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$PtCl_2$-Catalyzed Transannular Cycloisomerization of 1,5-Enynes: A New Efficient Regio- and Stereocontrolled Access to Tricyclic Derivatives

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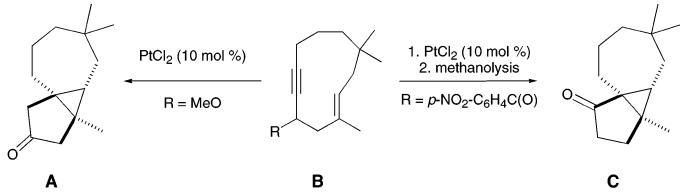
ABSTRACT



Transannular $PtCl_2$-catalyzed cycloisomerizations open a new route to cyclopropanic tricyclic systems. Ketones A or C were efficiently prepared from the same cycloundec-5-en-1-yne precursor B, depending on the substituent at the propargylic position (either benzoate or methoxy).

Transannular processes constitute a unique opportunity for achieving chemo-, regio-, and stereoselective synthesis. Because ring constraints are more predictable than acyclic ones and can also be tuned, versatile synthetic applications have already been devised, notably for cycloadditions,[1] and also for radical processes.[2] Our group, for instance, has reported the diastereoselective and efficient synthesis of polycyclic structures such as natural protoilludanes[3] or linear triquinanes[4] via 4-*exo*/6-*exo* or 5-*exo*/5-*exo* transannular radical cyclizations cascades. Surprisingly, besides coordination complexes incorporating polyunsaturated macrocycles or macrocyclic Lewis bases serving as ligands,[5] organometallic reactivities have been rarely envisaged in transannular fashion.[6]

In that context, $PtCl_2$-catalyzed cycloisomerizations of transannular enyne substrates appear as highly appealing reacting systems to be explored.[7,8] Further incentive was gained by considering the following facts. We have recently

(1) For a review, see: Marsault, E.; Toró, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4243−4260. See also: Caussanel, F.; Deslongchamps, P.; Dory, Y. L. *Org. Lett.* **2003**, *5*, 4799−4802.

(2) Handa, S.; Pattenden, G. *Contemp. Org. Synth.* **1997**, *4*, 196−215. See also: Dhimane, A. L.; Fensterbank, L.; Malacria, M. In *Radicals in Organic Synthesis*; Renaud, P., Sibi M. P., Eds.; Wiley-VCH: Weiheim, 2001; Vol. 2, pp 350−382.

(3) Rychlet Elliott, M.; Dhimane, A. L.; Malacria, M. *J. Am. Chem. Soc.* **1997**, *119*, 3427−3428.

(4) Dhimane, A. L.; Aïssa, C.; Malacria M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3284−3287.

(5) (a) Diyne transannular reactivity with rhodium: King, R. B.; Ackermann M. N. *J. Organomet. Chem.* **1974**, *67*, 431−441. (b) With iron: King, R. B.; Haiduc, I.; Eavenson, C. W. *J. Am. Chem. Soc.* **1973**, *95*, 2508−2516. (c) With cobalt: King, R. B.; Efraty, A. *J. Am. Chem. Soc.* **1972**, *94*, 3021−3025. (d) For a recent contribution: Pla-Quintana, A.; Roglans, A.; Torrent, A.; Moreno-Mañas, M.; Benet-Buchholz, J. *Organometallics* **2004**, *23*, 2762−2767 and references therein.

(6) (a) Transannular oxypalladation: Sasaki, T.; Kanematsu, K.; Kondo A. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2516−2520. (b) Transannular [3 + 2] TMM-like cycloaddition: Yamago, S.; Nakamura, E. *Tetrahedron* **1989**, *45*, 3081−3088. (c) Transannular carbopalladation: Ohe, K.; Miki, K.; Yanagi, S.-I.; Tanaka, T.; Sawada, S.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3627−3634.

