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Vicinal Bisheterocyclizations of Alkynes via Nucleophilic Interception of a Catalytic Platinum Carbene

Paul A. Allegretti and Eric M. Ferreira*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, United States

Supporting Information

ABSTRACT: A novel platinum-catalyzed double heterocyclization of propargylic ethers is described. The transformation exploits the intermediacy of a key α,β-unsaturated carbene. The reactivity of this carbene is such that systems can be developed which avoid a complicating 1,2-hydrogen migration, allowing remarkable versatility in the selective syntheses of oxygen- and nitrogen-containing vicinal bis-heterocyclic compounds.

Vicinal bisheterocycles are common structural motifs in several biologically relevant molecules. Most often these core structures are synthesized in a stepwise fashion, relying on sequential closures of each individual ring.[1] Toward achieving greater molecular complexity in a single synthetic step, there have been approaches in polycyclizations for these motifs, in both cascade and bidirectional strategies.[2] Example successful methods include polyepoxide opening cascades, halocyclizations, and S_N2 displacements. We anticipated that it would be advantageous to develop biscyclization processes predicated on the basic principles of catalytic alkyne activation in conjunction with two heteroatom nucleophiles.[3−5] In this work, we disclose the realization of such a process, wherein we illustrate that alkyne-bearing diols and derivatives can undergo double cyclizations to access an array of vicinal bisheterocycles.

Our hypothesis was that a propargylic ether precursor could be conceived as doubly electrophilic at the identified carbons (Figure 1), and it could therefore be intercepted by two

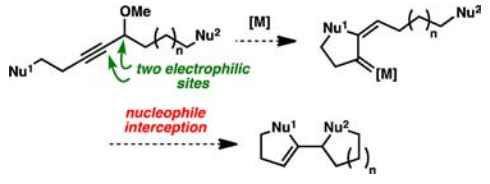

Figure 1. Proposed nucleophilic interception of an α,β-unsaturated carbene.[14]

tethered nucleophiles. This hypothesis was based on our[6] and others'[7] reports of a novel mechanistic process toward the formation of α,β-unsaturated carbene intermediates using catalytic platinum. These reactive species have been shown to participate in hydrogen migrations toward aromatic heterocycles,[6,8] as well as in various cycloadditions as 3-atom components.[7] Extrapolating this reactivity to bisheterocycle synthesis presents new challenges. The chief among them is that the traditional reactivity observed for alkynes with two heteroatom nucleophiles is *geminal* addition, dating back to the seminal work in gold catalysis by both Utimoto[9] and Teles.[10] This fundamental reactivity was subsequently expanded upon in a variety of acetalizations[11] and spiroketalizations.[11b,12] For this transformation to be successful, this standard reactivity profile would need to be overcome. Other challenges, such as selective additions to the activated alkyne (both Nu^1 vs Nu^2 and regioselectivity)[13] and competing hydrogen migration at the putative carbene stage, may also complicate the targeted process.

Homopropargylic alcohol **1** provided a platform to establish the feasibility of this reactivity. The presence of the propargylic geminal dimethyl substitution should enable the carbene to persist without the complication of a potential hydrogen shift; this strategy was employed in the aforementioned cycloaddition studies.[7] Diol **1** was subjected to the catalytic conditions we had developed to synthesize furans (Table 1, entry 1).[6a] Although we did not observe the expected diether (**2**), we were nevertheless delighted to observe the formation of acetal product **3**, indicative that the pendant primary alcohol could indeed intercept the putative carbene. We rationalized that the acetal was forming due to the mildly acidic reaction conditions engaging the enol ether.[15] Hence, the inclusion of various inorganic bases eliminated this pathway (entries 3−6), leading to the formation of the desired product (**2**) in generally good yields. The use of Zeise's dimer ($[(C_2H_4)PtCl_2]_2$) was crucial; $PtCl_2$ with either phosphine or olefin ligands (entries 7 and 8) resulted in very sluggish reactions, with minimal conversion to the polyether product after 72 h. Ultimately, we found the inclusion of phosphines generally provided an increase in yield, with PPh_3 being optimal (entry 13) and providing the desired diether in 90% isolated yield. It should be noted that this double cyclization is also effective for propargylic alcohols (entry 14), further increasing the transformation versatility.

