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Ruthenium-Catalyzed Intramolecular Homo-Diels–Alder Reaction of Alkyne-Tethered Norbornadienes. An Entry to Fused Angular Triquinanes

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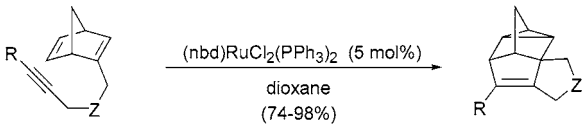
ABSTRACT



Z = $C(CO_2Me)_2$, $C(CH_2OAc)_2$, $C(CN)_2$, $C(SO_2Ph)_2$, acetal, $CHCO_2Me$, O or NTs
R = H, Br, CO_2Me, COMe, Ph, CH_2OH or $CH_2OTBDMS$

2-(Pent-4-ynyl)norbornadienes undergo an intramolecular [2 + 2 + 2] cycloaddition in the presence of $(nbd)RuCl_2(PPh_3)_2$ as a catalyst affording annelated deltacyclenes in good to excellent yields. The usefulness of the reaction is illustrated by the straighforward conversion of pentacyclene 2a into the angularly fused triquinane 19.

Cycloadditions are among the most efficient reactions in the repertoire of ring-forming procedures producing increased molecular complexity.[1] These reactions usually proceed with the formation of at least two carbon−carbon bonds and are achieved under photochemical or thermal conditions or promoted by Lewis acids. Transition-metal catalysts expanded the scope of cycloadditions allowing reactions between unactivated alkenes or dienes and alkynes[2] and giving access to enantioselective versions through the use of chiral ligands.[3] Recently, we reported the first ruthenium-catalyzed homo-Diels−Alder cycloaddition (HDA) between norbornadiene and alkynes affording tetracyclic alkenes, the so-called deltacyclenes.[4] Unfortunately, the reaction was restricted to electron-poor internal alkynes or required the presence of an oxygen atom at the propargylic position. Taking advantage of a significant decrease of the entropy for the intramolecular variant of this reaction,[5] we thought that it should be possible to perform the reaction of substrates (a) in which the tether of the two reactive components would be free of the propargylic oxygen atom and (b) featuring terminal or internal alkynes. In this paper, we report the successful ruthenium-catalyzed intramolecular HDA reaction of such alkynes tethered to norbornadiene, affording pentacyclenes in good to excellent yields under mild conditions, and the straightforward stereoselective synthesis of angular triquinane **19** based on the cleavage of two carbon−carbon bonds of cycloadduct **2a**.

(1) (a) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, 1990. (b) Kobayashi, J.; Jorgensen, K. A. *Cycloaddition Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2002.

(2) (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49−92. (b) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635−662.

(3) Recent examples: (a) [2 + 1]: Bigeault, J.; Giordano, L.; Buono, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4753−4757. (b) [2 + 2]: Shibata, T.; Takami, K.; Kawachi, A. *Org. Lett.* **2006**, *8*, 1343−1345. (c) [4 + 2] Aikawa, K.; Akutagawa, S.; Mikami, K. *J. Am. Chem. Soc.* **2006**, *128*, 12648−12649. (d) [2 + 2 + 2]: Shibata, T.; Arai, Y.; Tahara, Y. *Org. Lett.* **2005**, *7*, 4955−4957.

(4) Tenaglia, A.; Giordano, L. *Tetrahedron Lett.* **2004**, *45*, 171−174.

(5) The first intramolecular HDA reaction between norbornadiene and alkynes using a cobalt catalyst was reported by Lautens. See: (a) Lautens, M.; Tam, W.; Edwards, L. G. *J. Org. Chem.* **1992**, *57*, 8−9. (b) Lautens, M.; Tam, W.; Lautens, J. C.; Edwards, L. G.; Crudden, C. M.; Smith, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 6863−6879.