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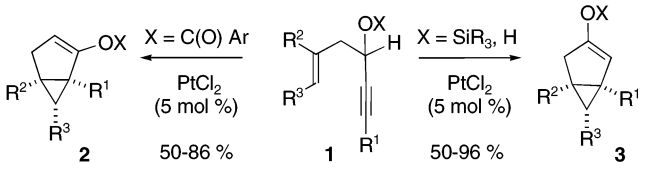
shown that such processes can be extended to a variety of partners such as allenynes[9] and ene-tosylynamides.[10] Moreover, as was the case for dienynol derivatives,[11] it has been shown that in acyclic 5-en-1-yn-3-ol precursors **1** the nature of the hydroxy protecting group at the propargylic position is a very practical handle for controlling the outcome of the reaction.[12] When this function is free, or appears as a silyl ether, bicyclic compound **3** is formed, while bicyclic enol ester **2** is isolated when an *O*-acyl group is present (Scheme 1). Electrophilic activation of the alkyne moiety triggers at

Scheme 1. $PtCl_2$-Catalyzed Cyclizations of Acyclic 1,5-Enyne Derivatives **1**

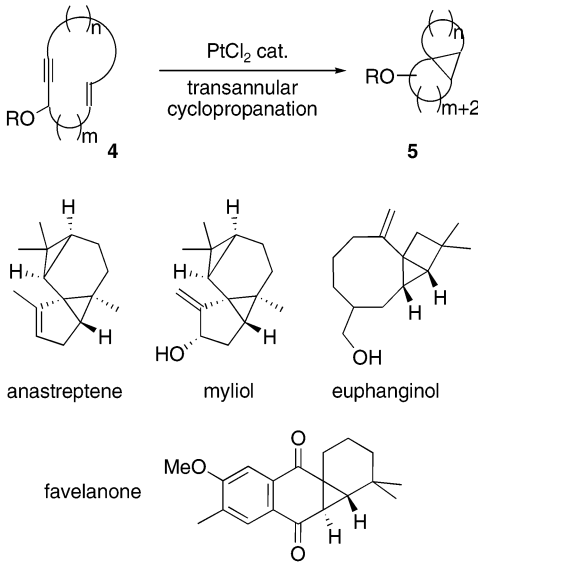


will a hydride or an *O*-acyl migration yielding to regioisomeric derivatives.

Since the macrocycles we have designed originate from the macrocylization of α,ω-ynal precursors by using the Nozaki−Hiyama−Kishi−Takai (NHKT) chromium(II)-mediated process,[13] they display the pivotal propargyl alcohol motif and so constitute ideal test substrates.

Thus, we anticipated that enyne macrocycle precursors of type **4** would undergo transannular cyclopropanations which would constitute a straightforward, modular, and unprecedented access to highly valuable tricyclic derivatives **5** incorporating an inner cyclopropane moiety.[14] Various natural products possess a related tricycloundecane framework ($n = 5$, $m = 1$) such as anastreptene[15] or myliol[16] isolated from liverwort plants. Some others, such as euphanginol[17] ($n = 2$, $m = 4$) and favelanone[18] ($n = 4$, $m = 2$), are obtained from *Euphorbia* species which present some antitumoral or cytotoxic activities (Scheme 2).

Scheme 2. Transannular $PtCl_2$-Catalyzed Cyclopropanation Strategy



Herein, we report the application of this transannular strategy to various 1,5-unsaturated eleven-membered rings such as cycloundecenynes **10** and **11** (Scheme 3) and cycloundecadienynes ***Z,E***- and ***E,E*-17** (Scheme 6) whose syntheses are, as previously mentioned, based on the efficient NHKT macrocyclization conditions. Thus, following the synthesis of the already described heptenal **6** as a TBS-ether,[19] we prepared it as a THP derivative. This one was first submitted to Horner−Wadsworth−Emmons olefination conditions modified by Masamune and Roush[20] to reach stereoselectively the corresponding *E,E*-nonadienoate **7**. Then, a five-step sequence including a LAH total reduction−iodination−alkynylation−alkyne deprotection−ether deprotection furnished undecenynol **8** in 47% overall yield.

The macrocyclization precursor was prepared by mild iodination of the triple bond, followed by IBX oxidation of the alcohol moiety. Slow addition of the resulting undecenynal to a suspension of chromium(II) chloride in THF was performed to produce cleanly cycloundecenynol ***E*-9** in 38% overall yield in three steps (Scheme 3).

