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New Annulations via Platinum-Catalyzed Enyne Cyclization and Cyclopropane Cleavage

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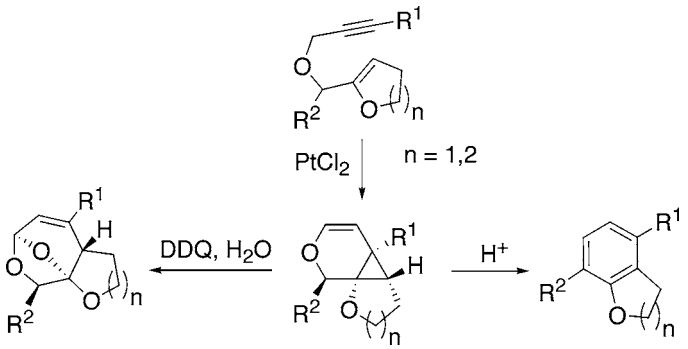
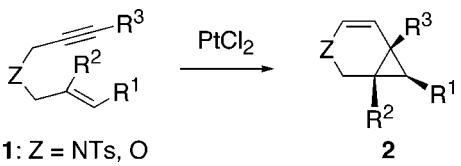
ABSTRACT



Oxidative ring opening of 3-oxabicyclo[4.1.0]hept-4-enes, formed by the intramolecular Pt(II)-catalyzed cyclopropanation of enol ethers by alkynes, gives oxepane derivatives. Alternatively, the acid-catalyzed opening of the cyclopropane ring leads to dihydrobenzofurans or 3,4-dihydro-2*H*-chromenes.

Enynes **1** (Z = NTs or O) react with $PtCl_2$ as a catalyst in nonpolar solvents to give 3-aza or 3-oxabicyclo[4.1.0]hept-4-ene derivatives **2** (Scheme 1).[1,2,3] This cyclopropanation

Scheme 1



1: Z = NTs, O **2**

of the alkene by the alkyne likely proceeds via platinum cyclopropyl carbenes as intermediates[1,2] and is therefore mechanistically related to the skeletal rearrangement and the alkoxycyclization of enynes catalyzed by electrophilic transition metals.[3]

This novel cyclopropanation provides a ready entry into bicyclic systems bearing a strained three-membered ring conjugated to an enol ether or an enamine. However, the synthetic potential of ring systems such as **2** has not yet been examined. We decided to explore the cyclization of substrates **1** bearing an enol ether function that would lead to intermediates **2** with an alkoxy substituent at R^2, which could

(1) (a) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785−6786. (b) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863−11869. (c) Blum, J.; Berr-Kraft, H.; Badrieh, Y. *J. Org. Chem.* **1995**, *60*, 5567−5569.

(2) (a) Méndez, M.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511−10520. (b) Nevado, C.; Charruault, L.; Michelet, V.; Nieto-Oberhuber, C.; Muñoz, M. P.; Méndez, M.; Rager, M.-N.; Genêt, J. P.; Echavarren, A. M. *Eur. J. Org. Chem.* **2003**, 706−713.

(3) (a) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813−834. (b) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, 215−236. (c) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317−1382. (d) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, in press.

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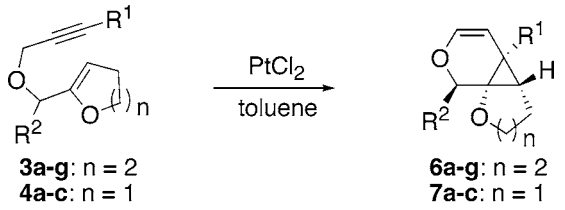
facilitate the selective cleavage of the cyclopropane[4] leading to seven-membered rings. Here we report results that illustrate the facile oxidative cleavage with DDQ or CAN to give seven-membered ring double acetals. In addition, a novel benzannulation has been found to take place by simply heating the cyclopropane derivatives in the presence of a protic acid.

