OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

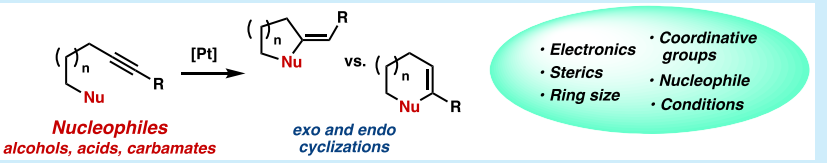
pubs.acs.org/OrgLett

Regioselectivity Influences in Platinum-Catalyzed Intramolecular Alkyne O−H and N−H Additions

Jeff P. Costello and Eric M. Ferreira*

Department of Chemistry, University of Georgia, Athens, Georgia 30602, United States

Supporting Information



ABSTRACT: The steric and electronic drivers of regioselectivity in platinum-catalyzed intramolecular hydroalkoxylation are elucidated. A branch point is found that divides the process between 5-exo and 6-endo selective processes, and enol ethers can be accessed in good yields for both oxygen heterocycles. The main influence arises from an electronic effect, where the alkyne substituent induces a polarization of the alkyne that leads to preferential heteroatom attack at the more electron-deficient carbon. The electronic effects are studied in other contexts, including hydroacyloxylation and hydroamination, and similar trends in directionality are predominant although not uniformly observed.

Enol ethers are highly useful functional groups because of the electron-rich nature of the π-bond, which enables unique reactivity across a range of transformations.[1] There are several methods available for the synthesis of enol ethers,[2] including a variety of metal-catalyzed processes such as alcohol/alkenyl halide cross coupling,[3] allylic ether isomerization,[4] and alkyne hydroalkoxylation.[5] This latter reaction class can be direct and convenient, although a primary consideration in this process is the regioselectivity of the addition.[6] Given the prevalence of enol ethers in natural products and bioactive molecules[7] that could arise from either selective endo or exo intramolecular cyclizations (Figure 1), methods that can achieve these processes selectively would be of high potential value.

We and others have been investigating the use of platinum catalysis to generate α,β-unsaturated carbene intermediates from propargylic ethers;[8] these carbenes have been demonstrated to undergo cycloadditions,[8a−e] hydrogen migrations,[8f−i] and vinylogous nucleophilic additions.[8j−l] Reactivity in this manifold is initiated by Pt catalyst coordination to an alkyne (Scheme 1A), followed by intramolecular 5-endo nucleophilic attack by a pendant alcohol. Loss of the ethereal group then leads to carbene formation. Rearranging the propargylic unit

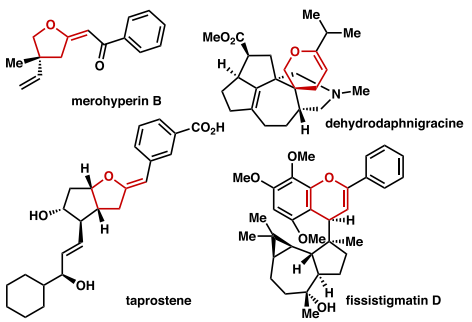
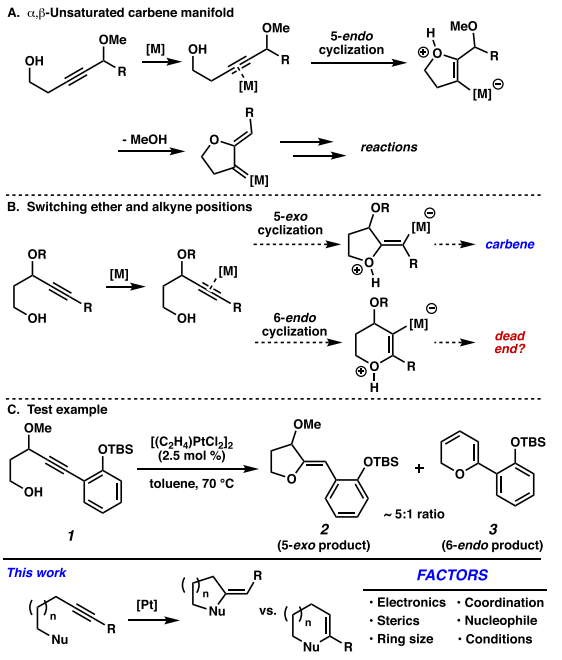


Figure 1. Enol-ether-containing natural products and bioactive molecules.

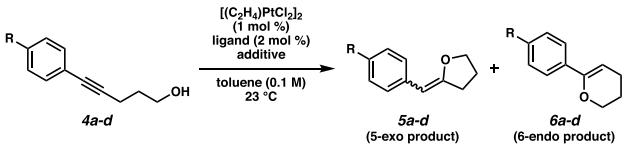
Scheme 1. Regioselectivity in Pt-Catalyzed Hydroalkoxylation