(7) For reviews, see: (a) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813−834. (b) Méndez, M.; Mamane, V.; Fürstner, A. *Chemtracts-Org. Chem.* **2003**, *16*, 397. (c) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215−236.

(8) For recent publications, see: (a) Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2003**, *9*, 2627−2635. (b) Chatani, N.; Kataoka, K.; Murai, S.; Furukawa, N.; Seki, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9104−9105. (c) Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 3801−3810. (d) Charruault, L.; Michelet, V.; Taras, R.; Gladiali, S.; Genêt, J.-P. *Chem. Commun.* **2004**, 850−851. (e) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863−11869. (f) Méndez, M.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511−10520.

(9) Cadran, N.; Cariou, K.; Hervé, G.; Aubert, C.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *J. Am. Chem. Soc.* **2004**, *126*, 3408−3409.

(10) Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509−1511.

(11) Mainetti, E.; Mouriès, V.; Fensterbank, L.; Malacria, M. Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2132−2135.

(12) (a) Harrak, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mainetti, E.; Mouriès, V.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656−8657. For similar findings, see: (b) Mamane, V.; Gress, T.; Krause, H.; Fürstner A. *J. Am. Chem. Soc.* **2004**, *126*, 8654−8655.

(13) (a) Takai, K.; Kuroda, T.; Nakatsukasa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5585−5588. (b) Rychlet Elliott, M.; Dhimane, A. L.; Hamon, L.; Malacria, M. *Eur. J. Org. Chem.* **2000**, 155−163.

(14) For other access to these intriguing skeletons, see: (a) Hannah, D. J.; Smith, R. A. J.; Teoh, I.; Weavers, R. T. *Aust. J. Chem.* **1981**, *34*, 181−188. (b) Marshall, J. A.; Peterson, J. C.; Lebioda, L. *J. Am. Chem. Soc.* **1984**, *106*, 6006−6015. (c) Ricci, A.; Fasani, E.; Mella, M.; Albini, A. *J. Org. Chem.* **2003**, *68*, 4361−4366.

(15) Warmers, U.; König, W. A. *Phytochemistry* **1999**, *52*, 1519−1524.

(16) Hayashi, K.-I.; Asano, K.-I.; Tanaka, M.; Takaoka, D.; Nozaki, H. *Phytochemistry* **1998**, *48*, 461−466.

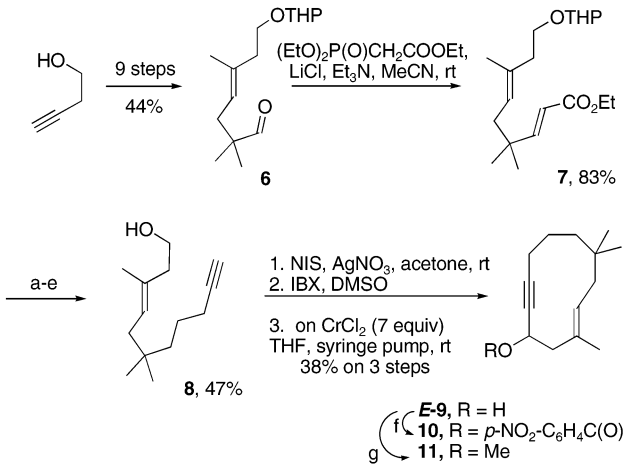
(17) Shi, J.-G.; Shi, Y.-P.; Jia, Z.-J. *Phytochemistry* **1997**, *45*, 343−347.

(18) Endo, Y.; Ohta, T.; Nozoe, S. *Tetrahedron Lett.* **1991**, *32*, 5555−5558.

(19) Aïssa, C.; Dhimane, A.-L.; Malacria, M. *Synlett* **2000**, 1585−1588.

