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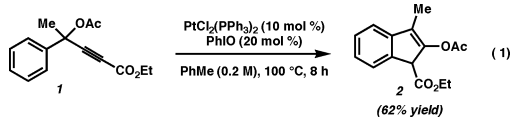
Pt-Catalyzed Tandem Epoxide Fragmentation/Pentannulation of Propargylic Esters

Brian G. Pujanauski, B. A. Bhanu Prasad, and Richmond Sarpong*

Department of Chemistry, University of California, Berkeley, California 94720

Received March 6, 2006; E-mail: rsarpong@berkeley.edu

The development of new pentannulation reactions continues to be an important pursuit in synthetic organic chemistry due to the prevalence of five-membered rings in natural products. While various traditional approaches such as the Nazarov,[1] Pauson−Khand,[2] and Karpf−Dreiding[3] reactions have provided access to pentacyclic structures, there remains a need to develop more efficient organic transformations in this regard.[4,5] Recently we reported a Pt-catalyzed pentannulation reaction, an example of which is outlined in eq 1.[6]



(1)

In these reactions, readily obtained propargylic esters such as **1** are converted to highly functionalized indenes (**2**) under platinum catalysis, presumably via the intermediacy of a metallocarbenoid.[7]

With the success of these processes, we sought to develop other bond forming transformations of propargylic esters. We envisioned a substrate such as **3** (Scheme 1) could undergo Pt-catalyzed 5-*exo*-dig cyclization to produce **4**. Zwitterion **4** could give rise to metallocarbenoid **5**, which should be electrophilic enough to be attacked by the epoxide oxygen. The resulting strained intermediate **6** should then undergo bond isomerization to yield pyran **7**, which may exist in equilibrium with the ring-opened tautomer, **8**, via an oxa-6π electrocyclization. We theorized that acetoxy-bearing dienone **8** would, in turn, cyclize to the pentannulated product **9**.[8]

The requisite substrates to test this hypothesis (e.g., **3**) were readily prepared in three steps in high overall yield, albeit as a mixture of diastereomers.[9] To our delight, exposure of a 3:1 diastereomeric mixture of propargylic acetate **3** to catalytic Pt(II) gave a single diastereomer of pentannulated bicyclic product **9** in 72% yield. As shown in Table 1, this reaction is general for a range of propargylic esters using an optimized set of conditions (10 mol % $PtCl_2$, 0.10 M in PhMe, 100 °C). Various ring sizes readily participate in this epoxide fragmentation pentannulation reaction (entries 1, 2, and 4) and lead to good yields of the desired bicyclic products. Methyl, ethyl, and benzyl esters are all easily tolerated at the terminus of the alkyne (entry 2). Likewise, propargylic acetates, benzoates, and pivalates are transformed to the pentannulated products (entry 3) in comparable yields. Additionally, acyclic compounds serve as competent substrates in the cycloisomerization to afford functionalized cyclopentenone products (entries 6 and 7).

We sought to extend the scope of this transformation by employing substrates that bear substituents other than alkyl carboxylates at the terminus of the alkyne. Our studies utilized epoxides **10**, **13**, and **16** (see eqs 2, 3, and 4, respectively).[11] Under our optimized conditions (see Table 1), **10** was converted over 6 h to the desired bicycle **11a/b** (60% yield)[12] along with pyran isomer **12** (19% yield). In contrast, **13** gave only trace conversion under the same conditions. However, under the protocol first reported by Yamamoto (10 mol % $PtCl_2$, 20 mol % cyclooctadiene, 0.2 M in PhMe, 100 °C, 6 h),[13] propargylic acetate **13** was transformed to dienone **14** in 65% yield.[14,15] Additional heating (12 h) under the same reaction conditions resulted in the net loss of AcOH and formation of bicyclic dienone **15** as the sole product. Furthermore, under the Yamamoto conditions, terminal alkyne **16** was smoothly converted in high yield to the pentannulated product **17**.[16]

Subsequent studies with the *p*-chlorobenzoate substrate **18** (Scheme 2) led to a 3:1 mixture of pentannulated bicycle **19** and pyran **20**, respectively, under our standard reaction conditions.

