The Effect of a Hydroxy Protecting Group on the $PtCl_2$-Catalyzed Cyclization of Dienynes—A Novel, Efficient, and Selective Synthesis of Carbocycles**

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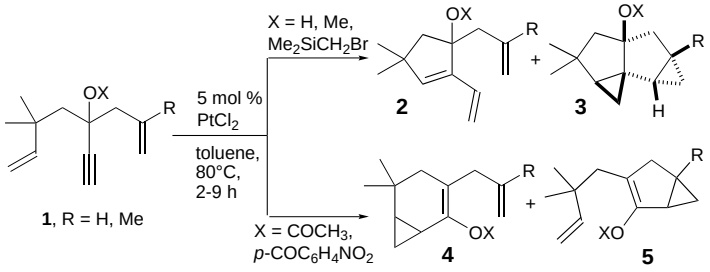
In the last decade, we worked on the development of highly chemo-, regio-, and stereoselective cascade processes, relying either on radical reactions[1] or on transition metal mediated processes.[2] With the perspective to reach new complex molecular architectures, we examined the possibility of running metathesis[3]–radical cyclization tandems on precursors of type **1** (Scheme 1). To the best of our knowledge, this



Scheme 1. General reaction.

functional–structural assembly has not been previously assayed in enyne metathesis reactions;[4] the most related substrates (branched dienynes) were reported by the groups of Grubbs,[5] Granja,[6] and Hanna.[7] After disappointing results with Grubbs' catalysts, we turned to platinum(II)-catalyzed cycloisomerizations as the first step because of their wide applicability with enyne systems.[8–11]

Under typical reaction conditions (5 mol% $PtCl_2$, toluene, 80 °C for 2.5 h), precursor **1a** provided a mixture of the expected formal metathesis adduct **2a**, as a minor fraction (7%), and a fairly complex structure, compound **3a**, in 48% yield (Table 1, entry 1). Its NMR spectroscopic data indicated no unsaturation and the presence of two cyclopropane rings (upfield resonances in the ^{1}H NMR spectrum between $\delta =$ 0.50 and 0.90 ppm). Finally, and more importantly, only one diastereomer was produced. Definitive structure determination was achieved by an X-ray analysis of the 4-nitrobenzoate ester derivative **3e** (Figure 1),[12] obtained by standard acylation of **3a**. Compound **3a** (Scheme 1) is a derivative of tetracyclo[4.4.0.0^{1,3}0^{8,10}]decane which has not been described before. Moreover, the formation of four C–C bonds and four new stereocontrolled centers in a synthetically simple and efficient operation (see Experimental Section) is spectacular in terms of chemo-, regio-, and stereoselectivity.[13]

Table 1. $PtCl_2$-promoted enyne cycloisomerization reaction on compounds **1** (see Scheme 1). Yields in [%].

Entry	Precursor	X	R	2	Yield	3	Yield	4	Yield
1	**1a**	H	H	**2a**	7	**3a**	48	–	
2	**1b**	$SiMe_2CH_2Br$	H	**2b**	5	**3b**	61	–	
3	**1c**	Me	H		0	**3c**	68	–	
4	**1d**	$COCH_3$	H	–		–		**4d**	88[a]
5	**1e**	p-$COC_6H_4NO_2$	H	–		–		**4e**	76[a]
6	**1f**	H	Me		0	**3f**	25	–	
7	**1g**	$SiMe_2CH_2Br$	Me		0	**3g**	16	–	
8	**1h**	Me	Me		0	**3h**	34	–	
9	**1i**	p-$COC_6H_4NO_2$	Me	–		–		**4i**	62[b]

[a] The corresponding product **5** was also formed in 5–10%. [b] The corresponding product **5** was also formed in 16%.

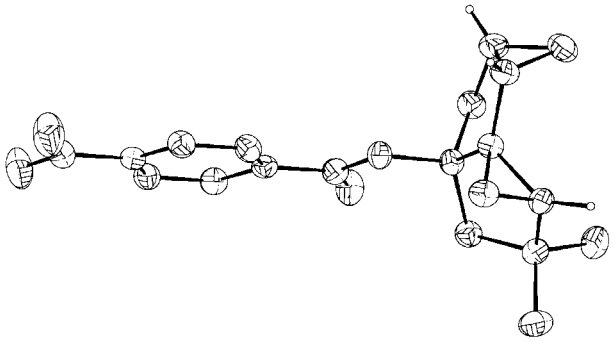


Figure 1. ORTEP presentation of the structure of compound **3e**.