Received: October 30, 2019

DOI: 10.1021/acs.orglett.9b03557
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Bidirectional Cyclization Optimization



entry	R	ligand	additive (equiv)	time (h)	% yield **5**[a]	% yield **6**[a]
1	H (**4a**)	—	—	16	54	20
2	OAc (**4b**)	—	—	16	30	8
3	OBoc (**4c**)	—	—	16	43	8
4	OMe (**4d**)	—	—	16	5	31
5	OBoc	PPh_3	—	16	22	7
6	OBoc	(*S*)-BINAP	—	2	52	11
7	OBoc	dppp	—	5	37	10
8	OBoc	$P(OPh)_3$	—	1.5	63	14
9	OBoc	$P(C_6F_5)$	—	0.5	71	18
10	OBoc	—	$Sc(OTf)_3$ (0.1)	16	20	8
11	OBoc	—	$MgCl_2$ (1.0)	16	32	5
12	OBoc	—	Na_2CO_3 (0.5)	0.5	75	13
13	OBoc	—	Na_2CO_3 (1.0)	0.5	85	10
14	OBoc	—	K_3PO_4 (1.0)	1	60	11
15	OBoc	$P(C_6F_5)$	*i*-Pr_2NEt (1.2)	17	<5	<5
16	*OBoc*	*$P(C_6F_5)$*	*Na_2CO_3 (1.0)*	*0.5*	*88 (86)*	*7*
17	OMe	—	Na_2CO_3 (1.0)	0.5	27	49
18	*OMe*	*$P(C_6F_5)$*	—	*0.5*	*21*	*75 (72)*
19	OMe	$P(C_6F_5)$	Na_2CO_3 (1.0)	0.5	45	52

[a]Yield determined by ^1H NMR using vanillin as a standard. Isolated yields in parentheses.

presents a challenge, as 6-endo cyclization could potentially compete with 5-exo cyclization (Scheme 1B). Thus, the regioselectivity of the initial nucleophile attack on the alkyne would potentially influence successful carbene formation, in that the 6-endo process may not be productive in catalysis. As an example, we found that the initial hydroalkoxylation toward carbene formation was not straightforward; substrate **1** was found to form both compounds **2** and **3** (Scheme 1C). In an effort to expand our understanding of carbene generation, we believed it necessary to investigate this hydroalkoxylation cyclization process in a more singular and methodical context. Herein, we ascertain the primary impact of electronic biasing in intramolecular alkyne hydroalkoxylation regioselectivity, demonstrating that high levels can be achieved to generate products of either 5-exo or 6-endo cyclizations.

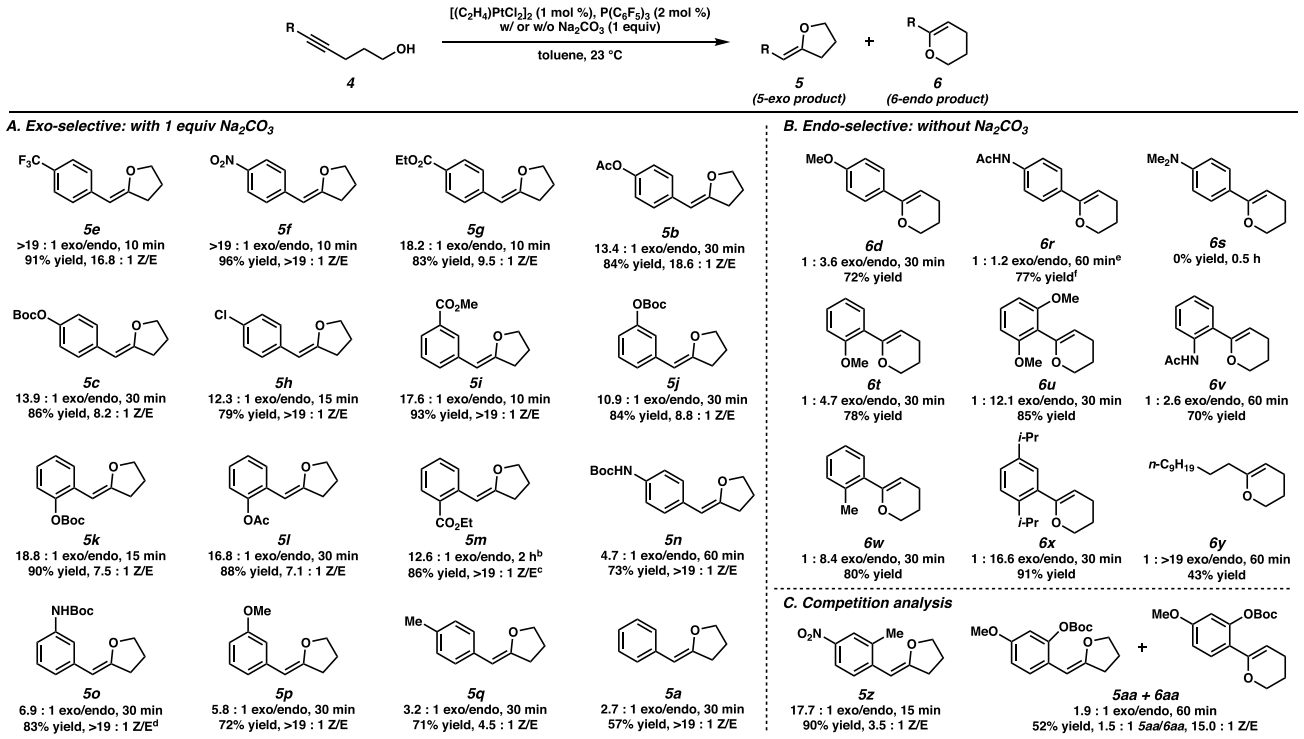
Regioselectivity in metal-catalyzed intramolecular alkyne hydroalkoxylation has been observed, but the determinants have been difficult to parse.[6] Mechanistic discrepancies (e.g., π-activation vs metal alkoxide alkyne insertion[9]) can dictate different outcomes. Within π-activation, terminal alkynes typically adhere to the propensity of the metal catalyst to reside on the unsubstituted carbon in a vinyl metal intermediate.[10] Internal alkynes appear more nuanced. The process will be governed in part by the inherent preference of the substrate to form a desired ring size (generally 5/6), but other factors could also be influential. For example, Liu and De Brabander showed that regioselectivity in nonbiased alkyl systems can be modulated by pendant Lewis basic groups that stabilize specific catalyst intermediates.[11] Other aspects such as catalyst choice and steric environment should also be taken into consideration. Selectivities have been reported in other nonmetal[12] and metal-catalyzed hydroalkoxylations (Au,[13] Pd[14]) that pointed to electronic biasing. Isolated cases in Pt-catalyzed cyclizations suggested that this attribute could be consequential,[15] although the degree to which was unclear. With the backdrop of our α,β-unsaturated Pt-carbene studies, we believed that a hydroalkoxylation analysis of aryl alkynes would be most informative, and we set out to directly address this question in this context.

