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Tandem Reactions

# Sequential Platinum-Catalyzed Cycloisomerization and Cope Rearrangement of Dienynes**

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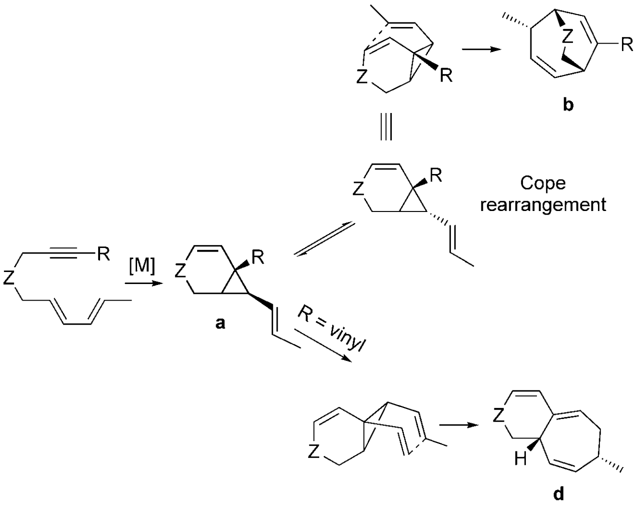
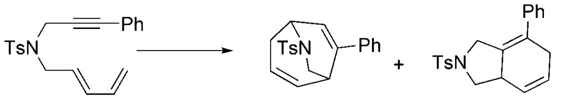
Transition-metal-catalyzed carbocyclization reactions of unsaturated hydrocarbons are known to be powerful methods for the construction of complex polycyclic systems.[1] Among them, transition-metal-catalyzed cycloisomerizations have recently received a great deal of attention owing to their ability to furnish a variety of structures from a single substrate by changing the catalyst and reaction conditions.[2] Interestingly, most of the reported transition-metal-catalyzed cycloisomerizations have focused on enyne substrates,[2,3] with comparatively little attention devoted to the cycloisomerization of dienynes,[4] perhaps because the [4+2] cycloaddition reaction is prevalent for dienynes.[5]

The synthetic potential of ring systems such as bicyclo[4.1.0]heptenes **a**, which are easily obtainable from the transition-metal-catalyzed cycloisomerization of enynes, has not yet been thoroughly examined.[6] We envisioned that if a dienyne bearing a divinylcyclopropane group was used as a substrate, such as 7-vinylbicyclo[4.1.0]hept-4-ene **a**, subsequent rearrangement might lead to the formation of bicyclic rings such as **b** and **d**.[7] (Scheme 1). Herein, we present a facile method for the stereoselective construction of bicyclo[3.2.2]nonadienes, 1,6,7,9a-tetrahydrocyclohepta[*c*]pyrans, and 1,6,7,9a-tetrahydrocyclohepta[*c*]pyridines, from dienyne substrates using a $PtCl_2$-catalyzed cycloisomerization and subsequent Cope rearrangement.

Initially, we tested a series of catalysts for the cycloisomerization reaction of dienyne **1** [Eq. (1)], under standard reaction conditions, which were adopted from previous studies (see the Supporting Information).[8] Despite expecting the formation of large amounts of [4+2] cycloaddition product, no such product was observed in the presence of gold or platinum catalysts. Compared with the previously reported gold-catalyzed [4+2] cycloaddition, this observed difference in reactivity [5f] may relate to the substrate used. An iridium catalyst afforded the [4+2] cycloaddition product in 21% yield; a relatively higher yield of **1b** (81%) was observed with a $PtCl_2$ catalyst.



***Scheme 1.*** The possible stereoselective construction of bicyclic rings by sequential metal-catalyzed cycloisomerization and Cope rearrangement.



(1)

| | 1 | 1b | 1c |
|---|---|---|---|
| | $[Au(PPh_3)]SbF_6$ | 45% | |
| | $[Ir(CO)(PPh_3)_2]OTf$ | | 21% |
| | $PtCl_4$ | 80% | |
| | $PtCl_2$ | 81% | |

We then investigated the scope of the reaction for various substrates (Table 1). Methyl-substituted dienyne **2** successfully afforded bicyclo[3.2.2]nona-2,8-diene **2b** as the sole cycloadduct in good yield (61%). Dienyne **3,** which contained a terminal alkyne and was known to decompose in the presence of a gold catalyst,[5f] afforded a modest yield of **3b** (34%) with the concomitant formation of a [4+2] cycloaddition product (44% yield). It has been reported that the Cope rearrangement of compounds containing an aryl substituent at the C3 position of 1,5-hexadiene proceeds faster than their unsubstituted analogues.[9] Thus, we focused our attention on dienynes which contained a phenyl-substituted alkyne (**1** and **4**–**12**). When an oxygen- or nitrogen-tethered dienyne containing a mono-substituted *E*-alkene was used as the substrate (**4**–**6**), the corresponding nonadienes **4b**–**6b**