This promising result prompted us to prepare other precursors for the Pt^{II}-mediated cycloisomerization and to define a mechanistic rationale. Whether the initial intermediate in these reactions is a metallacyclopentene[8c] or a carbocation[9–11], [14] has been a matter of recent debate. We felt that our system could serve as a good probe for new mechanistic insights, notably by tuning the nature of the propargylic O-protecting group X.

The bromomethyldimethylsilyl derivative **1b** gave products **2b** and **3b** in 5 and 61% yield, respectively (Table 1, entry 2). Desilylation of **3b** yielded **3a**, proving that we were dealing with the same type of reaction and that the relative configurations at all the newly formed stereocenters in compound **3b** were identical to those in product **3a**. Comparing the results for **1a** with those for **1b** we concluded that the free alcohol **1a** is slightly more fragile under our standard

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[**] Acknowledgement is made to the EU for the COST D12 Action "Cascade Free Radical Reactions" and for a short-term scientific mission to Madrid (EM). We thank Nieves Arroyo (CSIC) for preliminary experiments, Dr. J. Vaissermann (UPMC) for the X-ray analysis of **3e**, Dr. M. L. Jimeno (CNQO) for NMR studies on **3a**, Dr. M.-N. Rager (ENSCP) for NMR studies on **3h**, **6**, and **11**, and Matthieu Bernard (UPMC) for performing some of the experiments. We also thank Dr. Emmanuel Lacôte and Dr. Henri Rudler (UPMC) for helpful discussions.

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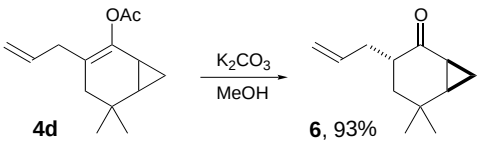
  1433-7851/02/4112-2132 $ 20.00+.50/0

reactions conditions than O-protected derivatives, which was confirmed by the fact that the methyl ether **1c** gave a diastereomerically pure material (**3c**) in 68% yield, with no detectable metathesis adduct **2** (Table 1, entry 3). The spectroscopic data for compounds **3c** and **3b** or **3a** were similar, thus confirming the same stereochemical features for all of them.

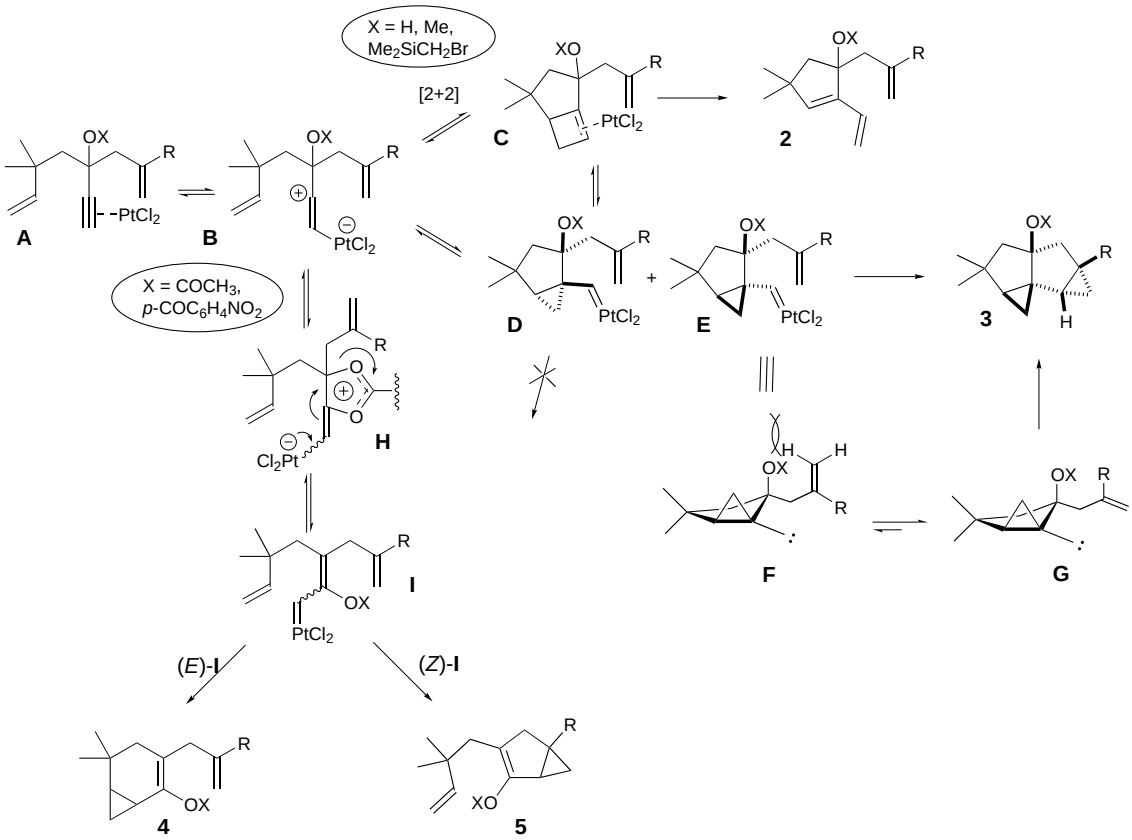
The methallyl precursors **1f**, **1g**, and **1h** showed the same pattern of reactivity: the tetracyclic derivatives **3** were still formed and isolated as single diastereomers, but in much lower yields (from 16 to 34%, Table 1, entries 6–8). No other product was identified from these reactions. The relative configurations at the newly formed stereocenters could be assigned based on NOESY studies and by comparison of the NMR data with those of the analogous compounds **3a–c**.

