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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 cycloaddition 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.

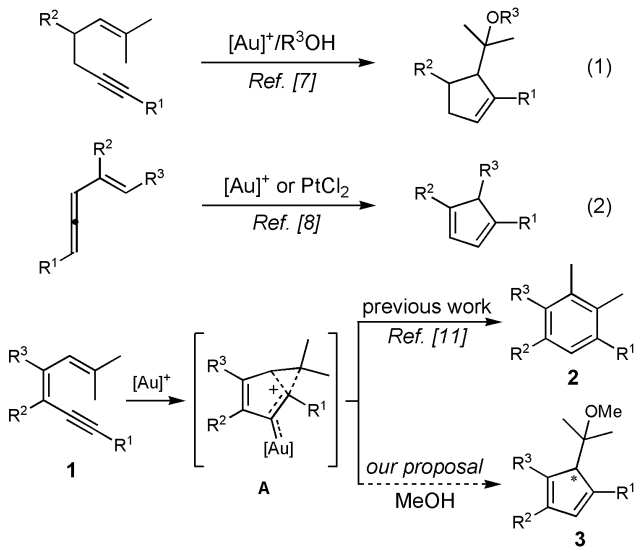
Keywords: gold; dienynes; cycloisomerization; cyclopentadienes; Diels-Alder reaction

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 electrocyclization 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.

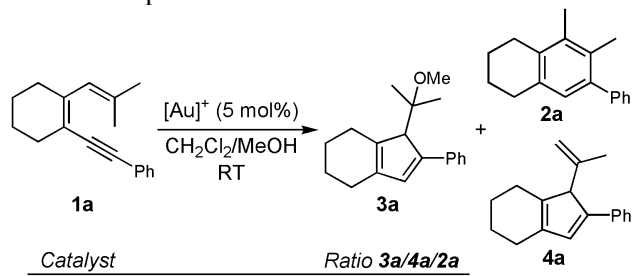
Continuing with our interest in gold-catalyzed transformations,[10] we have recently reported the cycloisomerization of 1,3-dien-5-ynes **1** via tandem 6-*endo* cyclization–selective migration providing a regiospecific method for the synthesis of highly substituted benzene derivatives **2**.[11] In this context, and considering our previous work in the gold-catalyzed cyclization of *o*-(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 enatioselective preparation of complex cycloadducts by Diels-Alder reactions.



Scheme 1. Previous related work and proposal for 5- vs. 6-*endo* cyclization of 1,1-disubstituted-1,3-hexadien-5-ynes **1**.

For the initial experiments we selected model substrate **1a**,[15] which was treated at room temperature with different gold(I) catalysts[16] in a ca. 2:1 CH_2Cl_2/MeOH mixture as solvent (Scheme 2). Gratifyingly, we found that the presence of MeOH seems to supress 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 $Ph_3PAuNTf_2$.[17] 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**.[18] Pleasantly, the bulkier and electron rich catalyst $XphosAuNTf_2$ 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**.[19]

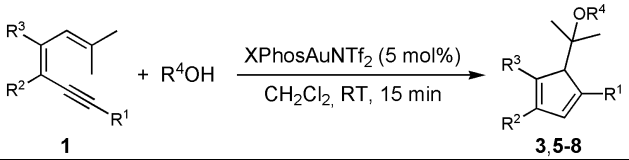


Catalyst	*Ratio **3a/4a/2a***
$Ph_3PAuNTf_2$	1 / 3.5 / 0
IPrAuCl/$AgSbF_6$	12 / 1 / 0
$XPhosAuNTf_2$	1 / 0 / 0 (87% isolated yield of **3a**)

Scheme 2. Initial experiments and proof of concept.

Having selected $XPhosAuNTf_2$ as the best catalyst, the extent of the reaction regarding the external nucleophile was studied (Table 1, entries 1–5). Dienyne **1a** reacted with different alcohols to furnish the alkoxy-functionalized cyclopentadienes **3a** and **5a-8a**, with variable yields depending on the nature of the alcohol.[20] Thus, unhindered primary alcohols (entries 1–3) afforded expected cyclopentadienes **3a**, **5a** and **6a** in high yields with minor amounts of triene **4a**, whereas the use of isopropanol gave rise to higher amounts of the elimination product **4a** allowing the isolation of **7a** in only moderate yield (entry 4). We also found that 1,3-cyclohexanedione could be employed as oxygen-centered nucleophile in this transformation (entry 5). Our results show that the role of the used alcohol as co-solvent seems to have a crucial influence on the reaction pathway, more than a mere external nucleophile.[21] Then, we prepared various 1,1-dimethyl-1,3-dien-5-ynes **1b-h** bearing different substituents at 3, 4, and 5-positions to assess the scope of this catalytic process using MeOH as nucleophile, as depicted in Table 1 (entries 6–12). This reaction is applicable to substrates **1b-d** with a cyclohexenyl moiety at R^2-R^3 and possesing different substituents at R^1, including electron-rich and electron-withdrawing aromatics as well as heteroaromatic ones (entries 6–8).[22] In addition, regarding the substitution at the central double bond (R^2, R^3), the reaction tolerates cyclic aliphatic groups, including functionalized ones (entries 6–9), as well as aromatic substituents (entry 10). However, when using dienyne **1g**, bearing linear subtituents at R^2 and R^3 positions, under standard conditions we obtained a mixture of **3g**, the corresponding triene **4g**, and benzene derivative **2g**. After some optimization we found that the desired cyclopentadiene **3g-h** could be prepared in high yield by performing the reaction in pure MeOH as solvent (entries 11–12).