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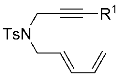
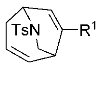
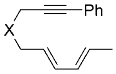
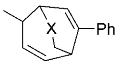
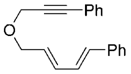
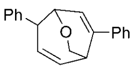
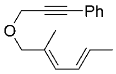
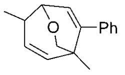
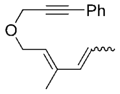
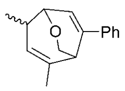
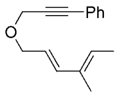
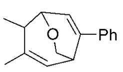
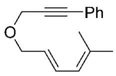
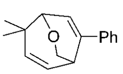
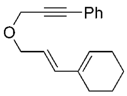
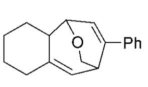
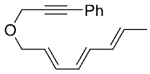
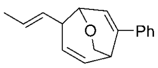
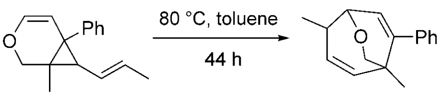
*Table 1:* Tandem platinum(II)-catalyzed cycloisomerization of dienynes and subsequent Cope rearrangement.[a]

| Substrate | | Conditions | Product | (Yield [%][b]) |
|---|---|---|---|---|
|  | | |  | |
| ($R^1$=Ph) | 1 | 80°C, 9 h | | **1b** (81) |
| ($R^1$=Me) | 2[c] | 80°C, 24 h | | **2b** (61) |
| ($R^1$=H) | 3 | 100°C, 24 h | | **3b** (34)[d] |
|  | | |  | |
| (X=O) | 4 | 80°C, 4 h | | **4b** (91) |
| (X=NTs) | 5 | 80°C, 2 h | | **5b** (86) |
|  | 6 | 60°C, 9 h |  | **6b** (68) |
|  | 7 | 130°C, 0.5 h |  | **7b** (77) |
|  | | |  | |
| (*E*:*Z*=1:2.3) | 8, 8′ | 70°C, 48 h | | **8b**/**8b′** (24/42) |
|  | 9 | 70°C, 7.5 h→ 130°C, 1.5 h |  | **9b** (68)[e] |
|  | 10 | 70°C, 5 h→ 130°C, 2.5 h |  | **10b** (45) |
|  | 11 | 75°C, 5 h→ 130°C, 1.5 h |  | **11b** (72) |
|  | 12 | 60°C, 7 h |  | **12b** (79) |

[a] 5 mol% $PtCl_2$; toluene was used for reactions under 110°C, xylene was used above 110°C. [b] Yield of isolated product. [c] 10 mol% $PtCl_2$. [d] [4+2] cycloaddition product **3c** was isolated in 44% yield. [e] [4+2] cycloaddition product **9c** was isolated in 8% yield.

were obtained in good yields (68–91%). The reaction time became more prolonged when additional substituents were introduced onto the diene (**7**–**11**). The reaction of 2,5-disubstituted diene **7** gave a mixture of **7a** and **7b** after 48 h in 7% and 52% yields, respectively. A pure sample of **7a** was used to examine whether the second step was a completely thermal process. When **7a** was heated in toluene at 80°C, **7b** was obtained as the sole product in 68% yield [Eq. (2)]. When **7** was heated in xylene at 130°C, **7b** was obtained in 77% yield after only 30 minutes.



**7a** **7b** (68%) (2)

Encouraged by this observation, substrates **8**–**11** were heated in xylene at 130°C. However, in the case of **8**, a mixture of **8b** and [4+2] cycloadduct **8c** was obtained, which suggested that a lower reaction temperature was required. When **8** was heated at 70°C for 48 h, **8b** was isolated as the sole product in 66% yield. Interestingly, the *E*/*Z* ratio of **8** (1:2.3) changed slightly to 1:1.8 in the product **8b**, presumably owing to the sterically unfavorable cyclic transition state of the *Z*-form during the rearrangement. Compound **9b** was isolated in 68% yield from dienyne **9** with the concomitant formation of **9c** in 8% yield. Compounds **10b** and **11b** were obtained in respectable yields from their starting dienynes (45% and 72%, respectively). The structure of **11b** was confirmed by X-ray diffraction analysis (Figure 1).[10] Nonadiene **12b** was obtained in 79% yield from **12** without further ring-expansion products. In all cases, apart from terminal alkyne **3**, a [4+2] cycloadduct was not obtained or was obtained in less than 10% yield. Moreover, because the bicyclo[4.1.0]heptene frame restricted the rotation of the divinylcyclopropane moiety, only a single diastereoisomer of nonadiene product was observed for each substrate (Scheme 1).

