 126.9 (2C), 125.0 (2C), 123.2, 108.9, 108.1, 82.2, 42.5, 26.4. HRMS (ESI) m/z calcd for $C_{19}H_{16}DNO_2Na$ ([M + Na]$^+$) 315.1220; found 315.1219.

Control Experiments with Stepwise OH Insertion/Conia-ene Cyclization Sequence. *5-(But-3-yn-1-yloxy)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione* (**4a**). 5-Diazo-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (45 mg, 0.25 mmol, 1.2 equiv) and but-3-yn-1-ol (15 mg, 0.20 mmol, 1.0 equiv) were dissolved in dry dichloromethane (0.5 mL). In a separate flask, $Rh_2(esp)_2$ (1 mol %) was dissolved in dichloromethane (0.5 mL). The diazo/alkynol solution was added to the catalyst mixture and heated to 40 °C. After 2 h, TLC confirmed product formation and the crude reaction solution was filtered over silica gel and concentrated to give a 3:1 mixture of insertion product **4a** to Conia-ene product **3k**. TLC: R_f 0.43 (30% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.10 (s, 3H), 5.26 (q, J = 2.1 Hz, 1H), 5.02 (q, J = 2.2 Hz, 1H), 4.47 (t, J = 7.1 Hz, 2H), 3.48 (s, 3H), 3.41 (s, 3H), 3.34 (s, 6H), 2.85 (tt, J = 7.1, 2.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 149.0, 128.3, 109.9, 108.2, 78.9, 70.9, 32.4, 31.5, 29.4. HRMS (ESI) m/z calcd for $C_{10}H_{12}N_2O_4Na$ ([M + Na]$^+$) 247.0695; found 247.0698

This mixture was then subjected to PPh_3AuCl (10 mol %) and AgOTf (10 mol %) dissolved in dichloromethane with powdered 4 Å molecular sieves. After 24 h at room temperature, no alkene

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conversion was detected by TLC, so the reaction was heated to reflux (40 °C). After 24 h at 40 °C, no alkene was present.

3-(But-3-yn-1-yloxy)-1-methylindolin-2-one (4b). 3-Diazo-1-methylindolin-2-one (15 mg, 0.086 mmol, 1.0 equiv) and but-3-yn-1-ol (7 mg, 0.095 mmol, 1.1 equiv) were dissolved in dry dichloromethane (200 μL). In a separate flask, $Rh_2(TFA)_4$ (1 mol %) was dissolved in dichloromethane (200 μL). The diazo/alkynol solution was added to the catalyst slowly, and bubbles began to form. Once bubbling stopped, product formation was confirmed by TLC and the crude reaction solution was filtered over silica gel and concentrated to give the desired insertion compound as a pale pink oil (8 mg, 81%). TLC: R_f 0.29 (20% EtOAc in hexanes). IR (NaCl): 3284, 3064, 2935, 2858, 2362, 2333, 1720, 1710. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.35 (ddt, *J* = 8.7, 7.7, 1.0 Hz, 1H), 7.10 (td, *J* = 7.5, 1.0 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 4.96 (s, 1H), 3.94 (dt, *J* = 8.9, 7.0 Hz, 1H), 3.83 (dt, *J* = 8.9, 6.9 Hz, 1H), 3.19 (s, 3H), 2.56 (tdd, *J* = 7.0, 2.7, 1.5 Hz, 2H), 2.01 (t, *J* = 2.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 144.1, 130.0, 125.3, 124.7, 122.9, 108.3, 80.8, 77.2, 76.6, 69.4, 66.8, 26.0. HRMS (ESI) *m*/*z* calcd for $C_{13}H_{13}NO_2Na$ ([M + Na]$^+$) 238.0844; found 238.0847.

Powdered 4 Å molecular sieves were activated by heat and allowed to cool to room temperature under vacuum in a 15 mL round-bottom flask. PPh_3AuCl (10 mol %) and AgOTf (10 mol %) were then added, followed by addition of a solution of 3-(but-3-yn-1-yloxy)-1-methylindolin-2-one (8.0 mg, 0.035 mmol, 1.0 equiv) in dry dichloromethane (350 μL, 0.1 M). The reaction vessel was sealed and stirred at room temperature. After 24 h at room temperature, no alkene conversion was detected by TLC, so the reaction was heated to reflux (40 °C). After 24 h at 40 °C, no alkene was present.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b03196.

X-ray diffraction data for compounds **3a**, **3b**; ^{1}H and ^{13}C NMR spectra for all new compounds **1g**, **2a–d**, **3a–v**, **4a**, **4b**; COSY spectra for compounds **3a**, **3c**, **3d**, **3f**; NOE spectra for compounds **3a–g**, **3m**, **3p**, **3u**, **3v** (PDF)

CIF data for **3a** (CIF)

CIF data for **3b** (CIF)

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Notes

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