We conducted a preliminary scan of 3-alkyn-1-ols with four differentially substituted arenes, using Zeise's dimer in toluene as baseline conditions (Table 1, entries 1−4). We observed a notable separation of cyclization directionality in this scan. Based on this initial data, we sought to further optimize conditions of exo/endo selectivity using the two ends of the spectrum, the *p*-OBoc aryl compound (**4c**) and the *p*-OMe aryl compound (**4d**). For compound **4c**, although added ligands had minor impacts on regioselectivity, it appeared that electron-deficient ligands ($P(OPh)_3$, $P(C_6F_5)_3$) gave a measurable boost in yield (entries 8 and 9). Added Lewis acids suppressed reactivity, while inorganic bases gave a moderate increase in regioselectivity, with the combination of $P(C_6F_5)_3$ (1:1 P/Pt ratio) and 1 equiv of Na_2CO_3 providing the optimal yield and selectivity for exo product **5c** (entry 16). In the endo-selective direction with compound **4d**, the base was counterproductive to enriched regioselectivity. The added electron-deficient phosphine, however, still proved beneficial to overall yield, and the endo product (**6d**) could be obtained in 72% isolated yield (entry 18).[16]

The enol ether products from substrates that are selective for 5-exo cyclization are depicted in Chart 1A. As illustrated, arenes substituted with electron-withdrawing groups are highly reactive and selective for the formation of the furanyl compound. This observation appears rather consistent across electron-withdrawing substituents, whether in a para, meta, or ortho relationship to the alkyne. Less inductively withdrawing groups, such as *p*-NHBoc, *m*-NHBoc, and *m*-OMe, begin to erode the exo/endo selectivity (**5n−5p**). If the arene is

DOI: 10.1021/acs.orglett.9b03557
Org. Lett. XXXX, XXX, XXX−XXX

Chart 1. Pt-Catalyzed Regioselectivities in Enol Ether Formation[a]



[a]Exo:endo selectivity is of crude reaction analysis by ^{1}H NMR. Yield and *Z*/*E* ratio are of isolated material, major isomer only unless otherwise noted. [b]Reaction performed at 40 °C with 2 mol % of $[(C_2H_4)PtCl_2]_2$ and 4 mol % of $P(C_6F_5)_3$. [c]Yield is of 12.5:1 mixture of **5m**/**6m**. Isomers were chromatographically inseparable. [d]Yield is of 7.0:1 mixture of **5o**/**6o**. Isomers were chromatographically inseparable. [e]Reaction performed at 40 °C. [f]Yield is of 1.2:1 mixture of **6r**/**5r**. Isomers were chromatographically inseparable.

electronically neutral, then exo/endo selectivity is more diminished (3:1), although synthetically useful yields can still be achieved. The predominance of the *Z*-isomer indicates an anti-selective addition process, although measurable formation of the *E*-enol ether was frequently observed. It has been reported that isomerization of this type of enol ether can occur under mild conditions,[17] which may be leading to this minor isomer.

Dihydrofurans arising from selective 6-endo cyclizations are shown in Chart 1B. Here, two main effects drive selectivity in this direction. Particularly, electron-rich arenes (e.g., (*p*-OMe)C_6H_4) were rather selective for the 6-endo product. A *p*-NMe_2 group shut down reactivity, however, likely due to its enhanced Lewis basicity disrupting catalysis. A substituent in the ortho position, if sufficiently nonwithdrawing, will also force the formation of the 6-endo products. This observation would be consistent with a steric destabilization of an intermediate arising from 5-exo cyclization (vide infra). An aliphatic alkyne substituent also drove 6-endo selectivity (**6y**), likely owing to its electron-rich nature.[18,19]

To interrogate different and potentially opposing electronic and other effects within this class, we performed two tests (Chart 1C). In the first case, substrate **4z** features a *p*-NO_2, electronically favoring 5-exo cyclization (see **5f**) and an *o*-Me sterically favoring 6-endo cyclization (see **6w**). In this example, the 5-exo cyclization dominates (**4z** → **5z**). The second test examines different effects. The *p*-OMe should electronically bias the reaction toward 6-endo cyclization, while the *o*-OBoc will promote 5-exo cyclization due to electronic and/or potential directing effects (vide infra). The 1.9:1 mixture of **5aa** and **6aa** reflects more of an equal combination of the two drivers, but the pronounced formation of the latter relative to **5k** (Chart 1A) indicates that electronic effects must continue to be accounted for in these expectations. In both cases, the presence or absence of Na_2CO_3 was less consequential on regioselection than what was observed in the cases in Table 1.[20]