Highlighting the unique nature of this reaction manifold, diol **1** was treated with both an alkynophilic Au-catalyst system and our optimized Pt-catalyst system (Scheme 1). As illustrated, divergent reactivity is achieved, where spiroketal **4** is formed using Au catalysis and diether **2** is formed with catalytic Pt.[16] This transformation encapsulates the ability to exploit the intermediacy of the α,β-unsaturated carbene toward advantageous reactivity.

With optimized conditions in hand, we evaluated the scope of the transformation. As depicted in Chart 1, a variety of bicyclic systems can be formed. With respect to diethers, the

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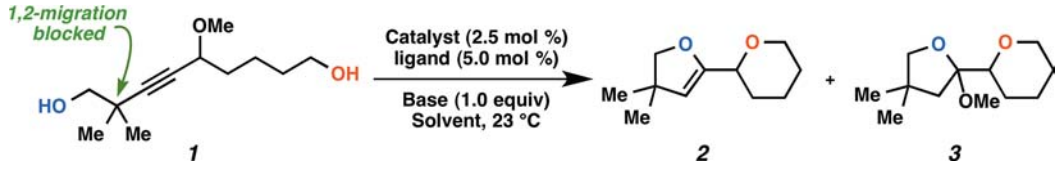
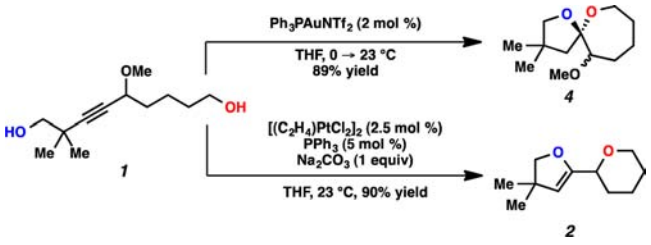
Table 1. Catalyst Optimization for the Double Cyclization of Diol 1



entry	catalyst	ligand	solvent	base	time	yield **2**/**3**[a]
1	$[(C_2H_4)PtCl_2]_2$		THF		10 min	0/83[b]
2	$[(C_2H_4)PtCl_2]_2$		THF	$NaHCO_3$	10 min	57/24
3	$[(C_2H_4)PtCl_2]_2$		THF	NaOAc	10 min	76/0
4	$[(C_2H_4)PtCl_2]_2$		THF	Cs_2CO_3	20 h	76/0
5	$[(C_2H_4)PtCl_2]_2$		THF	K3PO4	20 h	71/0
6	$[(C_2H_4)PtCl_2]_2$		THF	Na_2CO_3	10 min	76/0
7	$PtCl_2$[c]	PPh_3	THF	Na_2CO_3	72 h	14/0[d]
8	$PtCl_2$[c]	1 -octene[e]	THF	Na_2CO_3	72 h	12/0[d]
9	$[(C_2H_4)PtCl_2]_2$	-	1,4-dioxane	Na_2CO_3	10 min	78/0
10	$[(C_2H_4)PtCl_2]_2$	PPh_3	1,4-dioxane	Na_2CO_3	10 min	77/0
11	$[(C_2H_4)PtCl_2]_2$	$P(OPh)_3$	THF	Na_2CO_3	10 min	65/26
12	$[(C_2H_4)PtCl_2]_2$	PCy_3	THF	Na_2CO_3	10 min	84/0
13	$[(C_2H_4)PtCl_2]_2$	PPh_3	THF	Na_2CO_3	10 min	90/0[b]
14[f]	$[(C_2H_4)PtCl_2]_2$	PPh_3	THF	Na_2CO_3	10 min	74/0

[a]Yield determined by ^{1}H NMR using 4,4′-di-*tert*-butylbiphenyl as the internal standard. [b]Isolated yield. [c]5.0 mol %. [d]Reaction did not go to completion. [e]1 equiv. [f]Reaction performed on alcohol instead of methyl ether.