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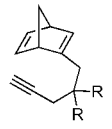
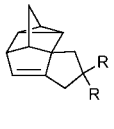
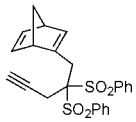
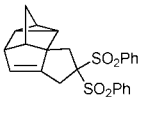
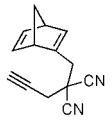
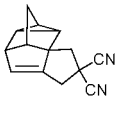
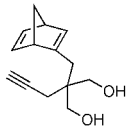
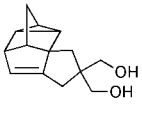
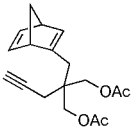
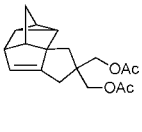
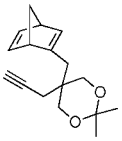
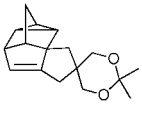
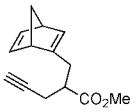
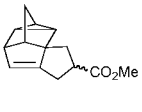
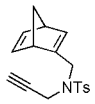
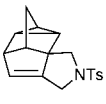
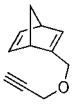
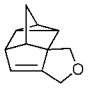
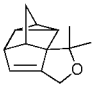
As a model, dienyne **1a** was readily prepared in a few steps by sequential alkylations of dimethyl malonate.[6] No reaction was observed for the thermal cycloaddition of **1a** carried out at 110 °C in toluene (*c* 0.1 M). Conducting the reaction in the presence of 5 mol % of (nbd)$RuCl_2(PPh_3)_2$[7] in dioxane at 60 °C for 4 h resulted in a complete conversion of **1a** and the formation of a single cycloadduct **2a** in 96% yield. Gratifyingly, these mild conditions allowed a rate enhancement (compared to the intermolecular reaction),[4] and more importantly, the cycloaddition with a terminal alkyne in the ruthenium-catalyzed reaction was observed for the first time. The structure of **2a** was deduced from NMR studies, being in full agreement with data of similar adduct **2b** (R = CO_2Et) observed from the cobalt-catalyzed [2 + 2 + 2] cycloaddition.[5,8] In contrast with the cobalt-catalyzed variant, which required a Ziegler−Natta-type catalyst consisting of anhydrous $Co(acac)_3$, dppe and Et_2AlCl, the present ruthenium catalyst is an air-stable, readily available complex from norbornadiene and $RuCl_2(PPh_3)_3$[7] and active without additives. Interestingly, for synthetic purposes (see below), the reaction of **1a** scaled up to 1 g afforded **2a** with a slight decrease of yield (88%).

The scope of the cycloaddition of 2-(pent-4-ynyl)-norbornadienes was examined by varying the substituents on the tether (Table 1). Under the conditions described for **1a**, alkynylnorbornadienes **1a**,**c**,**d**,**f**−**h**, **4**, and **6** were converted to the expected cycloadducts **2a**,**c**,**d**,**f**−**h**, **5**, and **7** in yields ranging from 74 to 98%. No other adduct was detected by ^1H NMR of the crude reaction mixture. The observation of two splitted cyclopropyl proton resonances and a broad singlet (1H) at δ 5.60−5.90 were diagnostic for the formation of these cycloadducts. Polar functional groups such as esters, acetals, ethers, sulfones, sulfonamides, and nitriles as well as the presence of an heteroatom on the tether are well tolerated. The reaction with dinitrile **1d** (Table 1, entry 3) required a higher temperature (90 °C) and a longer reaction time presumably due to the ability of these groups to coordinate with the metal center, thus decreasing the rate of the reaction. Dienyne **1e** bearing free hydroxyl groups afforded cycloadduct **2e** in only 26% yield (Table 1, entry 4) and gave the pentacyclic ether **3** as a major product (46%) (Scheme 1). The stereochemistry of **3** was tentatively assigned as depicted on the basis of the greater thermodynamic stability of cis- vs trans-fused diquinanes.[9] At first glance, the structure of **3** suggested a ruthenium-catalyzed etherification of **2e** by addition of the hydroxyl group across the double bond. However, a control experiment subjecting diol **2e** to the ruthenium catalyst under the above conditions led exclusively to the recovery of **2e**. We presume that the etherification step could arise concomitant to the cycload-

Table 1. Ru-Catalyzed Intramolecular [2 + 2 + 2] Cycloaddition of 2-Alkynylnorbornadienes Featuring a Terminal Alkyne[a]

entry	precursor	cycloadduct	yield (%)[b]
1	 **1a**, R = CO_2Me	 **2a**, R = CO_2Me	96
2	 **1c**	 **2c**	90
3[c]	 **1d**	 **2d**	74
4[d]	 **1e**	 **2e**	26
5	 **1f**	 **2f**	94
6	 **1g**	 **2g**	80
7	 **1h** (dr 1:1)[e]	 **2h** (dr 1:1)[e]	98
8	 **4**	 **5**	96
9	 **6**	 **7**	75
10	 **8**	 **9**	0

[a] Conditions: substrate (0.5 mmol), (nbd)$RuCl_2(PPh_3)_2$ (5 mol %), dioxane (*c* 0.1 M), 60 °C, 4 h. [b] Isolated yield after column chromatography. [c] Conditions: 90 °C, 8 h. [d] Ether **3** was the major product in this reaction (Scheme 1). [e] dr determined by ^1H NMR of the crude reaction mixture.