The most straightforward rationalization for the observed regioselectivities across these substrates is depicted in Figure 2. Looking strictly at electronic effects, the arene induces a polarization of the alkyne. For an electron-poor arene (i.e., **4e**,**f**,**h**), the alkyne *β*-carbon is more electron-deficient, and thus the electrophilic metal association favors the *α*-carbon. This leads to nucleophilic attack on the *β*-carbon and 5-exo

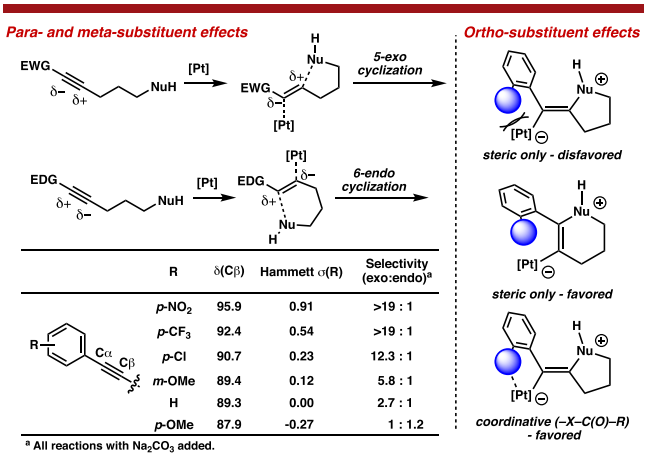


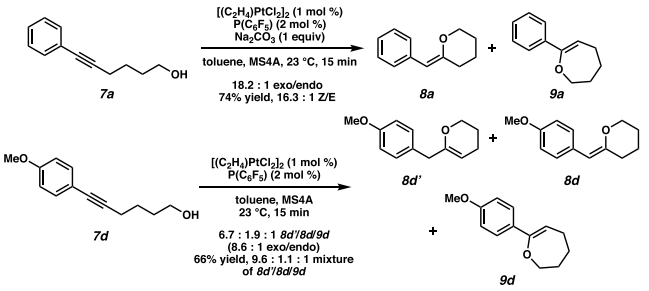
Figure 2. Rationales for observed regioselectivities.

DOI: 10.1021/acs.orglett.9b03557
Org. Lett. XXXX, XXX, XXX−XXX

cyclization. The reverse occurs with electron-rich arenes (i.e., **4d**), promoting 6-endo cyclizations. Electronic impacts correlate well with either Hammett sigma values[21] or ^{13}C NMR β-carbon chemical shifts.[22] Predictive tools for ortho-substituted arenes are not as clear-cut, as steric and/or directing effects can affect selectivity, and electronic effects are not as readily measured.[23] When present, an ortho substituent can sterically interfere with α-carbon metal association, steering the cyclization in the 6-endo direction (Figure 2), while a coordinative group would direct an exo cyclization if the alternative leads to an unfavorable ring size. The variations in cyclization preference based on an ortho-substituent track decently with this rationale (−Me endo-selective (**6w**); −OBoc, −OAc exo-selective (**5k,l**)), although an endo-selective outlier such as *o*-NHAc (**6v**) suggests there are more nuanced effects. The overall trend of electronic correlation aligns well with the aforementioned other metal- and nonmetal-catalyzed reactions.[12−15]

When examining larger rings (i.e., the competition between 6-exo and 7-endo cyclizations), electronics induce only a mild perturbation (Scheme 2). Formation of the 6-membered rings

Scheme 2. Larger Rings: 6-exo/7-endo Competition

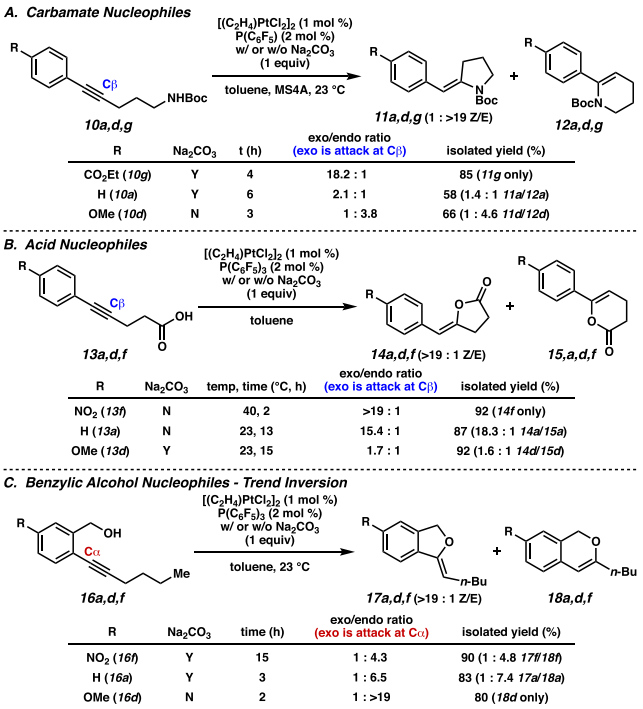


was substantially more preferred.[24] An electron-rich arene shifted the endo selectivity a minor amount only, even when using the base-free conditions that enhance this endo directionality. (The major product dihydropyran **8d′** is also indicative of an exo cyclization.)