Enynes **3**−**5** are readily assembled in two steps by the addition of α-lithiated enol ethers to aldehydes, followed by propargylation of the resulting secondary alcohols. Cyclization of **3**−**5** was cleanly carried out with 5 mol % $PtCl_2$ in toluene (Table 1).[5] Although the cyclizations were performed routinely in toluene at 80 °C, some of these reactions also proceed at 0−50 °C (Table 1, entries 2, 3, 6, and 8), which proved to be particularly convenient for substrates such as **6f** that decomposed at higher temperatures. The cyclizations could also be performed with $PtCl_4$ as a catalyst.[6] No skeletal rearrangement of enynes **3**−**5** was observed under these conditions.[3,7]

Table 1. Platinum-Catalyzed Cyclization of Enynes **3**−**5**[a]

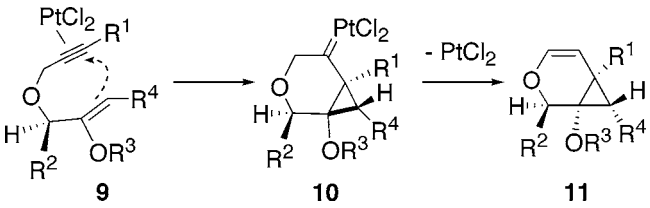


entry	enyne	R^1	R^2	*T* (°C)	time (h)	product (yield, %)
1	**3a**	Me	Ph	80	6	**6a** (84)
2	**3b**	Me	1-Napht	50	2	**6b** (97)
3	**3c**	Et	Ph	45	4	**6c** (79)
4	**3d**	Ph	Ph	80	12	**6d** (72)
5	**3e**	Me	CH=CHMe	80	48	**6e** (52)
6	**3f**	Me	CH=CHPh	0	17	**6f** (61)
7	**3g**	Me	*i*-Pr	80	4	**6g** (74)
8	**4a**	Me	Ph	50	24	**7a** (58)
9	**4b**	Et	*p*-Tol	80	1	**7b** (70)
10	**4c**	Me	*t*-Bu	70	1.5	**7c** (71)
11	**5a**	Me	Ph	80	2	**8a** (73)[c]
12[b]	**5b**	Me	*i*-Pr	80	2	**8b** (54)

[a] Reactions carried out with 5 mol % $PtCl_2$. [b] Reaction performed in the presence of 4 Å ms. [c] Mixture (5:1) of C-2 epimers.

The reactions of **3**−**5** proceeded with total regiocontrol by 6-*endo-dig* cyclization, as a result of the terminal substitution at the alkyne and the electronegative character of the tether.[5] In addition, these reactions are highly stereoselective.[8] A single diastereomer was observed in the crude reaction mixtures, with the exception of the reaction of **5a**, in which **8a** was formed along with its C-2 epimer in a 5:1 ratio. The cyclization presumably proceeds via η^2-alkyne-$PtCl_2$ complex **9**, by formation of two carbon−carbon bonds from the face of the alkene opposite to the R^2 substituent (Scheme 2). Platinum carbene **10** probably evolves by a β-hydrogen elimination[1] to give enol ether **11**.

Scheme 2

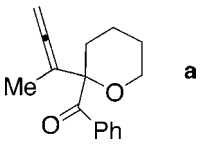


Being electron-rich systems, oxidative cleavage of the cyclopropane bond activated by the alkoxy substituent was attempted first (Scheme 3).[9−11] Epoxidation of the enol double bond of **6a** under a variety of conditions does not trigger the cleavage of the cyclopropane ring and gives **12** when the reaction was carried out in MeOH. In addition, 3,4-dihydro-2*H*-chromene **19a** was also obtained (see below). Inspection of the solid structure of **6b**[8] reveals a preference for the attack of electrophilic MCPBA at the convex face,

(4) Leading references: (a) Park, S.-B.; Cha, J. K. *Org. Lett.* **2000**, 2, 147−149. (b) Braun, N. A.; Spitzner, D. *Tetrahedron Lett.* **1996**, *37*, 9187−9188. (c) Kura, K.; Ryu, I.; Kambe, Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 1520−1521. (d) Murai, S.; Aya, T.; Sonoda, N. *J. Org. Chem.* **1973**, *38*, 4354−4356.

(5) Pt(II)- and Au(III)-catalyzed methoxycyclization of enol ethers with alkynes: Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2003**, *9*, 2627−2635.

(6) Reaction of **3a** with $AuCl_3$ (5 mol %) in toluene at 80 °C gives **6a** (40%), along with allene **a** resulting from 1,2-H shift and Claisen rearrangement: Nevado, C.; Echavarren, A. M. *Tetrahedron* **2004**, *60*, in press.



a

(7) Skeletal rearrangement of enynes catalyzed by $PtCl_4$: Oh, C. H.; Bang, S. Y.; Rhim, C. Y. *Bull. Korean Chem. Soc.* **2003**, *24*, 887−888.

