Enantioselective Synthesis of Cyclopentadienes by Gold(I)-Catalyzed Cyclization of 1,3-Dien-5-ynes

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Abstract. An asymmetric synthesis of elusive chiral cyclopentadienes has been developed by gold(I)-catalyzed alkoxycyclization of 1,3-dien-5-ynes. The application of these substrates in completely diastereoselective Diels-Alder cycladdition reactions, which can be carried out in one pot from achiral 1,3-dien-5-ynes, allow the preparation of highly functionalized products bearing five stereogenic centers with high enantiomeric excess.

Keywords: gold; dienynes; cycloisomerization; cyclopentadienes; Diels-Alder reaction

Cyclopentadienes are useful synthetic intermediates in organic as well as in organometallic chemistry. [1] For instance, they are reactive diene counterparts in the Diels-Alder cycloaddition, [2] one of the most useful synthetic reactions for the construction of the cyclohexane moiety, with up to four contiguous stereogenic centers being created in a single operation, usually through an endo-favouring transition state. In this context, enantiomerically pure cyclopentadienes [3] have been applied in the kinetic resolution of racemic dienophiles and as chiral templates. [4] However, these compounds are not readily available from the chiral pool and, moreover, the asymmetric synthesis of cyclopentadienes from achiral substrates is almost unknown. [5]

On the other hand, gold-catalyzed enyne cycloisomerization reactions have been shown as a versatile strategy for the construction of a wide variety of cyclic moieties. [6] In this area, 1,5-enynes with a 1,1-disubstituted alkene moiety are known to undergo 5-endo alkoxycyclization leading to functionalized cyclopentenes (Scheme 1, Eq. 1). [7] Related gold(I)- or platinum(II)-catalyzed cycloisomerization of vinyl allenes (1,2,4-trienes) lead to substituted cyclopentadienes through a metalla-Nazarov 4π electrolyclicization of pentadienyl cationic complexes (Scheme 1, Eq. 2). [8] Very recently, highly substituted cyclopentadienes have been obtained from ynamides and propargylic carboxylates. [9] However, the asymmetric synthesis of these derivatives has not been developed.

Continuing with our interest in gold-catalyzed transformations, [10] we have recently reported the cycloisomerization of 1,3-dien-5-ynes 1 via tandem 6-endo cyclization–selective migration providing a regiospecific method for the synthesis of highly substituted benzene derivatives 2 [11] In this context, and considering our previous work in the gold-catalyzed cyclization of α-(alkynyl)styrenes that gives rise to indene derivatives, [12] we envisaged that these 1,3-dien-5-ynes might be valuable precursors of substituted cyclopentadienes if a gold-catalyzed 5-endo cyclization was feasible (Scheme 1).

Whereas we and others have reported the benzannulation of 1,3-dien-5-ynes under gold- [11,13] or ruthenium-catalysis, [14] we surmised that cyclopentadiene derivatives such as 3 could be obtained instead of benzenes 2 if we were able to prevent the alkyl migration in the gold carbenoid intermediate initially generated from 1,1-disubstituted 1,3-dien-5-ynes. To this purpose the presence of an external nucleophile like methanol could be definitive for trapping the cationic gold intermediate (Scheme 1). Herein we report the application of this hypothesis to the development of an enantioselective synthesis of cyclopentadienes bearing a stereogenic center at C5 and, in addition, we demonstrate the usefulness of these functionalized dienes in the diastereo- and enantioselective preparation of complex cycloadducts by Diels-Alder reactions.
For the initial experiments we selected model substrate 1a, which was treated at room temperature with different gold(I) catalysts in a ca. 2:1 CH₂Cl₂/MeOH mixture as solvent (Scheme 2). Gratifyingly, we found that the presence of MeOH seems to suppress the formation of benzene derivative 2a, as cyclopentadiene derivatives 3a and 4a were mainly formed in just 15 min of reaction when 1a was treated with Ph₃PAuNTf₂. Changing to a catalyst with an electron-donating ligand, we found that the use of an N-heterocyclic carbene (IPr) ligated gold(I) complex clearly favoured the formation of 3a over triene 4a. Pleasantly, the bulkier and electron rich catalyst XphosAuNTf₂ completely favoured the addition of MeOH preventing both the elimination reaction and the cycloaromatization, allowing the isolation of 3a in 87% yield (Scheme 2). We also checked that a decrease of the amount of MeOH in the reaction mixture led to an increase of the elimination product 4a.

Scheme 2. Initial experiments and proof of concept.
the corresponding starting diyne 1. [c] 40% of 4a was also isolated. [d] 3-Oxocyclohex-1-en-1-yloxy. [e] Carried out in MeOH. 3-Th = 3-thienyl.