Scheme 1

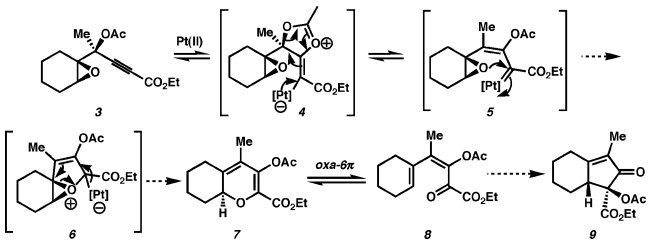
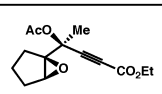
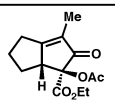
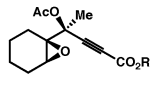
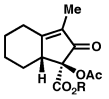
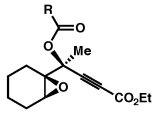
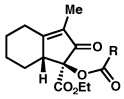
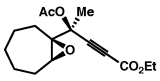
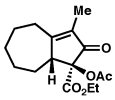
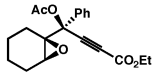
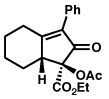
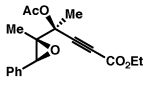
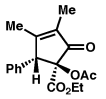
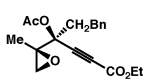
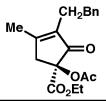
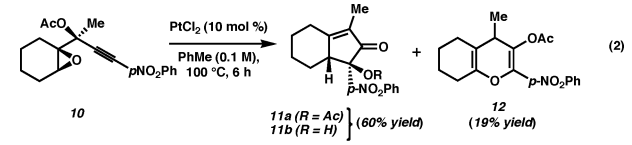


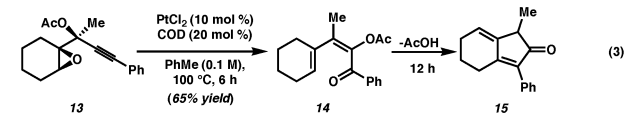
Table 1. Cycloisomerization of Epoxide Substrates[a]

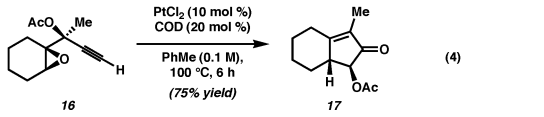
entry	substrate[b]	product[c]	time (h)	yield (%)
1			3	70
2				
	a) R = Me		3	70
	b) R = Et		3	72
	c) R = Bn		3	56
3				
	a) R = Ph		10	67
	b) R = *t*-Bu		10	58
	c) R = 3,4-$C_6H_3Cl_2$		10	55
	d) R = *p*-NO_2Ph		10	46
4			3	60
5			6	73
6			3	60
7			6	48

[a] Reaction conditions: 10 mol % $PtCl_2$, 0.10 M in PhMe, 100 °C. [b] Only the major diastereomer of the substrate is shown although syn/anti mixtures were used.[10] [c] Only a single diastereomer of the product was obtained in each case.

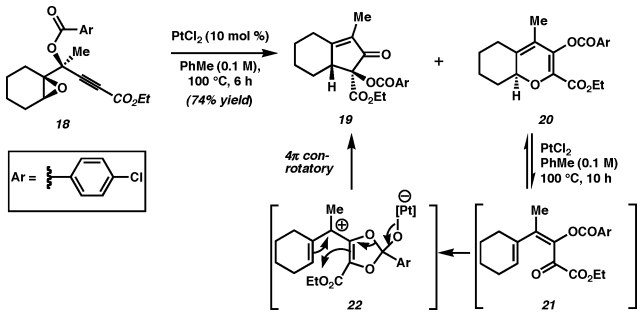
10.1021/ja061549m CCC: $33.50







Scheme 2



Bicycle **19** provided single crystals suitable for X-ray crystallography (Figure 1).

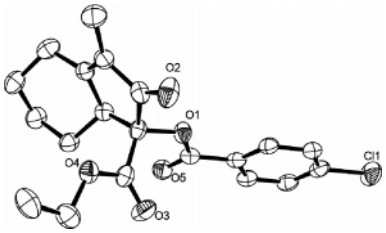


Figure 1. ORTEP illustration of cyclopentenone **19** with thermal ellipsoids drawn at 50% probability (hydrogens are omitted).

As shown in the ORTEP depiction of **19**,[17] a syn stereochemical relationship is evident between the bridgehead hydrogen and the *p*-chlorobenzoate moiety. Interestingly, re-exposure of pyran **20** to the reaction conditions afforded **19** exclusively upon heating over 10 h.[18]

On the basis of these observations, and in accordance with our proposed mechanism (Scheme 1), the pentannulated bicyclic products (e.g., **19**) likely arise from pyran intermediates such as **20**.[19] This may occur through an initial oxa-6π-electrocyclization to yield **21** followed by C−C bond formation with attendant acyl shift via the presumed intermediate **22**. The relative stereochemistry of the resulting vicinal stereocenters can be accounted for by a conrotatory 4π electrocyclic ring closure in the C−C bond-forming step.