Scheme 1



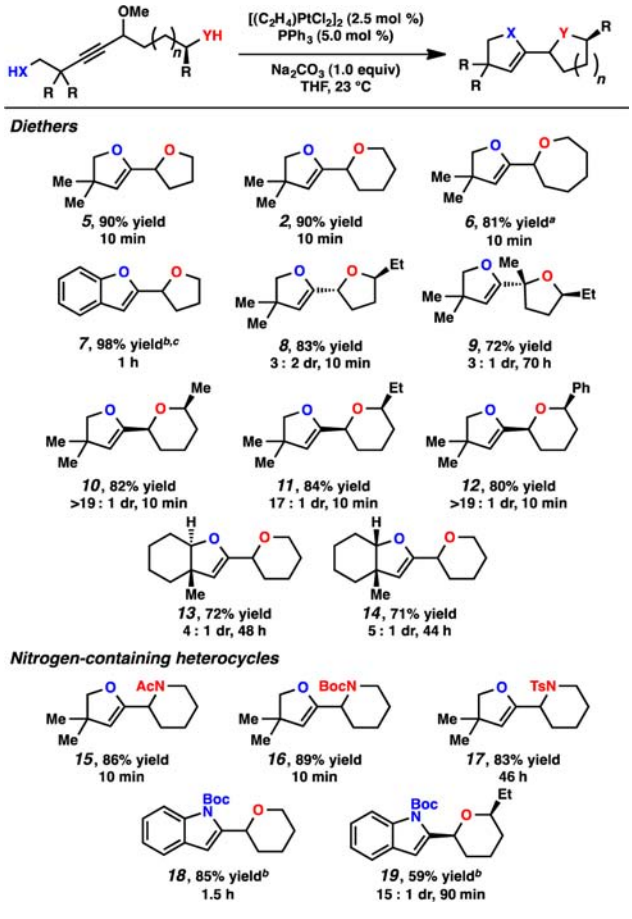
second cyclization can be induced to form 5-, 6-, and 7-membered rings. The formation of oxepane **6** is particularly notable; the synthesis of oxepanes from linear alcohols via C−O bond formation has historically been challenging.[17] The ease with which this ring formation occurs (10 min, 23 °C), with little entropic biasing, is reflective of the highly electrophilic reactivity of this carbene intermediate. Benzofuran compounds via phenolic nucleophiles (e.g., **7**) can also be formed.

Secondary alcohol nucleophiles afforded tetrahydrofurans with modest diastereoselectivity, although a *β*-disubstituted carbene species was intercepted with improved stereocontrol (i.e., **9**). Six-membered ring formation, with more pronounced energetic barriers between competitive transition states, occurred more selectively. Excellent diastereoselectivity can be achieved in the formation of *cis*-2,6-disubstituted tetrahydropyrans. More remote stereocenters also encouraged reasonable levels of diastereoselection in C−O bond formation (**13**, **14**).[18]

In addition to ethereal compounds, an array of nitrogen-based heterocycles can be formed via this transformation. Amides, carbamates, and sulfonamides are all competent *N*-nucleophiles toward the formation of functionalized piperidines. Additionally, indoles **18** and **19** were produced, where an *N*-Boc-aniline serves as the initial nucleophilic species for the 5-*endo* cyclization. Similar tetrahydropyran diastereoselectivities were observed when incorporating *N*-nucleophiles.

To date, any system in this catalytic-Pt manifold that has had the potential to undergo a 1,2-H migration has done precisely

Chart 1. Pt-Catalyzed Double Heterocyclizations[a,b,c]



[a]Reaction performed without PPh_3 in Et_2O using K_3PO_4 as the base. [b]Reaction performed without PPh_3 or Na_2CO_3 in 1,4-dioxane. [c]Reaction performed at 70 °C.