A catalytic cycle[23] that accounts for the formation of cyclopentadienes 3 and 5-8 is shown in Scheme 3. Coordination of the gold complex to the triple bond of starting diyne 1 would give an intermediate 9, which would undergo intramolecular attack of the alkene moiety leading to cationic intermediate 10. This could be represented as the contribution of several resonance structures (10', 10'',...), delocalizing the positive charge along different positions of the molecule. In the presence of an external nucleophile such as methanol, direct trapping of carbocation 10'' or nucleophilic attack on 10 with subsequent ring opening, would lead to vinyl gold intermediate 11.[24] Further protodeauration affords the corresponding cyclopentadiene 3, 5-8 regenerating the catalytic gold species. It is interesting that whereas in the absence of methanol a Wagner–Meerwein rearrangement exclusively takes place in 10' leading to benzene derivatives 2,[11] this pathway is mostly suppressed in the presence of the alcohol. This change in product distribution shows how important alcohols are for controlling the selectivity of the reaction.

Once we had developed an efficient method for the synthesis of cyclopentadienes we turned to our main goal: the synthesis of elusive enantioenriched cyclopentadienes by controlling the absolute stereochemistry of C5. Based on our previously reported enantioselective synthesis of indenes,[12a] as well as related gold-catalyzed enantioselective reactions involving alkyne activation,[25] and after several experiments on the enantioselective cycloisomerization of 1a using dinuclear chiral gold(I) catalysts, we found that, among the commonly used chiral biphosphine ligands with biphenyl skeletons, (S)-DM-MeO-BIPHEP gave the best results for enantio and chemoselectivity.[26] The screening of silver salts was performed in DCM solution at room temperature revealing that AgSbF6 was the better co-catalyst and, as expected, by lowering the reaction temperature better ee were observed. Thus, under the optimized conditions developed cyclopentadiene 3a was obtained with a remarkable 92% ee in good yield and reasonable reaction time (Table 2, entry 1).

With these reaction conditions in hand, the substrate scope for this highly interesting enantioselective synthesis of 3 was examined. As depicted in Table 2 (entries 1–5), 5-methoxalkyl cyclopentadienes 3a-g, previously prepared in a racemic manner (see Table 1) were now obtained as optically active products with high enantiomeric excess for dienynes 1a-d, bearing a cycloalkyl moiety at R2, R3 positions and with moderate ee in the case of 1g with linear substituents at these positions.[27] In addition, other 5-alkoxalkyl-substituted cyclopentadienes 5a-8a were also prepared with high enantioselectivity (Table 2, entries 6–9). Although in some cases chemical yields for the cyclopentadienes were only moderate due to the concurrent generation of the corresponding trienes 4, whose formation resulted to be more competitive at low temperature, their separation was very easy by column chromatography. Thus, new highly functionalized cyclopentadienes bearing a stereogenic center at C5 could be prepared in an enantioselective way. The absolute configuration of the synthesized dienes was determined to be S,[28] and interestingly, it resulted to be the same that we had previously observed in the enantioselective synthesis of indenes from o-(alkynyl)styrenes using the same chiral gold catalyst (12a).

<table>
<thead>
<tr>
<th>Entry</th>
<th>1a Ph</th>
<th>1b 4-MeOC6H4</th>
<th>1c 4-BrC6H4</th>
<th>1d 3-Th</th>
<th>1g Ph</th>
<th>1a Ph</th>
<th>1a Ph</th>
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<td>4</td>
<td>3</td>
<td>3</td>
<td>9</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>R2</td>
<td>(CH2)3</td>
<td>(CH2)3</td>
<td>(CH2)3</td>
<td>(CH2)3</td>
<td>n-Pr</td>
<td>(CH2)3</td>
<td>(CH2)3</td>
<td>(CH2)3</td>
</tr>
<tr>
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<td>Me</td>
<td>n-Pr</td>
<td>Et</td>
<td>Allyl</td>
<td>i-Pr</td>
</tr>
<tr>
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</table>

[a] Yield of isolated product based on the corresponding starting diyne 1. [b] Determined by HPLC on a chiral stationary phase, see Supporting Information for details.

![Scheme 3. Proposed mechanism for the synthesis of cyclopentadienes.](image-url)

Table 2. Au(I)-catalyzed enantioselective synthesis of alkoxyl-functionalized cyclopentadienes 3, 5-8.
The reactivity of some of the synthesized cyclopentadienes 3 in Diels-Alder cycloadditions was also examined. So, model cyclopentadiene 3a was reacted with a variety of dienophiles 12 at room temperature allowing the isolation of cycloadducts 13aa-ag as single diastereoisomers (Scheme 4). Highly reactive dienophiles such as maleimides 12a-d, maleic anhydride 12e, or 4-phenylurazole 12f underwent efficient cycloaddition to give the corresponding adducts 13aa-af in high yields with only an endo isomer detected by $^1$H and $^1$C NMR analysis of the reaction mixture. The use of plane nonsymmetrical dienes like 3a also implies the issue of facial (syn–anti) selectivity.\[29\] Notably, in all the reactions performed, only the anti-endo cycloadduct was observed. Moreover, when using diethyl fumarate 12g as dienophile two anti adducts are possible bearing each of them an endo ester group at R$^1$ or R$^2$ positions, respectively. Remarkably, only one anti isomer (13ag), whose structure was confirmed by X-ray analysis,\[30\] was obtained locating the endo substituent at R$^1$ (Scheme 4).