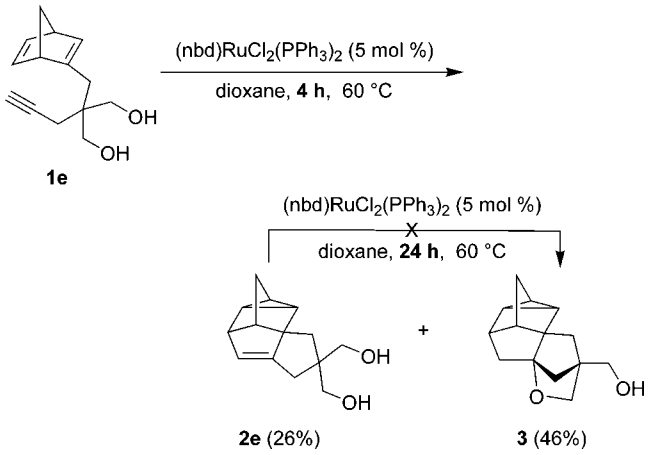
(6) See the Supporting Information.

(7) Robinson, S. D.; Wilkinson, G. *J. Chem. Soc.* **1966**, 300−301. nbd = norbornadiene.

(8) The pentacyclic structure of the cycloadducts was further confirmed with a single-crystal X-ray analysis of the dinitrile **2d**. CCDC-650416 contains the supplementary crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (int.) +44−1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk]. See also the Supporting Information.

(9) Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41−173.

Scheme 1. Ru-Catalyzed Intramolecular [2 + 2 + 2] Cycloaddition of Diol **1e**



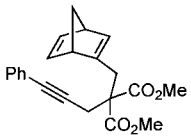
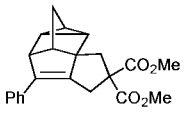
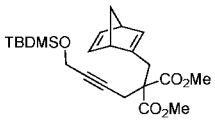
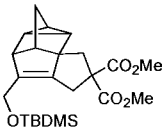
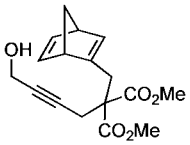
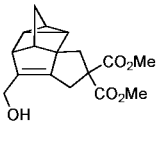
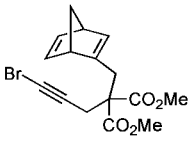
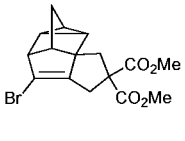
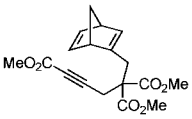
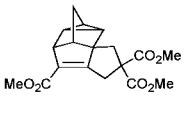
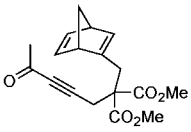
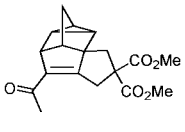
dition path.[10] In contrast with the cobalt-catalyzed [2 + 2 + 2] cycloaddition, the sterically demanding dienylpropargyl ether **8**, which afforded the expected adduct **9** albeit in poor yield (22%),[5] failed to undergo the ruthenium-catalyzed cycloaddition reaction (Table 1, entry 10).

The intramolecular [2 + 2 + 2] cycloaddition involving internal alkynes was also studied (Table 2). The desired cycloadducts were observed as sole products in good yields (75−91%) under the same conditions as above. A notable exception was observed with the phenyl-substituted alkyne **10a** which required different conditions (90 °C, 8 h) for the completion of the reaction (Table 2, entry 1). Additionally, ketones, TBDMS ethers and bromides proved to be compatible with the catalyst. Electron-poor or electron-rich alkynes were not detrimental to the cycloaddition (Table 2, entries 2, 3, 5, and 6). Although a free hydroxyl group is tolerated (Table 2, entry 3), the yield of the reaction was improved with the TBDMS-protected propargylic alcohol **10b** (Table 2, entry 2). Interestingly, alkynyl bromides such as **10d**, which were not examined before in the ruthenium-catalyzed [2 + 2 + 2] cycloaddition,[4] afforded the adduct **11d** in 83% yield (Table 2, entry 4).