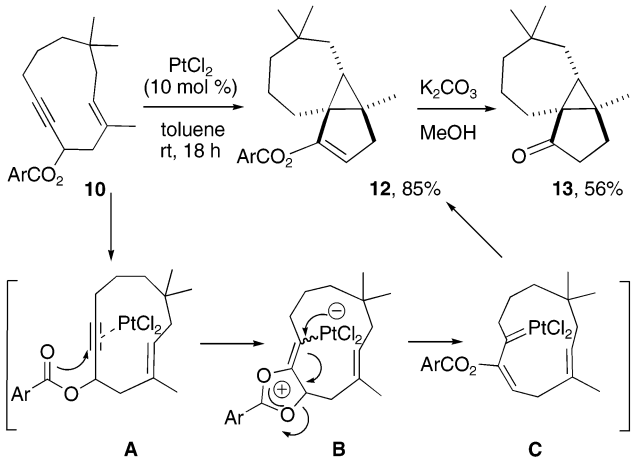
(20) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183-2186.

Scheme 3. Synthesis of Cycloundecadienynol Derivatives **10** and **11**



The corresponding 4-nitrobenzoate and methyl ether derivatives **10** and **11** were then exposed to a catalytic amount of $PtCl_2$ in toluene at rt. In both cases, a clean reaction took place giving, respectively, compounds **12** and **14** as single isomers[21] in good yields (Schemes 4 and 5).

Scheme 4. $PtCl_2$-Catalyzed Transannular Cyclization of Cycloundecenyne Derivative **10**

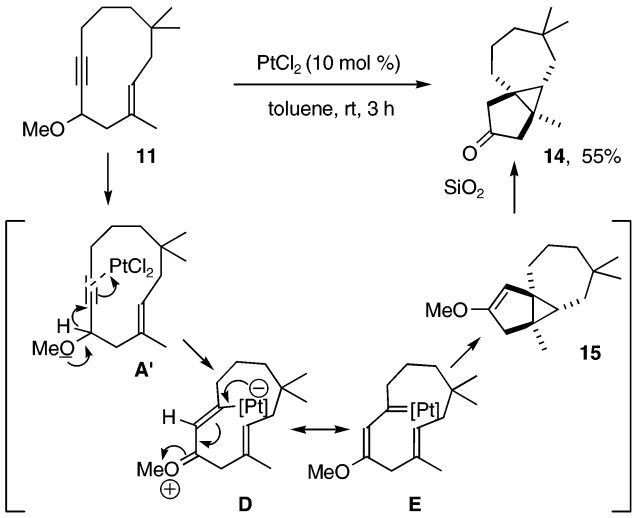


We could readily determine that product **12** was an enol ester and **14** a ketone. This led us to run a methanolysis on **12**. Careful spectroscopic analysis showed that the resulting products **13** and **14** were regioisomeric ketones that possess the same 5,3,7-tricyclic skeleton. Thus, as anticipated from the acyclic series, a completely different behavior for methoxy and acyloxy derivatives is observed.[12]

Based on the previous mechanistic rationale, we propose that an initial electrophilic π-complexation of the alkyne by the Pt(II) entity, shown in species **A** and **A′**, would trigger

(21) Stereochemical assignments were performed by using NOE studies. See the Supporting Information.

Scheme 5. $PtCl_2$-Catalyzed Transannular Cyclization of Cycloundecenyne Derivative **11**



two different pathways according to the nature of the hydroxy protecting group. In the case of ester precursor **10**, a [1,2]-migration of the benzoate group[11,22] via an oxocarbenium species **B** gives birth to an allylic platinacarbene **C** (Scheme 4). Cyclopropanation could then proceed and generate diastereoselectively the tricyclic enol ester **12** in 85% isolated yield.

Alternatively, in the case of the methoxy precursor **11**, the η^2-alkyne platinum complex **A′** would undergo a 1,2-hydride migration[23] to form, via oxonium of type **D**, an allylic carbene **E** which is stabilized by the donor methoxy group, followed by a diastereoselective cyclopropanation step which gives labile enol ether intermediate **15**. Tricyclo[5.4.0.0.^{1,8}]-undecan-10-one **14** is finally obtained as the isolated product in 55% yield after purification on silica gel (Scheme 5).

We next turned our attention to check the reactivity of cycloundecadienyne systems. By using the same synthetic approach, precursors *Z,E*- and *E,E*-cycloundecadienynols **16** and their corresponding nitrobenzoate derivatives **17** were prepared and submitted to $PtCl_2$ (Scheme 6).