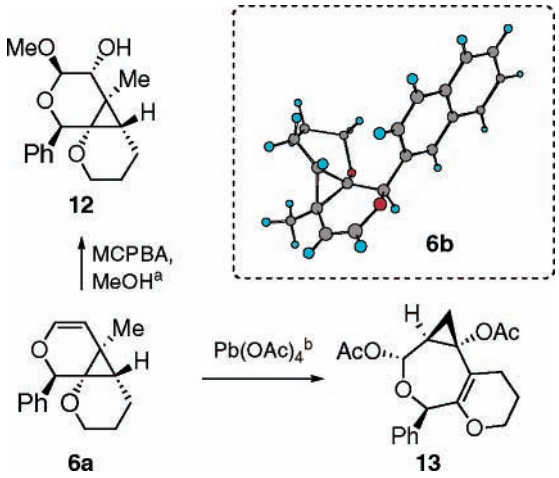
(8) Relative configuration of **6b** was determined by X-ray diffraction.

(9) Review: Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165−198.

(10) Recent leading references on the oxidative opening of cyclopropanes with metal oxidants: (a) Booker-Milburn, K. I.; Thompson, D. F. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2315−2321. (b) Booker-Milburn, K. I.; Baker, A.; Brailsford, W.; Cox, B.; Mansley, T. E. *Tetrahedron* **1998**, *54*, 15321−15344. (c) Takemoto, Y.; Yamagata, S.; Furose, S.; Hayase, H.; Echigo, T.; Iwata, C. *Chem. Commun.* **1998**, 651−652. (d) Kirihara, M.; Ichinose, M.; Takizawa, S.; Momose, T. *Chem. Commun.* **1998**, 1691−1692. (e) Takemoto, Y.; Ibuka, T.; Furuse, S.; Hayase, H.; Echigo, T.; Iwata, C.; Tanaka, T. *Chem. Commun.* **1999**, 2515−2516. (f) Nakamura, M.; Inoue, T.; Nakamura, E. *J. Organomet. Chem.* **2001**, *624*, 300−306. (g) Booker-Milburn, K. I.; Jones, J. L.; Sibley, G. E. M.; Cox, R.; Meadows, J. *Org. Lett.* **2003**, *5*, 1107−1109.

(11) Oxidations of cyclopropane acetals with DDQ or chloranil: (a) Oku, A.; Yamauchi, Y.; Schroeder, M. *Chem. Lett.* **2001**, 1194−1195. (b) Oku, A.; Takahashi, H.; Asmus, S. M. *J. Am. Chem. Soc.* **2000**, *122*, 7388−7389. (c) Oku, A.; Abe, M.; Iwamoto, M. *J. Org. Chem.* **1994**, *59*, 7445−7452.

Scheme 3[a]



[a] Reagents and conditions: (a) MCPBA (1 equiv), MeOH, 0 °C, 7 h [**12** (80%) + **19a** (15%)]. (b) $Pb(OAc)_4$ (1.5 equiv), HOAc, rt, 12 h [**13** (28%) + **19a** (15%)].

which is followed by opening of the epoxide by methanol. On the other hand, reaction of **6a** with $Pb(OAc)_4$ in HOAc gave **13** (28%) and **19a** (15%). In the transformation of **6a** into **13**, oxidative cleavage of the cyclopropane ring is followed by the formation of a second cyclopropane in a rare example of electrophilic cyclopropanation at the expense of a methyl group.[12]

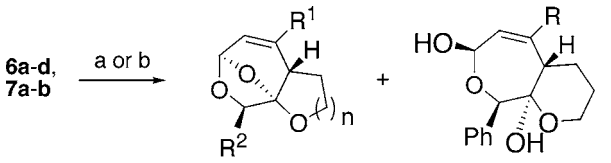
Successful cleavage of the cyclopropane was achieved with DDQ or CAN as the oxidants in aqueous solvents (Table 2). DDQ has been previously used for the opening of cyclopropanone acetals, although trapping of the intermediate radical cation initially formed by the quinone radical anion of DDQ was observed in most cases.[11]

The reactions of **6** and **7** with DDQ or CAN provide stereoselectively double acetals **14** and **15**, respectively, although in the cases of **6c** and **6d** the oxidation with DDQ also gave hemiacetals **16a**,**b** as minor products (Table 2, entries 5 and 6). Under these conditions, **8a**,**b** gave only complex mixtures.

