Hydroxy- and Alkoxy Cyclizations of Enynes Catalyzed by Platinum(II) Chloride

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Abstract: The cyclization of 1-en-6ynes catalyzed by PtCl₂ in the presence of water or alcohols affords five or six-membered ring carbocycles containing hydroxy or alkoxy functional groups in high yields. The alkoxy cyclizations can also be performed with AuCl₃ as catalyst. The reaction is stereospecific, atom-economical, and takes place in environmentally friendly solvents.

Key words: enynes, platinum, gold, cyclizations, carbenes

Introduction

Cyclization of α,ω-enynes catalyzed by transition metal complexes leads to different cyclization products depending on the catalyst and the reaction conditions.¹⁻² Electrophilic transition metal salts or complexes MX₃ coordinate alkynes and activate them towards nucleophilic attack. Thus, we found that alkynes react intramolecularly with allylsilanes and allylstannanes to give cyclic dienes,⁶ PtCl₂ is the best catalyst for this transformation, although salts or complexes of Pd(II), Ru(II), Cu(I), Ag(I), and Au(III) are also suitable catalysts.

Simple alkenes and enol ethers also act as nucleophiles towards alkynes and react in the presence of PtCl₂ as catalyst to give hydroxy- and alkoxy cyclization products, in which a molecule of water or an alcohol is incorporated in the cyclic product (Scheme 2).⁷

Computational studies indicate that the enynes react with PtCl₂ or AuCl₃ to give two types of cyclopropyl Pt- or Au-carbenes as the key intermediates. The cyclopropyl metal carbenes formed in the 5-exo-dig pathway are then attacked by water or ROH with cyclopropyl cleavage at carbons a or b to give five- I or six-membered rings II (Scheme 3). On the other hand, migration of the metal...
fragment towards C-2 of the alkyne (6-endo-dig pathway) leads to derivatives of type III.\(^8\) The reaction of alkynes with furans catalyzed by PtCl\(_2\) also involves cyclopropyl platinum carbenes as intermediates.\(^9\)

**Scope and Limitations**

The hydroxy- and alkoxycyclizations of enynes occur under mild conditions with 5 mol\% of PtCl\(_2\) and the nucleophile as solvent (alcohol) or co-solvent (water). Other Pt(II) complexes, such as [Pt(MeCN)\(_2\)Cl\(_2\)] or [Pt(MeCN)\(_4\)](BF\(_4\))\(_2\) can also be used as the catalysts (Schemes 1 and 4). A variety of functional groups are tolerated on the enyne. Although most transformations are remarkably clean, Alder ene-type reaction may take place as a secondary process in some cases.\(^7\) Thus, for example, malonate derivative 3 gave ene-type diene 7, in addition to the methoxycyclization derivative 11 (Scheme 4). Diene 7 does not arise by elimination of methanol from 11. Furthermore, no addition of methanol was observed when diene 7 was allowed to react with methanol and PtCl\(_2\).

It is noteworthy that in most cases the direct addition of R’OH or water to the alkyne to give enol ethers or carboxyl compounds does not compete significantly with the cyclization reactions. However, addition of these nucleophiles to the alkyne is observed with the less reactive enynes. Thus, substrates with substituents at C-1 of the alkyne react sluggishly in the cyclization process. Likewise, no cyclization was observed with enynes bearing monosubstituted alkenes.

When the reactions catalyzed by PtCl\(_2\) are carried out in non-nucleophilic solvents like 1,4-dioxane or acetone, cycloisomerization by Alder ene-type transformation takes place exclusively to give dienes in good yields (Procedure 4, Scheme 1).\(^7\)

The hydroxy- and alkoxycyclization reaction is stereospecific as shown in the reactions of diastereomeric enynes 12 and 14 (Scheme 5), and proceeds by the formal trans-addition of the electrophile (η\(^3\)-alkyne-metal complex) and the nucleophile (R’OH) to the double bond in a Markovnikov manner. Similar stereoselectivity is observed in the reactions catalyzed by AuCl\(_3\). This is a very active catalyst for these cyclizations. However, due to its hygroscopicity, the reactions with this catalyst are less reproducible and, occasionally, simple acid-catalyzed transformations are observed.

Six-membered carbo- or heterocycles of type II (Scheme 3) can also be obtained with certain enynes (Scheme 6). Six-membered rings are favored when less electron-withdrawing groups are at the tether of the enyne or with enynes bearing alkenes substituted at C-2 such as 20. In this case, skeletal rearrangement (metathesis-type) product 22 was also observed. Dienes formed by skeletal
rearrangement²–⁴ are presumably derived from the same cyclopropyl metal carbene intermediate proposed in the alkoxy cyclization mechanism (Scheme 3).