Both carbamate and carboxylic acid nucleophiles are subject to the same electronic principles in this chemistry. Three substrates in each class were evaluated (Scheme 3). Consistent with the analysis of the alcohol systems, the electronic effects of the arene directly impacted the 5-exo/6-endo competition.[25] For enamide formation, an electron-withdrawing group favored 5-exo cyclization (**11g**), while an electron-donating group promoted 6-endo cyclization (**11d**). As anticipated, the more neutral arene was in between on this spectrum, affording a mixture of the exo and endo products.[26] In the case of lactone formation, a "phase-shifted" trend was observed, where 5-exo cyclization was predominant regardless of arene substitution but to different degrees of selectivity based on the consistent electronic effects.

Inasmuch as it may be preferable toward our understanding for this electronic trend to be consistent across all substrate classes, curiously this was not the case. Benzylic alcohols **16a,d,f** were evaluated toward the synthesis of isochromenes (Scheme 3C). Interestingly, here the electronic effect was *inverted*. Methoxy-substituted isochromene **18d** was formed exclusively, while the nitro-substituted variant was observed with a small but measurable amount of the 5-exo isomer. We note the exo/endo directionality trend is the same as the

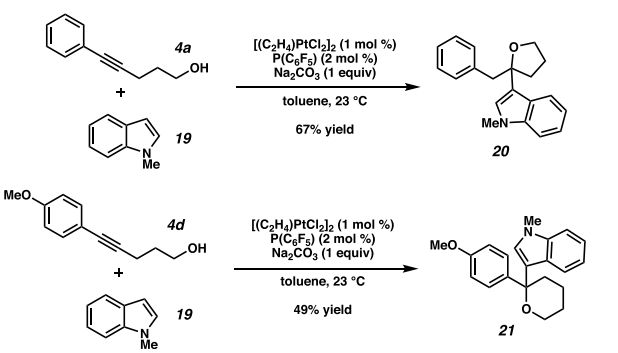
Scheme 3. Regioselectivity Analysis with Alternative Nucleophiles



earlier cases, but this substrate class is different in that exo represents nucleophilic attack at Cα and endo at Cβ. ^{13}C NMR analysis suggested nothing extraordinary regarding the electronic effects on Cβ, raising questions about what else could be dictating regioselectivity in this family. The positioning of the nucleophile is different, which would explain different product distributions relative to the other groups of substrates, but certainly not the inverted trend. Although presently unclear, the underlying message is that substrate classes are subject to multiple effects including but not limited to electronic induction, and each class should be evaluated along these lines.[27]

These regioselective cyclizations can also be linked to cascade transformations (Scheme 4). Cheng and co-workers have reported the combination of alkynyl alcohols and indoles to produce tetrahydrofurans and tetrahydropyrans.[28] In this study, selectivity for oxygen ring size was not analyzed in general. When alcohol **4a** is subjected to the cyclization conditions in the presence of *N*-methylindole, tetrahydrofuran **20** is afforded as the major product. Alternatively, alcohol **4d**

Scheme 4. Tandem Hydroalkoxylation/Heteroarylation



DOI: 10.1021/acs.orglett.9b03557
Org. Lett. XXXX, XXX, XXX−XXX

will prefer endo cyclization, and the related tetrahydropyran (**21**) is produced as the major compound.[29] These experiments illustrate how the selectivity can be leveraged in convergent processes to form decorated heterocyclic compounds.

Catalytic transition metal hydroalkoxylation processes have been proven to be an important fixture in synthetic chemistry due to their capacity to promote the formation of a variety of oxygen-containing heterocycles. The results described here highlight the ability to generate these heterocycles regioselectively under mild, platinum-catalyzed conditions. We anticipate that the studies herein may prove beneficial to their integration in the development of the platinum carbene manifold. Future studies toward application of these methods in the capture of α,β-unsaturated carbenes are ongoing, and their results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03557.

Experimental procedures, compound characterization data, and spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: emferr@uga.edu.

ORCID

Eric M. Ferreira: 0000-0001-9412-0713

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The National Institutes of Health (NIGMS, R01GM110560) is gratefully acknowledged. Mass spectrometry data were acquired on an instrument supported by the NIH (S10RR028859).

■ REFERENCES

(1) (a) Danishefsky, S. Siloxy Dienes in Total Synthesis. *Acc. Chem. Res.* **1981**, *14*, 400−406. (b) Martín Castro, A. M. Claisen Rearrangement over the Past Nine Decades. *Chem. Rev.* **2004**, *104*, 2939−3002. (c) Bauld, N. L.; Yang, J. A Two Step, Non-Stereospecific Cation Radical Diels-Alder Reaction. *Tetrahedron Lett.* **1999**, *40*, 8519−8522.

(2) For a review, see: Winternheimer, D. J.; Shade, R. E.; Merlic, C. A. Methods for Vinyl Ether Synthesis. *Synthesis* **2010**, *2010*, 2497−2511.

(3) For select recent examples see: (a) Han, S.-J.; Doi, R.; Stoltz, B. M. Nickel-Catalyzed Intramolecular C−O Bond Formation: Synthesis of Cyclic Enol Ethers. *Angew. Chem., Int. Ed.* **2016**, *55*, 7437−7440. (b) Ding, J.; You, Y.; Weng, Z. Copper-Mediated Trifluoroethoxylation of Vinyl Bromides. *Tetrahedron Lett.* **2016**, *57*, 1724−1727. (c) Jouvin, K.; Bayle, A.; Legrand, F.; Evano, G. Copper-Catalyzed Coupling of 1,1-Dibromo-1-alkenes with Phenols: A General, Modular, and Efficient Synthesis of Ynol Ethers, Bromo Enol Ethers, and Ketene Acetals. *Org. Lett.* **2012**, *14*, 1652−1655. (d) Kundu, D.; Maity, P.; Ranu, B. C. Copper-Assisted Nickel Catalyzed Ligand-Free C(sp^2)−O Cross-Coupling of Vinyl Halides and Phenols. *Org. Lett.* **2014**, *16*, 1040−1043.