$$\text{OMe} \quad \text{Ph} \quad \begin{array}{c} \text{CH}_2\text{Cl}_2 \text{RT} \end{array} \quad \text{OMe} \quad \text{Ph} \quad \begin{array}{c} \text{R}^1 \text{R}^2 \end{array}$$


We then performed the cycloisomerization/Diels-Alder sequence in one pot, starting from dienynes 1 and just adding different maleimides 12a-c when consumption of 1 was detected by TLC, without purification of the corresponding cyclopentadiene 3 or 6. This approach also produced the cycloadducts 13, when using methanol, or 14 when allyl alcohol replaced methanol, in usually good yields for the two steps (Table 3).\[31\] With this approach three C–C and one C–O bonds, as well as five stereogenic centers, have been created in a single operation with good overall yields and complete diastereoselectivity.\[32\]

<table>
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<tr>
<th>Ent</th>
<th>R$^1$</th>
<th>R$^2$</th>
<th>R$^3$</th>
<th>Yield [%]</th>
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<tr>
<td>1</td>
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<td>Me</td>
<td>74</td>
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<tr>
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<td>Me</td>
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<td>9</td>
<td>Ph</td>
<td>−(CH$_2$)$_3$−</td>
<td>Me</td>
<td>74</td>
</tr>
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</table>

\[a\] Yield of isolated products 13 and 14 based on the starting dienyne 1. A ca. 3–15% of the corresponding cycloadducts derived from loss of methanol were also formed, see Supporting Information for details.

An exciting advance in asymmetric Diels-Alder chemistry is the use of chiral dienes as stereodirecting elements to render cycloadducts with high enantiomeric and diastereomeric excesses. So, selected cycloadducts 13 and 14 previously obtained as racemic mixtures (see Scheme 4) were also enantioselectively prepared by using the combined catalytic system we had previously optimized, consisting of a gold complex with the (S)-DM-MeOBIPHEP ligand and AgSbF$_5$. In this case, the one-pot two-step approach was employed, i.e. addition of the corresponding dienophile 12 after cyclopentadiene formation and removal of the silver salt, in order to avoid further elimination of methanol in the alkoxy-functionalized cycloadduct. Using MeOH as solvent for the cycloaddition reaction allows easy isolation by simple filtration of the final products that are obtained in high combined yields over two steps (referred to starting dienynes 1) and with high enantioselectivity that could be further improved after simple recrystallization (Scheme 5). It is worthy to note that the Diels-Alder reactions proceeded with complete conservation of enantiomeric purity of the chiral diene and so, cycloadducts 13 and 14, which possess five contiguous stereocenters including two quaternary ones, have been created from achiral starting materials in a complete diastereoselective and highly enantioselective manner.
Scheme 5. Sequential enantioselective cycloisomerization/Diels–Alder reaction of dienynes 1.

In conclusion, we have developed an asymmetric gold-catalyzed synthesis of cyclopentadienes by alkoxy cyclization of 1,3-dien-5-yne. These substrates had previously been used as precursors of benzene derivatives and this work shows the utility of these easily available starting materials as precursors of (enantioenriched) cyclopentadienes. The synthesized dienes are useful partners for Diels–Alder cycloaddition reactions with selected dienophiles allowing the synthesis of functionalized cycloadducts with five stereogenic centers in a complete diastereomeric and highly enantioselective way.

Experimental Section

General Remarks

All reactions involving air sensitive compounds were carried out under a N₂ atmosphere (99.99%). All glassware was oven-dried (120 °C), evacuated and purged with nitrogen. All common reagents and solvents were obtained from commercial suppliers (VWR, Alfa and Aldrich) and used without any further purification. Solvents were dried by standard methods. Hexane and ethyl acetate were purchased as extra pure grade reagents and used as received. Gold and silver catalysts were purchased from Aldrich or Strem. Chiral gold (I) complexes were prepared according to the methods described in the literature. For the preparation of starting dienynes see the Supporting Information. TLC was performed on aluminum-backed plates coated with silica gel 60 with F254 indicator; the chromatograms were visualized under ultraviolet light and/or by staining with a Ce/Mo reagent and subsequent heating. Rp values are reported on silica gel. Flash column chromatography was carried out on silica gel 60, 230-240 mesh. NMR spectra were measured on Varian Mercury-Plus 300 MHz and Varian Inova-400 MHz spectrometers. High resolution mass spectra (HRMS) were recorded on a Micromass Autospec spectrometer using EI at 70eV. Melting points were measured on a Gallenkamp apparatus using open capillary tubes and are uncorrected. GC-MS and low resolution mass spectra (LRMS) measurements were recorded on an Agilent 6890N/5973 Network GC System, equipped with a HP-5MS column. Agilent HPLC chromatography equipped with V-UV Diode-Array detectors was used for the determination of the enantiomeric ratio; Chiralcel-OD-H and Chiralpack-AD-H were employed as chiral columns.