The behavior of the *O*-acyl derivatives **1d**, **1e**, and **1i** proved quite distinct. The reaction of **1d** was rapid and clean and afforded a compound in good yield (88%, Table 1, entry 4), whose spectroscopic and analytical data suggested a more simple, completely different adduct. NMR analysis confirmed that **4d** with a bicyclo[4.1.0] framework and an enolester conjugated with the cyclopropane ring was formed. The 4-nitrobenzoates **1e** and **1i** afforded the corresponding products **4e** and **4i** in consistent and similar high yields (Table 1, entries 5 and 9). Additional proof for the structure was obtained when compound **4d** was transformed into the *trans* ketone **6**[15] after methanolysis [Eq. (1)]. Minor adducts with structures that, based on the NMR spectra, correspond to **5** (Scheme 1) were also observed.



(1)

In Scheme 2, we propose a simple mechanistic picture for these findings. After π complexation of the alkyne moiety onto the platinum salt,[16] the intermediate **A** evolves via a slipped, polarized η^1-alkyne complex bearing a positive charge at the β position (**B**).[9], [17] For X = H, Me, and Me_2SiCH_2Br, two pathways are reasonable: 1) The identification of metathesis products **2** as minor products suggests the formation of a formal [2+2] adduct **C** through the cationic manifold proposed by Fürstner,[9d] and its reopening to provide **2**. 2) For the products **3** carbene complexes like **D** and **E** are probable intermediates. Such cyclopropyl Pt complexes have been first mentioned by Murai et al.[10] and then shown by Echavarren et al., through DFT calculations,[11b] to be key intermediates in the alkoxy cyclization of enynes. In our case, only **E**, having the *cis* disposition between the alkyl chain and the carbene entity, can evolve in a further intramolecular diastereoselective cyclopropanation (conformer **G** preferred over **F**) leading to the diquinanes **3**. This is not possible for **D**. The driving force for these reactions might be the delivery of the diene **2** or of the tetracyclic derivative **3** as the formation of **C**, **D**, and **E** is presumably reversible.



Scheme 2. Mechanistic considerations for the formation of products **2–5**.