Table 1. Au(I)-catalyzed alkoxycyclization of dienynes **1**. Synthesis of cyclopentadienes **3**, **5-8**.[a]

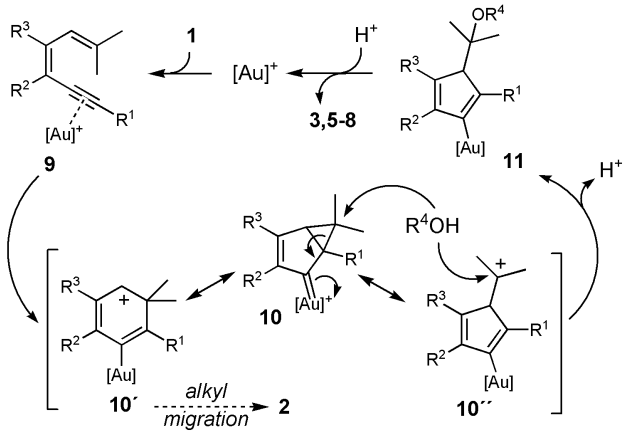


Entry	**1**	R^1	R^2	R^3	R^4	Product	Yield [%][b]
1	**1a**	Ph	$-(CH_2)_4-$		Me	**3a**	87
2	**1a**	Ph	$-(CH_2)_4-$		Et	**5a**	81
3	**1a**	Ph	$-(CH_2)_4-$		Allyl	**6a**	78
4	**1a**	Ph	$-(CH_2)_4-$		*i*-Pr	**7a**	35[c]
5	**1a**	Ph	$-(CH_2)_4-$		[d]	**8a**	66
6	**1b**	4-$MeOC_6H_4$	$-(CH_2)_4-$		Me	**3b**	74
7	**1c**	4-BrC_6H_4	$-(CH_2)_4-$		Me	**3c**	66
8	**1d**	3-Th	$-(CH_2)_4-$		Me	**3d**	86
9	**1e**	Ph	$-(CH_2)_2OCH_2-$		Me	**3e**	81
10	**1f**	Ph	$-(o\text{-}C_6H_4)(CH_2)_2-$		Me	**3f**	67
11[e]	**1g**	Ph	*n*-Pr	*n*-Pr	Me	**3g**	76
12[e]	**1h**	3-Th	*n*-Pr	*n*-Pr	Me	**3h**	58

[a] Reactions stirred at room temperature for 15 min using 30 equiv of the corresponding alcohol (3 equiv for 1,3-cyclohexanedione). [b] Yield of isolated product based on

the corresponding starting dienyne **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 dienyne **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.

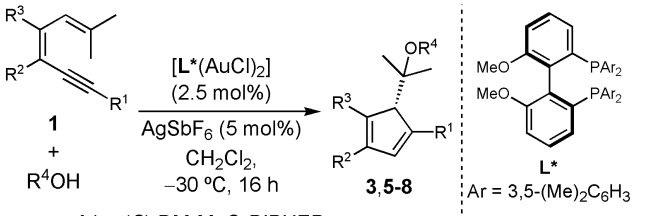


Scheme 3. Proposed mechanism for the synthesis of cyclopentadienes.

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 $AgSbF_6$ 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-methoxyalkyl 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 R^2, R^3 positions and with moderate *ee* in the case of **1g** with linear substituents at these positions.[27] In addition, other 5-alkoxyalkyl-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 C-5 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 complex.[12a]

Table 2. Au(I)-catalyzed enantioselective synthesis of alkoxy-functionalized cyclopentadienes **3**, **5-8**.