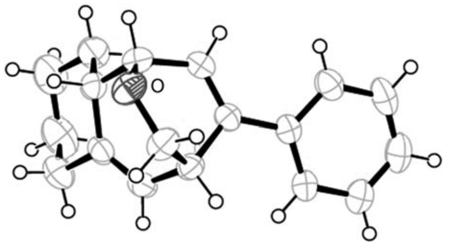
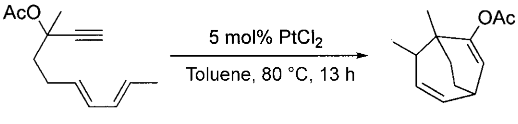


*Figure 1.* ORTEP structure of **11b**. Ellipsoids are set at 30% probability.

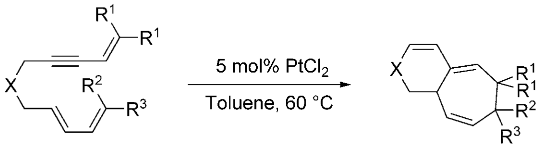
Next, we investigated the cyclization of enynes with a carbon tether [Eq. (3)]. It has been reported that the platinum-catalyzed cycloisomerization of hept-1,6-enynes yields the conventional Alder-ene type products.[11] Recently, there has been extensive research on the reactivity of propargyl esters, preferably acetates, because of their intriguing reactivity, especially regarding their high propensity to undergo 1,2- and 1,3-acyl migrations.[12] Thus, nonadiene **13b** was successfully isolated from dienyne **13** in 53% yield.



**13** **13b** (53%) (3)

Next, we investigated the use of vinyl-substituted dienynes as substrates (Table 2). We expected that the intermediate divinyl cyclopropanes would undergo facile rearrangement to **d**-type bicycles, rather than **b**-type nonadienes, because of the facile rearrangement of *cis*-divinylcyclopropane. This kind of reaction has been reported for the synthesis of tetrahydrocyclohepta[*c*]pyrans and tetrahydrocyclohepta[*c*]pyridines, which are constituents of some natural products such as Sepedonin, alstonisine, and plagiochiline.[13]

***Table 2:*** Tandem platinum(II)-catalyzed cycloisomerization of vinyl-substituted dienynes and subsequent Cope rearrangement.[a]



**14–19** **14d–19d**

| Entry | Substrate | X | R1 | R2 | R3 | Product (Yield [%][b]) |
|---|---|---|---|---|---|---|
| 1 | **14**[c] | O | H | H | H | **14d** (34)[d] |
| 2 | **15**[c] | O | Me | H | H | **15d** (36) |
| 3 | **16** | O | Ph | H | H | **16d** (55) |
| 4 | **17** | O | Ph | H | Me | **17d** (83) |
| 5 | **18** | O | Ph | Me | Me | **18d** (59) |
| 6 | **19** | NTs | Ph | H | H | **19d** (80) |

[a] 5 mol% $PtCl_2$, toluene, 60 °C. [b] Yield of isolated product. [c] 80 °C. [d] [4+2] cycloaddition product **14c** was isolated in 41% yield.

When oxygen-tethered dienyne **14** was heated in the presence of a $PtCl_2$ catalyst in toluene at 80 °C for 48 hours (Table 2, entry 1), the expected product (**14d**) was isolated along with a [4+2] cycloaddition product (**14c**) in 34% and 41% yields, respectively. When two methyl groups were introduced onto the vinyl terminus, no [4+2] cycloaddition product was observed and there was no improvement in the yield of **15d** (36%; Table 2, entry 2). When the vinyl group was furnished with two phenyl groups (Table 2, entry 3), a higher yield was observed in a shorter reaction time (3 h; 55% yield). When methyl groups were introduced at the diene terminus (Table 2, entries 4 and 5), the corresponding tetrahydrocyclohepta[*c*]pyrans **17d** and **18d** were obtained in good yields (83% and 59%, respectively). The structure of **17d** was confirmed by X-ray diffraction analysis (See the Supporting Information).[10] Compound **19d** was isolated in 80% yield from the *N*-tethered dienyne (Table 2, entry 6).

In conclusion, we have demonstrated the usefulness of a tandem $PtCl_2$-catalyzed cycloisomerization and Cope rearrangement in the synthesis of bicyclo[3.2.2]nonadienes, and 1,6,7,9a-tetrahydro-cyclohepta[*c*]pyrans and -pyridines. Recently, transition-metal-catalyzed cyclopropanation has been widely developed. Thus, the methodology reported in this manuscript could become a highly versatile tool for obtaining cycloaddition products that cannot easily be attained by other methods. Further research into the synthetic utility of these reactions is in progress.

## Experimental Section

General procedure: $PtCl_2$ and toluene (2 mL) were added to a Schlenk flask equipped with a stirring bar and capped with a rubber septum. The substrate (0.3 mmol) and toluene (4 mL) were then added to the flask. The resulting mixture was stirred until the substrate was completely consumed (reaction monitored by TLC). The product was purified by flash chromatography on a silica gel column by eluting with *n*-hexane/ethyl acetate.

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**Keywords:** alkynes · cyclization · dienes · isomerization · platinum

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[10] The synthetic procedures and spectroscopic data are provided in the Supporting Information. CCDC 733910 (**11b**) and CCDC 748426 (**17d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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