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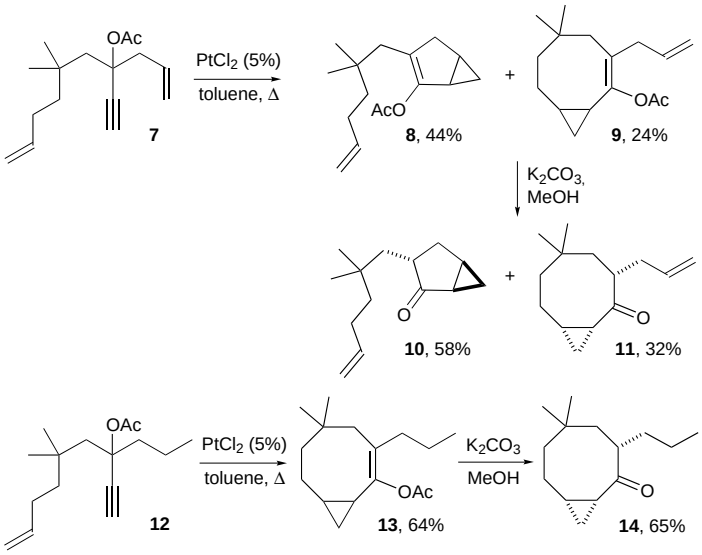
To rationalize the completely distinct behavior of the *O*-acyl precursors, we invoke further stabilization of the initial vinylcarbocation intermediate **B** through formation of the oxocarbenium species **H** (Scheme 2). Adjustment of electrons involving an *O*-acyl migration at the β carbon atom then furnishes the vinyl platinum carbene **I**, which adds, in the *E* form, to the pending double bond to give adducts **4**, whereas the minor *Z* intermediate gives adducts **5**. This whole new $PtCl_2$-catalyzed transformation was intriguing, and we next sought for a confirmation on the generality of this reactivity and versatile synthetic applications.

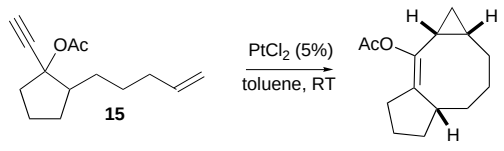
For that purpose, we examined the behavior of precursors **7** and **12** (Scheme 3). The former provided the two bicyclic derivatives **8** and **9** suggesting that the same type of



Scheme 3. Synthesis of cyclooctane derivatives.

mechanism is operating with a competition between the formation of five-membered ring **8** via a *Z* vinyl carbene species and the formation of eight-membered ring **9** involving the *E* vinyl carbene species. Presumably, these two species are in equilibrium and their relative stability and possible evolution account for the ratio. Without such a competition (compound **12**) a fair yield of the cyclooctene (64% **13**) was obtained, considering that the efficient assembly of a functionalized cyclooctane from an acyclic precursor still remains a difficult task.[18] Final methanolysis led completely diastereoselectively to the bicyclic ketones **10**, **11**, and **14**.[15]

Finally, in order to illustrate the synthetic potential of this reaction, a different type of substrate, the diastereomeric mixture **15**, was exposed to a catalytic amount of $PtCl_2$. In a completely stereoconvergent process a single diastereomer of the tricyclic adduct **16** was formed in 66% yield [Eq. (2)].[15]



(2)

In conclusion, we have shown that $PtCl_2$-catalyzed cyclizations of dienyne systems with a hydroxy group at the propargylic position can be chemo-, regio-, and stereocontrolled by tuning the nature of the protecting group at this position. With a free hydroxy group or the corresponding ethers, the previously unknown tetracyclo[4.4.0.0^{1,3}0^{8,10}]decane skeleton was obtained diastereoselectively. An *O*-acyl protecting group completely shifted the reaction towards a previously undescribed rearrangement, which afforded bicyclic enolesters with a fused cyclopropane ring in α,β position that were methanolyzed to versatile [*n*.1.0]bicylic ketones as single diastereomers. This combined two-steps protocol can be regarded as an equivalent of the well-known cycloisomerization of unsaturated α-diazocarbonyl compounds[19] with obvious advantages.

Particularly attractive is the extension of this process to efficiently produce medium-sized rings such as cyclooctanes, still a challenge in organic synthesis.[18] Because of their oxygenated functionalities and the presence of intriguing cyclopropane moieties,[20] these compounds should also be an interesting platform for further elaboration.[21] Our results provide strong support for a cationic mechanism of their formation, notably the intervention of a slipped polarized η^1-alkyne complex.