(4) For select recent examples see: (a) Kocen, A. L.; Brookhart, M.; Daugulis, O. Palladium-Catalysed Alkene Chain-Running Isomerization. *Chem. Commun.* **2017**, *53*, 10010−10013. (b) Romano, C.; Mazet, C. Multicatalytic Stereoselective Synthesis of Highly Substituted Alkenes by Sequential Isomerization/Cross-Coupling Reactions. *J. Am. Chem. Soc.* **2018**, *140*, 4743−4750. (c) Seo, K.; Kim, Y. J.; Rhee, Y. H. Ru-Catalyzed Chemoselective Olefin Migration Reaction of Cyclic Allylic Acetals to Enol Acetals. *Org. Lett.* **2018**, *20*, 979−982. (d) Varela-Álvarez, A.; Sordo, J. A.; Piedra, E.; Nebra, N.; Cadierno, V.; Gimeno, J. Ruthenium(IV)-Catalyzed Isomerization of the C=C Bond of *O*-Allylic Substrates: A Theoretical and Experimental Study. *Chem. - Eur. J.* **2011**, *17*, 10583−10599. (e) Gauthier, D.; Lindhardt, A. T.; Olsen, E. P. K.; Overgaard, J.; Skrydstrup, T. In Situ Generated Bulky Palladium Hydride Complexes as Catalysts for the Efficient Isomerization of Olefins. Selective Transformation of Terminal Alkenes to 2-Alkenes. *J. Am. Chem. Soc.* **2010**, *132*, 7998−8009.

(5) For select reviews, see: (a) Alonso, F.; Beletskaya, I. P.; Yus, M. Transition-Metal-Catalyzed Addition of Heteroatom-Hydrogen Bonds to Alkynes. *Chem. Rev.* **2004**, *104*, 3079−3159. (b) Zeng, X. Recent Advances in Catalytic Sequential Reactions Involving Hydroelement Addition to Carbon-Carbon Multiple Bonds. *Chem. Rev.* **2013**, *113*, 6864−6900. (c) Patil, N. T.; Yamamoto, Y. Coinage Metal-Assisted Synthesis of Heterocycles. *Chem. Rev.* **2008**, *108*, 3395−3442. (d) Weiss, C. J.; Marks, T. J. Organo-f-Element Catalysts for Efficient and Highly Selective Hydroalkoxylation and Hydrothiolation. *Dalton Trans* **2010**, *39*, 6576−6588.

(6) For a review, see: Goodwin, J. A.; Aponick, A. Regioselectivity in the Au-Catalyzed Hydration and Hydroalkoxylation of Alkynes. *Chem. Commun.* **2015**, *51*, 8730−8741.

(7) (a) Tanaka, N.; Niwa, K.; Kashiwada, Y. Merohyperins A-C, Meroterpenes from the Leaves of *Hypericum chinense*. *Tetrahedron Lett.* **2016**, *57*, 3175−3178. (b) Li, L.; He, H.-P.; Di, Y.-T.; Tian, J.-M.; Hao, X.-J. New Alkaloids from *Daphniphyllum longeracemosum* Rosenth. *Helv. Chim. Acta* **2006**, *89*, 1457−1462. (c) Schneider, J.; Friderichs, E.; Koegel, B.; Seipp, U.; Stahlberg, H.-J.; Terlinden, R.; Heintze, K. Taprostene Sodium. *Cardiovasc. Drug Rev.* **1993**, *11*, 479−500. (d) Porzel, A.; Lien, T. P.; Schmidt, J.; Drosihn, S.; Wagner, C.; Merzweiler, K.; Sung, T. V.; Adam, G. Fissistigmatins A-D: Novel Type Natural Products with Flavonoid-Sesquiterpene Hybrid Structure from *Fissistigma bracteolatum*. *Tetrahedron* **2000**, *56*, 865−872.

(8) (a) Saito, K.; Sogou, H.; Suga, T.; Kusama, H.; Iwasawa, N. Platinum(II)-Catalyzed Generation and [3 + 2] Cycloaddition Reaction of α,β-Unsaturated Carbene Complex Intermediates for the Preparation of Polycyclic Compounds. *J. Am. Chem. Soc.* **2011**, *133*, 689−691. (b) Shu, D.; Song, W.; Li, X.; Tang, W. Rhodium- and Platinum-Catalyzed [4 + 3] Cycloaddition with Concomitant Indole Annulation: Synthesis of Cyclohepta[*b*]indoles. *Angew. Chem., Int. Ed.* **2013**, *52*, 3237−3240. (c) Kusama, H.; Sogo, H.; Saito, K.; Suga, T.; Iwasawa, N. Construction of Cyclohepta[*b*]indoles via Platinum-Catalyzed Intermolecular Formal [4 + 3]-Cycloaddition Reaction of α,β-Unsaturated Carbene Complex Intermediates with Siloxydienes. *Synlett* **2013**, *24*, 1364−1370. (d) Yang, W.; Wang, T.; Yu, Y.; Shi, S.; Zhang, T.; Hashmi, A. S. K. Nitrones as Trapping Reagents of α,β-Unsaturated Carbene Intermediates − [1,2]Oxazino[5,4-*b*]indoles by a Platinum-Catalyzed Intermolecular [3 + 3] Cycloaddition. *Adv. Synth. Catal.* **2013**, *355*, 1523−1528. (e) Huynh, K. Q.; Seizert, C. A.; Ozumerzifon, T. J.; Allegretti, P. A.; Ferreira, E. M. Platinum-Catalyzed α,β-Unsaturated Carbene Formation in the Formal Syntheses of Frondosin B and Liphagal. *Org. Lett.* **2017**, *19*, 294−297. (f) Allegretti, P. A.; Ferreira, E. M. Generation of α,β-Unsaturated Platinum Carbenes from Homopropargylic Alcohols: Rearrangements to Polysubstituted Furans. *Org. Lett.* **2011**, *13*, 5924−5927. (g) Allegretti, P. A.; Ferreira, E. M. Platinum-Catalyzed Cyclizations *via* Carbene Intermediates: Syntheses of Complementary