General procedure for the gold (I)-catalyzed synthesis of cyclopentadienes 3a-f and 5a-8a

A solution of the corresponding 1,3-dien-5-yne 1 (0.5 mmol) in dry CH₂Cl₂ (0.5 mL) was added to a solution of XPhosAuNTf₂ (5 mol%, 24 mg) and the appropriate nucleophile [(3 equiv, 1.5 mmol) or (3 equiv, 15 mmol) for 1,3-cyclohexanedione] in dry CH₂Cl₂ (0.5 mL). The reaction mixture was stirred at room temperature until complete disappearance of the diene derivative was observed by TLC (10–15 min). The mixture was diluted with hexane/EtOAc (9:1), and filtered through celite. Then, the solvent was removed under reduced pressure and the remaining residue was purified by flash chromatography on silica gel using mixtures of hexane/EtOAc as eluents. The corresponding cyclopentadienes 3a-f or 5a-8a were isolated in the yields reported in Table 1. Characterization data and NMR spectra are presented in the Supporting Information.

General procedure for the gold (I)-catalyzed enantioselective synthesis of cyclopentadienes 3a-d and 5a-8a

Ag₂SbF₆ (5 mol%, 5.1 mg) was added to a solution of (S)-DM-MeO-BIPHEP(AuCl)₅ (2.5 mol%, 8.7 mg) in dry CH₂Cl₂ (0.3 mL) and the resulting reaction mixture was stirred 10–15 min under N₂. The appropriate nucleophile [(30 equiv, 9 mmol) or (3 equiv, 0.9 mmol, 100 mg for 1,3-cyclohexanedione)] was added and the mixture was cooled to –30 °C, –25 °C or –15 °C (see Table 2). Then a solution of the corresponding 1,3-dien-5-yne 1 (0.3 mmol) in dry CH₂Cl₂ (0.3 mL) was added and the reaction mixture was stirred until complete disappearance of starting material, as monitored by TLC (16 h). The mixture was diluted with a 9:1 mixture of hexane/EtOAc, and filtered through a pad of celite. The solvent was removed under reduced pressure and the remaining residue was purified by flash chromatography on silica gel (except for 3g which was purified on neutral alumina) using mixtures of hexane/EtOAc as eluents. The corresponding enantioenriched cyclopentadienes 3a-d or 5a-8a were isolated in the yields and ee reported in Table 2. HPLC traces for the prepared compounds are presented in the Supporting Information.

Acknowledgements

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References


[16] No reaction was observed with other metal complexes such as PtCl₄ or AgSbF₆.


[18] Triene 4a, probably derived from a competitive elimination pathway, was obtained in variable amounts with different catalysts. See Supporting Information for details about optimization of the reaction conditions.

[19] The use of 1.5 equiv of MeOH gave rise to a ca. 10:1 mixture of 3a:4a.

[20] Water was also checked as nucleophile by using a 4:2:1 CH₂Cl₂/acetone/H₂O ternary mixture that gave only 30% of the expected alcohol.

[21] Carbon-centered nucleophiles such as allyltrimethylsilane, acetylacetone or electron-rich aromatic compounds, as well as acetic acid, do not participate in the reaction being benzene 2a the obtained product.

[22] An alkyl (n-Bu) substituent at R¹ position gave rise to a mixture of products including the corresponding benzene derivative 2. In pure MeOH as solvent decomposition was observed.


[26] (S)-DM-SEPHOS gave similar results. See Supporting Information for details.

[27] Reaction of 1g was carried out in neat MeOH to minimize the formation of 4g and 2g. Although the lower ee obtained could be due to the higher temperature needed as well as to a solvent effect (78% ee was obtained for 1a in MeOH), the substrate moiety could also play an important role.

[28] Determined by X-ray analysis of cycloadduct 13ad. The configuration of the remaining cyclopentadienes was assigned by analogy. Structural parameters for 13ad are freely available from The Cambridge Crystallographic Data Centre under CCDC 929962.


[30] CCDC 929963 (13ag) contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[31] Small amounts of the cycloadducts derived from loss of MeOH were also obtained probably due to the presence of the gold catalyst.

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