A rationale for this transformation is provided in Scheme 4 on the basis of a single electron-transfer oxidation of **6** and **7** to form radical cations **17**, which would be trapped by water and further oxidized to form **18**. Intermediates **18** could cyclize to form triclyclic derivatives **14** and **15**. Alternatively, trapping of oxonium ion **18** by water would give **16**.

In some of the oxidations of **6a**,**b**, 3,4-dihydro-2*H*-chromenes **19a** and **19b** were observed as secondary products. This intriguing transformation, which corresponds to a dehydration reaction, could be simply performed by heating **6a**−**e** with aqueous HCl in THF or with *p*-TsOH in toluene to give 3,4-dihydro-2*H*-chromenes **19a**−**e** (Scheme 5).

Table 2. Oxidation of **6** and **7** with DDQ or CAN



14a: n = 2, R^1 = Me, R^2 = Ph
14b: n = 2, R^1 = Me, R^2 = 2-Naph
14c: n = 2, R^1 = Et, R^2 = Ph
14d: n = 2, R^1 = R^2 = Ph
15a: n = 1, R^1 = Me, R^2 = Ph
15b: n = 1, R^1 = Et, R^2 = *p*-Tol

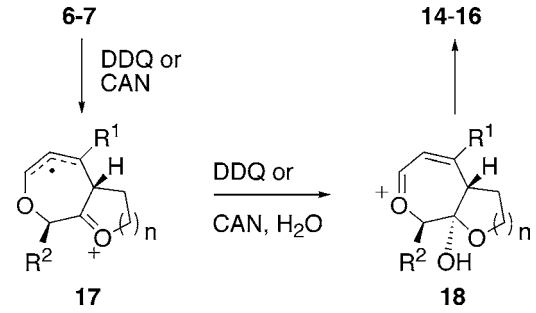
16a: R = Et
16b: R = Ph

a: DDQ, CH_2Cl_2-H_2O
b: CAN, MeCN-H_2O

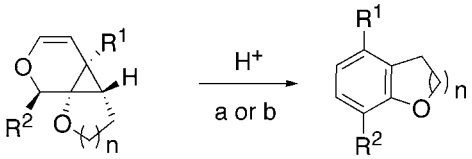
entry	substrate	conditions[a]	time (h)	product(s) (yield, %)
1	**6a**	a	2	**14a** (60)[b]
2	**6a**	b	1	**14a** (60)[c]
3	**6b**	a	1	**14b** (54)
4	**6b**	b	1	**14b** (58)[d]
5	**6c**	a	2	**14c** (63) + **16a** (18)
6	**6d**	a	2	**14d** (58) + **16b** (24)
7	**7a**	a	2	**15a** (84)
8	**7b**	b	1	**15b** (83)

[a] Conditions a: DDQ (2 equiv), 10:1 CH_2Cl_2−H_2O, 40 °C. Conditions b: CAN (1 equiv), 10:1 MeCN−H_2O, 70−90 °C. [b] **19a** (24%) was also obtained. [c] **19a** (8%) was also obtained. [d] **19b** (23%) was also obtained.

Scheme 4



Scheme 5[a]



6a-e: n = 2
7a-b: n = 1

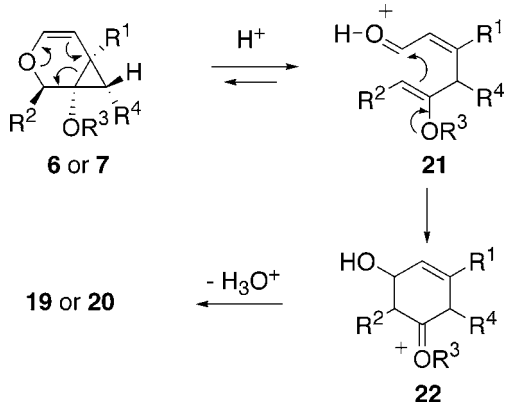
19a: n = 2, R^1 = Me, R^2 = Ph
19b: n = 2, R^1 = Me, R^2 = 2-Napht
19c: n = 2, R^1 = Et, R^2 = Ph
19d: n = 2, R^1 = R^2 = Ph
19e: n = 2, R^1 = Me, R^2 = CH=CHMe
20a: n = 1, R^1 = Me, R^2 = Ph
20b: n = 1, R^1 = Et, R^2 = *p*-Tol

[a] Reagents and conditions: (a) aq HCl, THF, reflux, 2−14 h [**19a** (72%); **19b** (72%); **19c** (64%)]. (b) *p*-TsOH (1 equiv), toluene, 70−110 °C, 2−30 min [**19d** (80%); **19e** (52%); **20a** (95%); **20b** (82%)].