In conclusion, we have developed an efficient method for pentannulation using acyloxy-functionalized pyrans that evolve from readily available propargylic esters. Utilizing a range of epoxides, pentannulation is achieved using $PtCl_2$ to obtain bicycles containing a tertiary stereocenter. To the best of our knowledge, this work represents the first example of the use of pyrans such as **20** in the construction of carbon−carbon bonds. Further studies to probe the mechanism of this transformation and broaden the scope to include enantio- and diastereoselective examples and applications thereof in natural product synthesis are currently ongoing and will be reported in due course.

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Supporting Information Available: Experimental details and characterization data for all new compounds are available free of charge via the Internet at http://pubs.acs.org.

References

(1) For recent reviews, see: (a) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193−2206. (b) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577−7606.

(2) For a recent review, see: Geis, O.; Schmälz, H.-G. *Angew. Chem., Int. Ed.* **1998**, *37*, 911−914.

(3) Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* **1979**, *62*, 852−856.

(4) For seminal examples of pentannulations, see: (a) Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950−952. (b) Mainetti, E.; Mouriés, V.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2132−2135.

(5) For recent examples of pentannulations, see: (a) Shintani, R.; Okamoto, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 2872−2873. (b) Yamabe, H.; Mizuno, A.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc.* **2005**, *127*, 3248−3249. (c) Shi, X.; Gorin, D.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802−5803. (d) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442−1443.

(6) Bhanu Prasad, B. A.; Yoshimoto, F. K.; Sarpong, R. *J. Am. Chem. Soc.* **2005**, *127*, 12468−12469.

(7) For early examples of metallocarbenoids generated from propargylic acetates, see: (a) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654−8655. (b) Miki, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2003**, *68*, 8505−8513. (c) Harrak, Y.; Biaszykowski, C.; Benard, M.; Cariou, K.; Mainetti, E.; Mouriés, V.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656−8657.

(8) To the best of our knowledge, transformations of the type **8**→**9** are unprecedented.

(9) For complete synthesis details, see Supporting Information and (a) Marson, C. M.; Harper, S. *J. Org. Chem.* **1998**, *63*, 9223−9231. (b) Marson, C. M.; Harper, S.; Oare, C. A.; Walsgrove, T. *J. Org. Chem.* **1998**, *63*, 3798−3799.

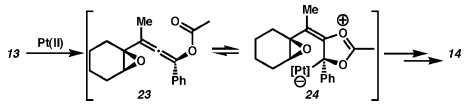
(10) For a definition of syn/anti and assignment of major diastereomer, see: Marson, C. M.; Benzies, D. W. M.; Hobson, A. D. *Tetrahedron* **1991**, *47*, 5491−5506.

(11) For experimental details of the synthesis of substrates **10**, **13**, and **16**, see Supporting Information.

(12) Obtained as an inseparable mixture (1:1.2) of **11a** and **11b**, respectively.

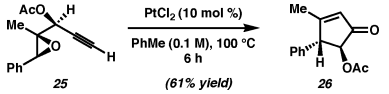
(13) (a) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022−15023. (b) Subsequent studies have revealed $PtCl_2$ alone effects the conversion **13**→**15** over prolonged heating (=12 h).

(14) The conversion **13**→**14** likely proceeds via **24**, which results from an initially formed allenyl intermediate **23**. For Pt(II)-catalyzed reactions of propargylic esters bearing a phenyl at the alkyne terminus, see: Cariou, K.; Mainetti, E.; Fensterbank, L.; Malacria, M. *Tetrahedron* **2004**, *60*, 9745−9755.



(15) Substrates similar to **13** bearing either a cyclopropane or 1-cyclohexene at the terminus of the alkyne demonstrated analogous reactivity.

(16) The secondary propargylic acetate **25** bearing a terminal alkyne is also efficiently converted to cyclopentenone **26** under Pt(II) catalysis.



(17) The ORTEP depiction of **19** is enantiomeric to the structure drawn in Scheme 2. Stereoviews and crystallographic data are in the Supporting Information.

(18) In the absence of $PtCl_2$, pyran **20** remained unchanged upon heating.

(19) Isolation of pyran isomer 12 (eq 2) and subsequent ^{1}H NMR studies with **10** also corroborate this hypothesis. Using propargylic acetate **10** as substrate (0.1 M in PhMe, 10 mol % $PtCl_2$) and monitoring aliquots of the reaction mixture at 3-h intervals, initially observed proton resonances characteristic of dienone and pyran intermediates converged over 10 h at 100 °C to resonances corresponding to bicycles **11a** and **11b**.

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