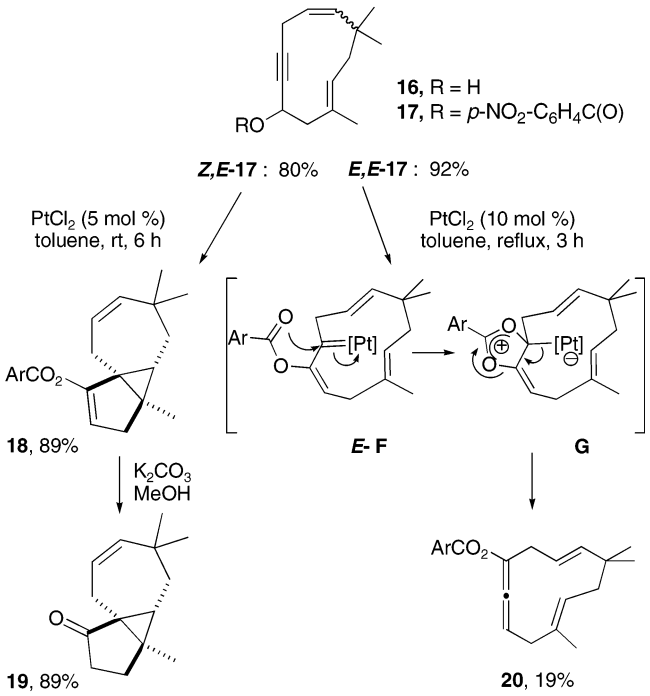
Z,E-Dienyne precursor **17** followed the same reactivity pattern as its enyne equivalent **10.** After methanolysis, it gave the expected tricyclic ketone **19** diastereoselectively with the carbonyl moiety α to the junction of the rings. Stereochemical assignment of the isolated unique diastereomer of tricyclo[5.4.0.0.^{1,8}]undeca-3,10-diene **18** was established by X-ray analysis.[24] The spectroscopic data for **12** and **18** being similar, this confirmed the stereochemistry deduced from the NOE for **12**.

(22) (a) For pioneering findings, see: Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950−952. (b) For an intermolecular version, see: Miki, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2003**, *68*, 8505−8513.

(23) Whether involving carbenoid or carbocationic intermediates, similar 1,2-hydrogen transfers have been observed by Echavarren, Fürstner, and us on several precursors; see refs 8e,f and 12a,b.

(24) CCDC 243389 contains the supplementary crystallographic data for **18** that can be obtained, free of charge, from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/conts/retrieving.html.

Scheme 6. $PtCl_2$-Catalyzed Transannular Cyclization of *Z,E*- and *E,E*-Cycloundecadienyne Derivatives **17**



Moreover, *E,E*-cycloundecadienyne benzoate **17**, submitted to the same conditions as its *Z,E*-diastereomer, showed a different behavior. After 6 h at rt, no conversion was observed. So we pursued the reaction overnight at 80 °C and one product appeared slowly. After an additional 3 h under reflux, cycloundeca-1,2,5,9-tetraene **20**[25] was isolated in 15% yield along with 60% of recovered material. No trace of the corresponding tricyclic compound was detected. Optimized conditions afforded 19% of allene **20** after 3 h of reflux conditions. More drastic conditions yielded to complete degradation. An explanation for the formation of this intriguing bis-allylic allene **20** resides in the *E*-stereochemistry of the disubstituted double bond. Due to this geometric constraint, formation of the *E*-seven-membered ring from *Z*-allyl carbene **F** becomes impossible. Instead, another oxocarbenium species **G** could be generated from ***E*-F**. *O*-Acyl migration would occur one more time and yield to the formation of the allenyl ester moiety present in **20**.

In conclusion, we have reported the first examples of a transannular $PtCl_2$-catalyzed reactivity of 1,5-enynes. This particularly efficient synthetic strategy opens a diastereoselective access to various tricyclic ketones possessing an internal cyclopropane motif. By simple variation of the hydroxy protecting group, the regioselectivity of the carbonyl group incorporation is completely controlled. Modeling the adequate precursor to reach natural bioactive products is under active investigation in our laboratory.

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

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(25) For related formation of allenes, see refs 9 and 23b and references therein.