We took advantage of the alkenyl bromide moiety of **11d** to further expand the scope of the reaction by functional exchange with the bromine atom, thus providing an entry to multifunctional cycloadducts that are difficult to achieve via direct cycloaddition. For instance, Sonogashira coupling[11] between **11d** and 2-methylbut-3-yn-2-ol **(12)** provided **13** in 89% yield, and Suzuki−Miyaura coupling[12] between **11d** and phenylboronic acid **14** gave pentacyclene **11a** in 79% yield (Scheme 2).

A mechanism rationale accounting for the ruthenium-catalyzed [2 + 2 + 2] cycloaddition based on Ru(II) and

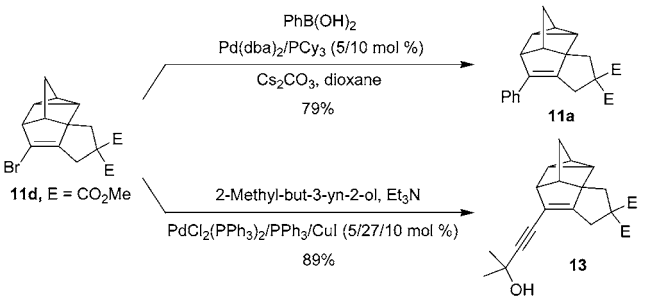
Table 2. Ru-Catalyzed Intramolecular [2 + 2 + 2] Cycloaddition of 2-Alkynylnorbornadienes Featuring an Internal Alkyne[a]

entry	precursor	cycloadduct	yield (%)[b]
1[c]	 **10a**	 **11a**	75
2	 **10b**	 **11b**	91
3	 **10c**	 **11c**	80
4	 **10d**	 **11d**	83
5	 **10e**	 **11e**	87
6	 **10f**	 **11f**	91

[a] Conditions: substrate (0.5 mmol), (nbd)$RuCl_2(PPh_3)_2$ (5 mol %), dioxane (*c* 0.1 M), 60 °C, 4 h. [b] Isolated yield after column chromatography. [c] Conditions: 90 °C, 8 h.

Ru(IV) intermediates is depicted in Scheme 3. The η^4-dienyl ligand exchange between the precatalyst (nbd)$RuCl_2(PPh_3)_2$

Scheme 2. Pd-Catalyzed Suzuki−Miyaura and Sonogashira Couplings of Cycloadduct **11d**

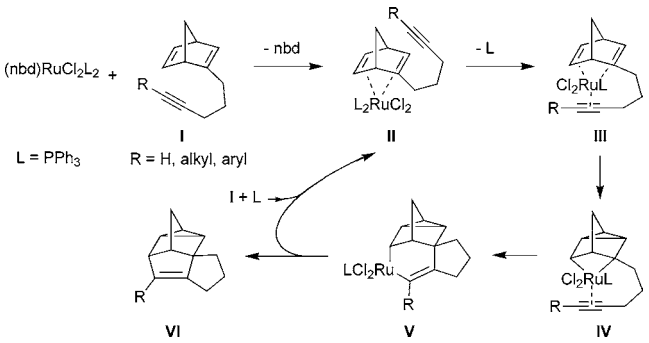


(10) This unexpected etherification is currently being investigated in our laboratories.

(11) Sabourin, E. T.; Onopchenko, A. *J. Org. Chem.* **1983**, *48*, 5135−5137.

(12) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028.

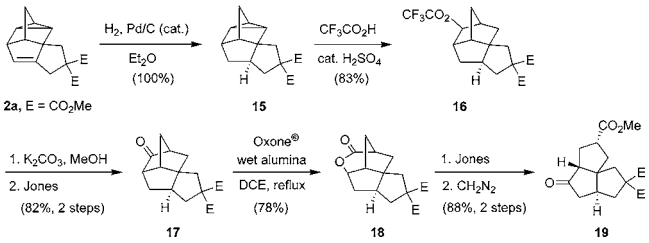
Scheme 3. Proposed Mechanism for the Ru-Catalyzed HDA Reaction



and dienyne **I** followed by dissociation of PPh_3 and coordination of the alkyne component would lead to complex **III**. Upon oxidative coupling, **III** would form ruthenacyclobutane **IV**. Carboruthenation of the alkyne moiety would yield ruthenacyclohexene **V**, which undergoes reductive elimination of the metal species to release the cycloadduct **VI**.