**Procedures**

We report here general procedures for the PtCl₂ catalyzed alkoxy cyclization of enynes. In Procedure 1, we describe a representative example of hydroxycyclization reaction from readily available enyne 1. In the second example, Procedure 2, elaborates the addition of allyl alcohol to enyne 3 to give an allyl-protected homoallylic alcohol 4. In the third procedure (Procedure 3), the stereoselective methoxy cyclization of 5 to give 6 is detailed. The last example, Procedure 4, is a simple platinum-catalyzed enyne cycloisomerization process to give 1,4-diene 7 (Scheme 3).

The reaction can also be applied to enol ethers as nucleophiles to give acetals such as 24 (Scheme 7).³ Endo-digonal cyclization (products of type III, Scheme 3) was observed in the cyclization of 25, and similar substrates bearing enynes with substituted alkynes.

**Conclusion**

In summary, we have developed new methodology to obtain catalytically, under very mild conditions, carbo- or heterocycles with hydroxy or alkoxy functions at the side chain that can be further functionalized. This general cyclization of 1,6-enynes, easily prepared from commercial sources, is experimentally very simple, and occurs in environmentally friendly solvents. The reactions catalyzed by PtCl₂ in polar but non-nucleophilic solvents lead to ene-type cycloisomerized dienes.

PtCl₂ was used as received and AuCl₃ was dried at 50 °C under vacuum and stored under argon. [Pt(MeCN)₂Cl₂](BF₄)₂ was prepared according to the known procedure.⁶ All reactions were carried out under Ar.

[Pt(MeCN)₂Cl₂]³

This complex was prepared by the procedure described for the synthesis of [Pt(PhCN)₂Cl₂].¹¹

A solution of PtCl₂ (200 mg, 0.75 mmol) in anhyd MeCN (10 mL) was refluxed for 12 h. The reaction was cooled to r.t. to give a pale yellow solid. The solid was filtered off and washed with hexane to give the pure complex (230 mg, 88%).

4,4-Bis(phenylsulfonyl)-7-methyloct-6-en-1-yn (1)

(a) To a suspension of NaH (60% in mineral oil, 240 mg, 10.00 mmol) in DMF (10 mL) at 0 °C was added a solution of bisphenylsulfonyl methane (2.60 g, 10.00 mmol) in DMF (30 mL), followed by prenyl bromide (1.20 mL, 10.00 mmol). The mixture was stirred for 12 h at 23 °C. After quenching with H₂O, extractive work-up (Et₂O), and chromatography (4:1 hexane–EtOAc), 5,5-bis(phenylsulfonyl)-2-methyl-2-pentene was obtained as a white solid (2.90 g, 80%); mp 116–118 °C (Lit.¹² mp 118 °C).

(b) A solution of 5,5-bis(phenylsulfonyl)-2-methylpent-2-ene (1.24 g, 3.41 mmol) in DMF (10 mL) was added to a suspension of NaH (60% in mineral oil, 137 mg, 3.41 mmol) in DMF (20 mL) at 0 °C,
followed by the addition of propargyl bromide (80% in toluene, 0.38 mL, 3.41 mmol). The mixture was stirred 13 h at 23 °C. After quenching with H2O, extractive work-up (Et2O), and chromatography (4:1 hexane–EtOAc), J was obtained as a white solid (1.13 g, 82%); mp 73–75°C.

1H NMR (300 MHz, CDCl3): δ = 8.14–8.11 (m, 4 H), 7.74–7.71 (m, 2 H), 7.60–7.55 (m, 4 H), 5.40–5.37 (m, 1 H), 3.17 (d, J = 2.8 Hz, 2 H), 3.04 (d, J = 5.7 Hz, 2 H), 2.10 (t, J = 2.80 Hz, 1 H), 1.76 (s, 3 H), 1.57 (d, J = 5.7 Hz, 3 H).

13C NMR (75 MHz, CDCl3): DEPT: δ = 137.01 (C), 136.45 (C), 134.36 (C), 134.67 (CH), 134.53 (CH), 131.05 (CH), 128.70 (CH), 115.58 (CH2), 91.95 (C), 72.59 (C), 53.54 (CH), 40.57 (CH2), 33.49 (CH3), 18.24 (CH2).