5). Similarly, heating of **7a**,**b** with *p*-TsOH in toluene gave dihydrobenzofurans **20a**,**b** in good yields.

This new benzannulation reaction probably proceeds by retro-hetero-Diels−Alder opening of **6** and **7** to form **21**,[13,14] followed by an acid-catalyzed aldol-type cyclization and dehydration of **22** to afford 3,4-dihydro-2*H*-chromenes **19** or dihydrobenzofurans **20** (Scheme 6).[15]

Scheme 6

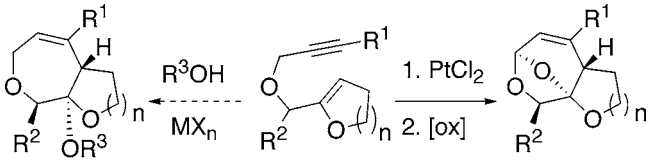


In summary, the cyclopropane ring of 3-oxabicyclo[4.1.0]-hept-4-enes, obtained by $PtCl_2$-catalyzed cyclization of **3** and **4**, can be oxidatively cleavaged to form oxepanes **14** and **15** (or hemiacetals **16**). This transformation is an alternative to the yet unknown alkoxycyclization of 1,6-enynes by *endo-dig* pathway that, in the case of **6** and **7**, should have afforded **23** and **24** (Scheme 7).[5] A new benzannulation that gives 3,4-dihydro-2*H*-chromenes **19** or 2,3-dihydrobenzofurans **20**, with a substituent pattern difficult to obtain by other methods,

(12) This transformation is presumably initiated by the cleavage of the cyclopropane to form an organolead intermediate. For reviews on electrophilic cyclopropanation: (a) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625−1647. (b) Taylor, R. E.; Engelhardt, F. C.; Schmitt, M. *Tetrahedron* **2003**, *59*, 5623−5634.

(13) Retro-Diels−Alder reactions of bicyclo[4.1.0]hept-4-enes: Sellers, S. F.; Dolbier, W. R.; Koroniak, H.; Al-Fekri, D. M. *J. Org. Chem.* **1984**, *49*, 1033−1036.

Scheme 7



has also been uncovered from enynes, which are modularly assembled from an enol ether, an aldehyde, and a propargyl bromide.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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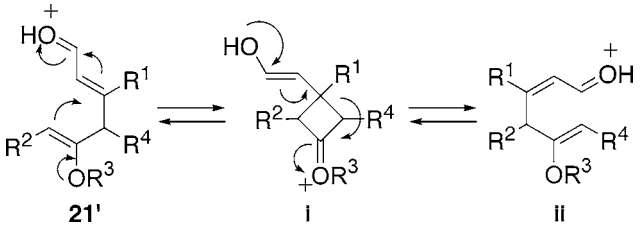
(14) In the case of **6d**, reaction with *p*-TsOH gave 5,6-diphenyl-3,4-dihydro-2*H*-chromene as a byproduct (ca. 5%), the result of an unexpected rearrangement. Rearrangement products (5,6-disubstituted 3,4-dihydro-2*H*-chromenes) were observed as minor products (15:1 ratio) when the cyclizations of substrates **19a** and **19c** were carried out with *p*-TsOH in toluene instead of aqueous HCl. Formation of these rearranged products could be explained by *E*/*Z* isomerization of **21** to **21′**, followed by Michael addition to form **i**, which could open to give **ii**. Aldol-type cyclization of **ii** as in Scheme 6 forms 5,6-disubstituted 3,4-dihydro-2*H*-chromenes.



(15) Curiously, a 3,4-dihydro-2*H*-chromene was formed by acid-catalyzed reaction of 13-methoxy-trioxadispiro[4.1.5.3]pentadecane by a mechanism that resembles that proposed for the **21** → **19** and **20** transformation. See: Dorta, R. L.; Martín, A.; Suárez, E. *J. Org. Chem.* **1997**, *62*, 2273−2274.