DOI: 10.1021/acs.orglett.9b03557
Org. Lett. XXXX, XXX, XXX−XXX

Positional Isomers of Isoxazoles. *Chem. Sci.* **2013**, *4*, 1053−1058. (h) Kwon, Y.; Kim, I.; Kim, S. Platinum-Catalyzed Synthesis of Substituted Phenanthrenes from Biphenyl Propargyl Alcohols via a Carbene Intermediate. *Org. Lett.* **2014**, *16*, 4936−4939. (i) Li, F.; Cho, J.; Tan, S.; Kim, S. Synthesis of Quinolizinium-Type Heteroaromatics via a Carbene Intermediate. *Org. Lett.* **2018**, *20*, 824−827. (j) Allegretti, P. A.; Ferreira, E. M. Vicinal Bisheterocyclizations of Alkynes via Nucleophilic Interception of a Catalytic Platinum Carbene. *J. Am. Chem. Soc.* **2013**, *135*, 17266−17269. (k) Shu, D.; Winston-McPherson, G. N.; Song, W.; Tang, W. Platinum-Catalyzed Tandem Indole Annulation/Arylation for the Synthesis of Diindolylmethanes and Indolo[3,2-*b*]carbazoles. *Org. Lett.* **2013**, *15*, 4162−4165. (l) Allegretti, P. A.; Huynh, K.; Ozumerzifon, T. J.; Ferreira, E. M. Lewis Acid Mediated Vinylogous Additions of Enol Nucleophiles into an α,β-Unsaturated Platinum Carbene. *Org. Lett.* **2016**, *18*, 64−67.

(9) For examples of metal alkoxide insertion, see: (a) Seo, S.; Yu, X.; Marks, T. J. Intramolecular Hydroalkoxylation/Cyclization of Alkynyl Alcohols Mediated by Lanthanide Catalysts. Scope and Reaction Mechanism. *J. Am. Chem. Soc.* **2009**, *131*, 263−276. (b) Pouy, M. J.; Delp, S. A.; Uddin, J.; Ramdeen, V. M.; Cochrane, N. A.; Fortman, G. C.; Gunnoe, T. B.; Cundari, T. R.; Sabat, M.; Myers, W. H. Intramolecular Hydroalkoxylation and Hydroamination of Alkynes Catalyzed by Cu(I) Complexes Supported by *N*-Heterocyclic Carbene Ligands. *ACS Catal.* **2012**, *2*, 2182−2193.

(10) For examples, see: (a) Harkat, H.; Weibel, J.-M.; Pale, P. Synthesis of Functionalized THF and THP through Au-Catalyzed Cyclization of Acetylenic Alcohols. *Tetrahedron Lett.* **2007**, *48*, 1439−1442. (b) Pale, P.; Chuche, J. Silver-Catalyzed Cyclization of Acetylenic Alcohols: Synthesis of Functionalized 2-Methyleneoxolanes. *Eur. J. Org. Chem.* **2000**, *2000*, 1019−1025. (c) Genin, E.; Antoniotti, S.; Michelet, V.; Genêt, J.-P. An Ir^{I}-Catalyzed exo-Selective Tandem Cycloisomerization/Hydroalkoxylation of Bis-Homopropargylic Alcohols at Room Temperature. *Angew. Chem., Int. Ed.* **2005**, *44*, 4949−4953.

(11) Liu, B.; De Brabander, J. K. Metal-Catalyzed Regioselective Oxy-Functionalization of Internal Alkynes: An Entry into Ketones, Acetals, and Spiroketals. *Org. Lett.* **2006**, *8*, 4907−4910.

(12) For example, see: Park, J. H.; Bhilare, S. V.; Youn, S. W. NHC-Catalyzed Oxidative Cyclization Reactions of 2-Alkynylbenzaldehydes under Aerobic Conditions: Synthesis of O-Heterocycles. *Org. Lett.* **2011**, *13*, 2228−2231.

(13) For example, see: Lu, D.; Zhou, Y.; Li, Y.; Yan, S.; Gong, Y. Copper(II)-Catalyzed Asymmetric Henry Reaction of *o*-Alkynylbenzaldehydes Followed by Gold(I)-Mediated Cycloisomerization: An Enantioselective Route to Chiral 1*H*-Isochromenes and 1,3-Dihydroisobenzofurans. *J. Org. Chem.* **2011**, *76*, 8869−8878.