To illustrate the synthetic usefulness of these annelated deltacyclenes, cycloadduct **2a** was transformed into angularly fused triquinane **19** (Scheme 4). The basic triquinane framework is present in a great number of naturally occurring sesquiterpenoids with interesting biological activities.[13] Our stategy was based on Nickon's selective oxidative cleavage of the cyclopropane unit of deltacyclane[14] and on our former synthetic studies[15] to transform the brendane skeleton to diquinanes.[16] Reduction of pentacyclene **2a** (H_2, Pd/C) afforded quantitatively pentacyclane **15**. Modified Nickon's conditions (CF_3CO_2H instead of AcOH) allowed the cyclopropane cleavage (**15** → **16**) to occur faster. Hydrolysis of trifluoroacetate **16** followed by Jones' oxidation yielded ketone **17** which underwent a regioselective Baeyer−Villiger oxidation to give the crystalline lactone **18**. A single-crystal X-ray analysis of **18**[17] secured both the structure and the stereochemical outcome of the hydrogenation step (**2a** → **15**). The lactone ring-opening proved to be difficult to achieve under diverse acidic or basic conditions, and **18** was recovered unchanged or in some cases with partial hydrolysis of the ester groups. Finally, using Jones' oxidation protocol, the acidic media allowed the equilibrium between the lactone and the hydroxyacid (not shown) which was oxidized in situ to the ketoacid (not shown) and esterified with diazomethane to gave the desired angular triquinanone **19** in 45% overall yield (seven steps from **1a**).

Scheme 4. Synthesis of Fused Angular Triquinane **19** from Cycloadduct **1a**



In summary, we have provided the first examples of the ruthenium-catalyzed intramolecular [2 + 2 + 2] cycloaddition of norbornadiene-tethered alkynes affording pentacyclenes in good yields. The reaction was achieved using the readily available air-stable (nbd)$RuCl_2(PPh_3)_2$ and applied to both terminal or internal alkynes, including bromoalkynes, allowing the formation of densely functionalized cycloadducts. Additionally, the synthetic value of the cycloadduct **2a** for the construction of the fused angular triquinane **19** through the cleavage of two carbon−carbon bonds of the cyclopropane component was also demonstrated.

Acknowledgment. We thank Dr. I. De Riggi (ECM, Université P. Cézanne, Marseille) for help with the NMR, the MENRT for a graduate fellowship (to S.G.), and the CNRS for financial support.

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

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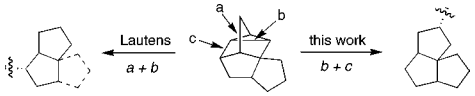
(13) (a) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1−163. (b) Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry*; Springer-Verlag: Berlin, 1987. (c) Hudlicky, T.; Price, J. D. *Chem. Rev.* **1989**, *89*, 1467−1486. (d) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671−719.

(14) Nickon, A.; Kwasnik, H. R.; Mathew, C. T.; Swartz, T. D.; Williams, R. O.; DiGiorgio, J. B. *J. Org. Chem.* **1978**, *43*, 3904−3916.

(15) (a) Heumann, A.; Kaldy, S.; Tenaglia, A. *J. Chem. Soc., Chem. Commun.* **1993**, 420−422. (b) Heumann, A.; Kaldy, S.; Tenaglia, A. *Tetrahedron* **1994**, *50*, 539−558.

(16) Lautens suggested the selective cleavage of two carbon−carbon bonds of the cyclopropane unit as a route to functionalized linearly or angularly fused triquinanes but achievement of this strategy was only demonstrated to the bicyclic structure (diquinanes). See: (a) Lautens, M.; Tam, W.; Blackwell, J. *J. Am. Chem. Soc.* **1997**, *119*, 623−624. (b) Lautens, M.; Blackwell, J. *Synthesis* **1998**, 537−546. Our strategy is complementary and based on the cleavage of one cyclopropane bond and one adjacent carbon-carbon bond, see below:



It should be noted that the diquinanes obtained by Lautens required an alkoxy substituent on the methano bridge of deltacyclanes to achieve regiochemistry and used an environmentally unfriendly stoichiometrical oxymercuriation step for cleavage of the cyclopropane.

(17) CCDC-650417 contains the supplementary crystallographic data. See the Supporting Information for details.