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that.[19] Toward expanding the versatility of this transformation, we turned our attention to compounds where a 1,2-H migration could be competitive. Diol **20** was investigated as a suitable test case (Figure 2). Under the aforementioned

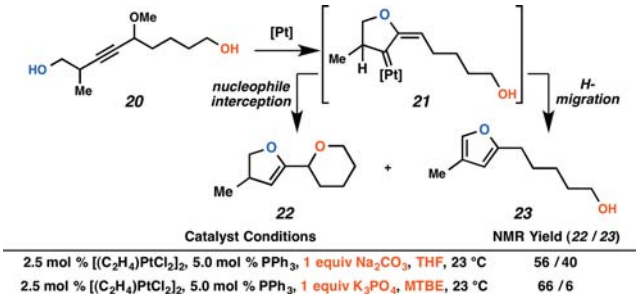
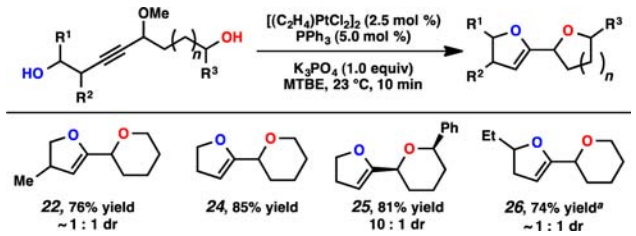


Figure 2. Catalyst optimization for diol **20**, avoiding hydrogen shifts.

optimized conditions, we observed the formation of both diether **22** and furan **23** (56% and 40% yield, respectively). Furan production, arising from the 1,2-H migration and subsequent isomerization, was clearly competitive with the nucleophilic interception. In our previous studies, we had observed that the net 1,2-H migration was favorable with more Lewis basic solvents and donating ligands, consistent with a process involving catalyst counterion dissociation and proton shuttling.[20] We ultimately found that MTBE, a relatively noncoordinating ethereal solvent, with added PPh_3 and K_3PO_4 greatly favored the formation of diether **22** (a 10:1 ratio of diether to furan production).[21] These conditions appeared to strike an appropriate balance of promoting reactivity through the carbene intermediate without concomitant shifts, and the target bicycle was produced in good yield overall.

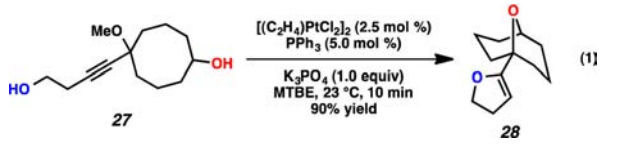
As shown in Chart 2, these double cyclization conditions continued to prove effective in cases where the 1,2-H shift can

Chart 2. Double Cyclizations, Avoiding the 1,2-H Shift[a]



[a]Reaction conducted for 14 h.

be competitive. An array of polyethers were formed in good yields overall. Primary and secondary alcohols can be used as nucleophiles, and high diastereoselectivities can again be achieved. The nucleophilic attack can also be applied in the synthesis of bridging bicycles such as compound **28** (eq 1).[22]



Select alkyne substrates were reflective of some of the current limitations of this chemistry (Figure 3). Both alkynes **29** and **31** did not form the expected bicyclic compounds. Presumably, the ring sizes of the oxocane and the azepane were too difficult to form via this method. The failure of diol **33** was also notable.

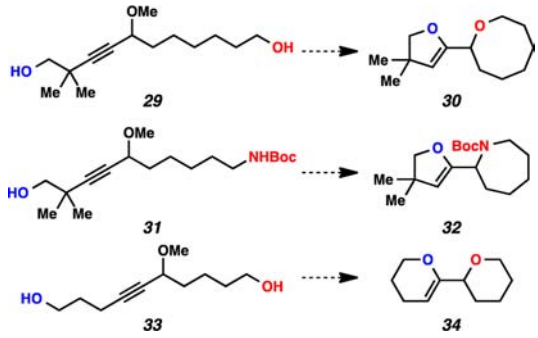


Figure 3. Failed double cyclizations.