(14) (a) Nakamura, H.; Ohtaka, M.; Yamamoto, Y. Tandem Nucleophilic Allylation-Alkoxylallylation of Alkynylaldehydes via Amphiphilic Bis-π-Allylpalladium Complexes. *Tetrahedron Lett.* **2002**, *43*, 7631−7633. (b) Ramana, C. V.; Mallik, R.; Gonnade, R. G.; Gurjar, M. K. Palladium Mediated Cycloisomerization of Sugar Alkynols: Synthesis of Cyclic Enol-Ethers and Spiroketals. *Tetrahedron Lett.* **2006**, *47*, 3649−3652.

(15) (a) Diéguez-Vázquez, A.; Tzschucke, C. C.; Lam, W. Y.; Ley, S. V. $PtCl_4$-Catalyzed Domino Synthesis of Fused Bicyclic Acetals. *Angew. Chem., Int. Ed.* **2007**, *47*, 209−212. (b) Patil, N. T.; Kavthe, R. D.; Raut, V. S.; Shinde, V. S.; Sridhar, B. Gold- and Platinum-Catalyzed Formal Markownikoff's Double Hydroamination of Alkynes: A Rapid Access to Tetrahydroquinazolinones and Angularly-Fused Analgoues Thereof. *J. Org. Chem.* **2010**, *75*, 1277−1280.

(16) (a) Regioselectivity is improved without ligand (5.2:1 endo/exo), but the improvement in yield in the presence of ligand was more preferable for synthetic access. (b) Additional optimization experiments are included in the Supporting Information.

(17) Tanzawa, T.; Schwartz, J. The Preparation of (α-Alkylidene)-tetrahydrofurans by Tungsten Catalyzed Decarboxylation of Aldol Precursors. *Tetrahedron Lett.* **1992**, *33*, 6783−6786.

(18) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. Room Temperature Au(I)-Catalyzed *exo*-Selective Cycloisomerization of Acetylenic Acids: An Entry to Functionalized γ-Lactones. *J. Am. Chem. Soc.* **2006**, *128*, 3112−3113.

(19) Only the endo product was observed, but accounting for the modest yield, we cannot rule out nonspecific decomposition of an exo product under these conditions. No keto alcohol products were detected, but when base was added to the reaction, minor quantities of the exo products were observed.

(20) The **5z**/**6z** ratio was 16.4:1 without Na_2CO_3 added. The **5aa**/**6aa** ratio was 1.3:1 without Na_2CO_3 added.

(21) Hansch, C.; Leo, A.; Taft, R. W. A Survey of Hammett Substituent Constants and Resonance and Field Parameters. *Chem. Rev.* **1991**, *91*, 165−195.

(22) All chemical shifts are reported in $CDCl_3$. See the Supporting Information. From our observations, if the Cβ chemical shift was >91 ppm, then exo selectivity was highly favored (>18:1). From 89 to 91 ppm, mixtures favoring exo cyclization were observed, but the direct correlation was not perfectly linear.

(23) Rubin, M.; Trofimov, A.; Gevorgyan, V. Can Polarization of Triple Bond in Tolanes Be Deduced from ^{13}C NMR Shifts? Re-evaluation of Factors Affecting Regiochemistry of the Palladium-Catalyzed Hydrostannation of Alkynes. *J. Am. Chem. Soc.* **2005**, *127*, 10243−10249.

(24) MS4A was added to the reaction mixture to suppress observed ketone formation, presumably arising from hydrolysis of the enol ether.

(25) For the substrate classes in Scheme 3, the presence or absence of Na_2CO_3 was found to be less impactful in magnitude than for that represented in Table 1.

(26) The switch from *Z*- to *E*-selectivity using these nitrogen nucleophiles is curious but likely attributable to a postcyclization *Z*-to-*E* isomerization. Compound **11g** was photoisomerized to a 1.2:1 *E*/*Z* mixture and when subjected to the catalytic reaction conditions was found to convert back to the *E*-isomer only (>19:1). The enol ether products were less prone to isomerization. See the Supporting Information for details. We thank a referee for this suggestion.

(27) For an interesting example of alkyne hydroamination that demonstrates a fluorination effect which appears counter to electronic biasing, see: Fustero, S.; Ibáñez, I.; Barrio, P.; Maestro, M. A.; Catalán, S. Gold-Catalyzed Intramolecular Hydroamination of *o*-Alkynylbenzyl Carbamates: A Route to Chiral Fluorinated Isoindoline and Isoquinoline Derivatives. *Org. Lett.* **2013**, *15*, 832−835.

(28) (a) Bhuvaneswari, S.; Jeganmohan, M.; Cheng, C.-H. Platinum-Catalyzed Multistep Reactions of Indoles with Alkynyl Alcohols. *Chem. - Eur. J.* **2007**, *13*, 8285−8293. Also see: (b) Zanardi, A.; Mata, J. A.; Peris, E. An Ir-Pt Catalyst for the Multistep Preparation of Functionalized Indoles from the Reaction of Amino Alcohols and Alkynyl Alcohols. *Chem. - Eur. J.* **2010**, *16*, 13109−13115.

(29) (a) Electron-rich arenes were necessary for reactivity in the indole trapping step. (b) The moderate yield of tetrahydropyran **21** is attributable to the relative instability of the bisbenzylic ether functional group to slightly Lewis acidic conditions.

DOI: 10.1021/acs.orglett.9b03557
Org. Lett. XXXX, XXX, XXX−XXX