Experimental Section

To a degassed solution of 5-ethynyl-5-methoxy-3,3-dimethylocta-1,7-diene **1c** (173 mg, 0.9 mmol) in dry toluene (40 mL, 0.025 M), under argon and at room temperature (RT), $PtCl_2$ (13 mg, 0.05 mmol, 0.05 equiv) was added. The mixture was warmed to 80 °C and stirred until the reaction was complete (ca. 2.5 h). Then the mixture was cooled to RT and the solvent was evaporated under vacuum. Purification by flash chromatography on silica gel (pentane/Et_2O, 98/2) afforded the diquinane **3c** in 68% yield (118 mg) as an oil. IR (neat): $\tilde{\nu}$ = 2950, 1480, 1380 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.28 (s, 3H), 2.36 (dd, *J* = 14.3, 7.0 Hz, 1H), 1.61 (m, 1H), 1.52 (dd, *J* = 14.3, 2.5 Hz, 1H), 1.52 (d, *J* = 14.3 Hz, 1H), 1.33 (td, *J* = 7.4, 3.4 Hz, 1H), 1.08 (d, *J* = 14.3 Hz, 1H), 1.06 (s, 3H), 0.90 (s, 3H), 0.89 (td, *J* = 8.4, 4.4 Hz, 1H), 0.82 – 0.70 (m, 3H), 0.47 ppm (q, *J* = 4.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 104.0, 51.9, 46.2, 43.8, 39.2 (2C), 35.8, 30.7, 28.3, 22.1, 21.7, 21.2, 12.2 ppm; elemental analysis (%) calcd for $C_{13}H_{20}O$: C 81.20, H 10.48; found: C 81.07, H 10.59.

Received: January 22, 2002
Revised: April 8, 2002 [Z18566]

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Dioxygen Activation by a Mononuclear Ir^{II} – Ethene Complex

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In an attempt to gain a mechanistic insight into the rhodium- and iridium-catalyzed oxygenation of olefins, we have recently investigated stoichiometric oxygenation of N ligand Rh^{I}– and Ir^{I} – olefin complexes by O_2 (olefin = ethene, propene, 1,5-cyclooctadiene).[1, 2]

The reactivity of Rh^{I}– and Ir^{I} – ethene fragments towards dioxygen varied between ethene displacement (Figure 1a), formation of mixed O_2 – ethene complexes (Figure 1b), C–O bond making (giving a 3-metalla(III)-1,2-dioxolane; Figure 1c), and combined C–O bond making and O–O bond breaking (giving a 2-metalla(III)oxetane; Figure 1d) The outcome of the oxygenation reaction varies with the N ligand and the central metal.

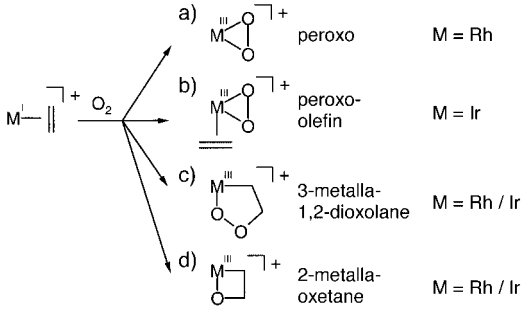

Figure 1. Oxygenation products from the reaction of $[(N\ ligand)M^{I}(olefin)]^{+}$ (M = Rh/Ir) complexes with O_2.

Recently, we described the oxygenation of the iridium(I) – ethene complex $[(\kappa^4\text{-}Me_3\text{-}tpa)Ir^{I}(C_2H_4)]^{+}$ (**1**; Me_3-tpa = *N*,*N*,*N*-tri((6-methyl-2-pyridyl)methyl)amine) by O_2 to the peroxo – ethene complex $[(\kappa^3\text{-}Me_3\text{-}tpa)Ir^{III}(C_2H_4)(O_2)]^{+}$ (Figure 1b) and unidentified paramagnetic species.[2] We now report the one-electron oxidation of the Ir^{I} – ethene complex **1** to the unprecedented Ir^{II} – ethene complex $[(\kappa^4\text{-}Me_3\text{-}tpa)Ir^{II}(C_2H_4)]^{2+}$ (**2**; see Scheme 1), and the reactivity of **2** towards O_2.

Treatment of **1**-PF_6 with ferrocinium hexafluorophoshate ([Fc]PF_6) in CH_2Cl_2 resulted in precipitation of **2**-$(PF_6)_2$ as a brown powder. Thus, one-electron oxidation of Ir^{I} – ethene complex **1** with Fc^{+} results in the clean formation of the stable Ir^{II} – ethene complex **2** (Scheme 1).

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  1433-7851/02/4112-2135 $ 20.00+.50/0