This process would require initiation by a 6-*endo* cyclization of the initial alcohol. A competitive 5-*exo* cyclization onto the coordinated alkyne may be complicating this process in this case. Further investigations will ultimately be necessary to fully understand the various factors determining successful and unsuccessful double cyclizations.

Initial results indicate that this interception process can also be expanded to carbon-based nucleophiles. In Scheme 2, alkyne

Scheme 2

35 is converted to bicycle **36** under Pt catlaysis in good yield and excellent diastereoselectivity. In this example, a trisubstituted alkene is acting as the second nucleophile, reacting in a net ene-type fashion. It is also notable that this process apparently supersedes the previously described [3 + 2] cycloaddition manifold.[7a]

In summary, we have developed a highly versatile catalytic double heterocyclization based on alkyne activation. The transformations occur under very mild conditions, using a readily accessible propargylic ether as the centerpiece functional group, and a diverse spectrum of vicinal bicyclic structures can be formed in good to excellent yield. Importantly, this transformation generates significant structural complexity and diversity from generally linear precursors. Oxygen-, nitrogen-, and carbon-based nucleophiles are all competent in cyclization. High diastereoselectivities, as well as the avoidance of a complicating 1,2-H migration, are possible within this catalytic manifold. Importantly, this reaction represents a significant departure from π-acid-catalyzed alkyne/diol-based spiroketalizations and variants, exploiting the unique properties of this α,β-unsaturated carbene. Our method ultimately establishes the use of propargylic ethers as surrogates for the 1,2-dioxygenated motif. This vicinal bicyclic structure is a prevalent subunit in several classes of biologically relevant molecules, and the reactivity of the enol ether functional group as an electron-rich π-system[23] positions these products to be exploited in subsequent selective transformations. Future plans include establishing the full breadth of potential cyclizations that can be achieved via this method, understanding the factors governing these cyclizations, and pursuing synthetic applications. Findings in these areas will be reported in due course.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

emferr@mail.colostate.edu

Notes

The authors declare no competing financial interest.

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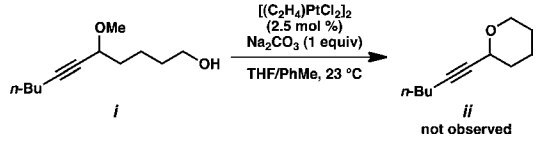
(14) While an earlier version of this manuscript was under review, a manuscript from the Tang group was published that demonstrated that nucleophilic interception of these carbenes was feasible. See Shu, D.; Winston-McPherson, G. N.; Song, W.; Tang, W. *Org. Lett.* **2013**, *15*, 4162−4165.

(15) Acetal formation from enol ethers has been observed in catalytic Au/acid systems. See refs 11a and 11b, for example.

(16) (a) Only spiroketal **4** is observed with Au and only diether **2** is observed with Pt. (b) An alternate mechanism involving an initial etherification via propargylic substitution, followed by hydroalkoxylation, was ruled out. For a relevant reference, see De Brabander, J. K.; Liu, B.; Qian, M. *Org. Lett.* **2008**, *10*, 2533−2536 We have eliminated this possible mechanism based on the observation that **ii** was not produced from **i**. Greater than 90% of starting material **i** was recovered.



i *ii* not observed

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(18) The relative stereochemistries of diethers **13** and **14** are presently unestablished.

(19) The lone exception, to our knowledge, is a selective Si- over H-migration we observed in our furan studies. See ref 6a.

(20) This observation was consistent with DFT calculation studies evaluating selective migratory processes of hydrogen and bromine in Au-catalyzed syntheses of furans. See: Xia, Y.; Dudnik, A. S.; Gevorgyan, V.; Li, Y. *J. Am. Chem. Soc.* **2008**, *130*, 6940−6941.

(21) For a more comprehensive table of optimization conditions, see the Supporting Information.

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