**Dimethyl 2-(Cyclohex-2-en-1-yl)-2-(prop-2-ynyl)malonate (5)**

To a suspension of NaH (60% in mineral oil, 250 mg, 6.25 mmol) in DMSO (25 mL) at 0 °C was added dimethyl propargyl malonate (0.89 mL, 6.25 mmol). After 5 min, 3-bromocyclohexene (0.72 mL, 6.25 mmol) was added and the resulting solution was stirred for 14 h at 23 °C. After extractive work-up (Et2O) and chromatography (9:1 hexane–EtOAc), 5 was obtained as a colorless oil (1.49 g, 95%).

1H NMR (300 MHz, CDCl3): δ = 5.72 (m, 2 H), 3.76 (s, 3 H), 3.73 (s, 3 H), 1.31 (m, 1 H), 2.89 (dd, J = 16.9, 2.6 Hz, 1 H), 2.82 (dd, J = 16.9, 2.6 Hz, 1 H), 2.01 (t, J = 2.6 Hz, 1 H), 1.95 (m, 1 H), 1.82 (m, 2 H), 1.58 (m, 1 H), 1.38 (m, 1 H).

13C NMR (75 MHz, CDCl3): δ = 170.08, 170.06, 129.24, 127.32, 79.54, 60.42, 52.52, 52.35, 39.04, 24.87, 23.62, 22.51, 22.28.


**Dimethyl (1R*,2R*)-2-Methoxy-9-methylenebicyclo[4.3.0]nonane-7,7-dicarboxylate (6)**

To a 25 mL round bottom flask, equipped with a magnetic stirring bar, and a reflux condenser was added 5 (248 mg, 0.99 mmol) and PtCl2 (13 mg, 0.05 mmol, 5 mol%). MeOH (5 mL) was added and the mixture was refluxed for 17 h. The solvent was evaporated and the crude mixture was purified by flash chromatography (hexane–EtOAc, 9:1) to give 6 as a colorless oil (187 mg, 67%).

1H NMR (500 MHz, CDCl3): δ = 5.03 (dd, J = 5.0, 2.3 Hz, 1 H), 4.80 (dd, J = 5.1, 2.6 Hz, 1 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.63 (dd, J = 5.5, 2.8 Hz, 1 H), 3.38 (s, 3 H), 3.25 (dd, J = 18.4, 2.4 Hz, 1 H), 3.05 (br s, 1 H), 2.93 (dd, J = 18.5, 5.5 Hz, 1 H), 2.87 (dd, J = 18.4, 1.0 Hz, 1 H), 1.80–1.70 (m, 1 H), 1.58 (q, J = 13.4, 3.4 Hz, 1 H), 1.43 (m, 1 H), 1.42 (m, 1 H), 1.31 (dm, J = 18.1 Hz, 1 H), 0.93 (dd, J = 16.6, 13.0, 3.6 Hz, 1 H).

13C NMR (75 MHz, CDCl3): δ = 170.15, 170.12, 148.10, 147.64, 147.47, 119.88, 75.94, 60.82, 56.03, 52.69, 52.46, 46.04, 41.80, 37.73, 25.47, 23.82, 18.55.


**Dimethyl 3-(Isopropenyl)-4-methylenecyclopentane-1,1-dicarboxylate (7)**

To a 25 mL round bottom flask, equipped with a magnetic stirring bar, and a reflux condenser was added 3 (248 mg, 0.99 mmol) and PtCl2 (13 mg, 0.05 mmol, 5 mol%). MeOH (5 mL) was added and the mixture was refluxed for 17 h. The solvent was evaporated and the crude mixture was purified by flash chromatography (hexane–EtOAc, 9:1) to give the known 7a as a colorless oil (150 mg, 86%).

1H NMR (300 MHz, CDCl3): δ = 5.02 (q, J = 2.7 Hz, 1 H), 4.83 (s, 2 H), 4.80 (q, J = 2.7 Hz, 1 H), 3.74 (s, 6 H), 3.28 (tt, J = 7.5, 2.7 Hz, 1 H), 3.08 (td, J = 16.8, 1.1 Hz, 1 H), 2.91 (dd, J = 16.8, 2.7 Hz, 1 H), 2.53 (dd, J = 12.0, 7.5, 1.6 Hz, 1 H), 2.12 (dd, J = 12.0, 2.7 Hz, 1 H), 1.65 (3 H).

13C NMR (75 MHz, CDCl3): δ = 172.07, 171.97, 149.19, 144.65, 113.44, 108.06, 58.70, 52.74, 51.06, 40.88, 38.61, 18.10.
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References