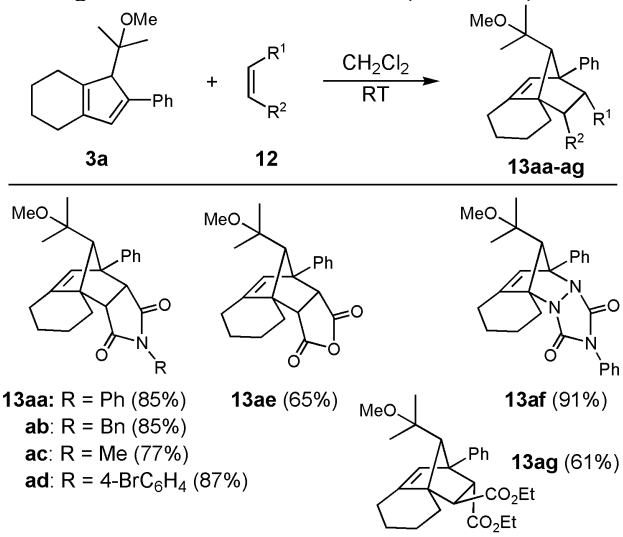


Entry	**1**	R^1	R^2	R^3	R^4	Product	Yield [%][a]	*ee* [%][b]
1	**1a**	Ph	$-(CH_2)_4-$		Me	**3a**	74	92
2[c]	**1b**	4-$MeOC_6H_4$	$-(CH_2)_4-$		Me	**3b**	40[d]	92
3[c]	**1c**	4-BrC_6H_4	$-(CH_2)_4-$		Me	**3c**	45	84
4	**1d**	3-Th	$-(CH_2)_4-$		Me	**3d**	71	88
5[e]	**1g**	Ph	*n*-Pr	*n*-Pr	Me	**3g**	56	40[f]
6	**1a**	Ph	$-(CH_2)_4-$		Et	**5a**	68	93
7	**1a**	Ph	$-(CH_2)_4-$		Allyl	**6a**	80	89
8	**1a**	Ph	$-(CH_2)_4-$		*i*-Pr	**7a**	31	84
9[c]	**1a**	Ph	$-(CH_2)_4-$		[g]	**8a**	48	93

[a] Yield of isolated product based on the corresponding starting dienyne **1**. Variable amounts of the corresponding triene **4** were obtained, see Supporting Information for details. [b] Determined by HPLC on a chiral stationary phase, see Supporting Information for details. [c] Carried

out at –25 °C. [d] An unidentified product was also obtained along with **3b**. [e] Carried out in MeOH at –15 °C. [f] The *ee* was determined from cycloadduct **13ga**. [g] 3-Oxocyclohex-1-en-1-yloxy.

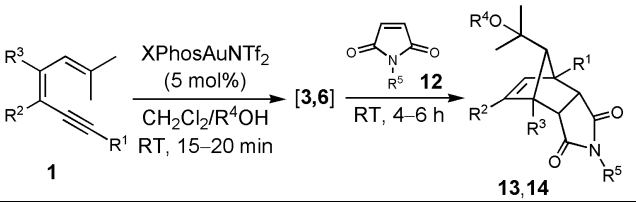
The reactivity of some of the synthesized cyclopentadienes **3** in Diels-Alder cycloadditions was also examined. So, model cyclopentadiene **3a** was reacted with a variety of dienophiles **12** at room temperature allowing the isolation of cycloadducts **13aa-ag** as single diastereoisomers (Scheme 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 ^{13}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).



Scheme 4. Diels-Alder reactions of cyclopentadiene **3a**.

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]

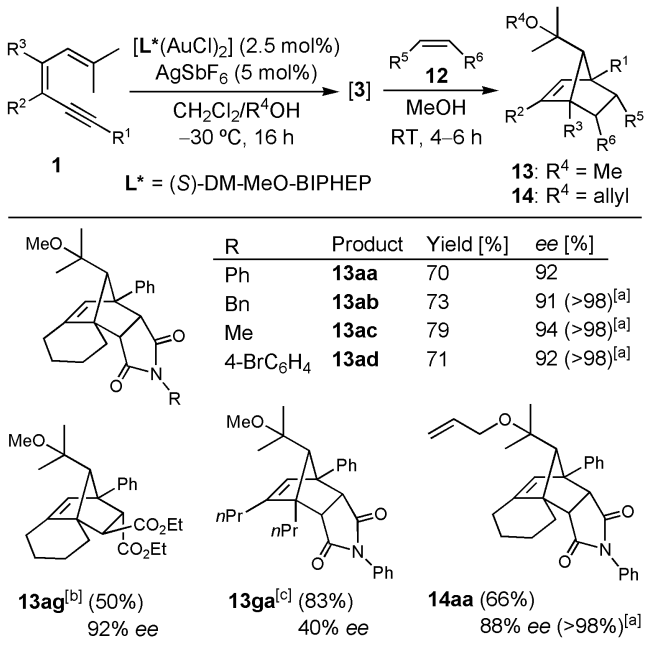
Table 3. One-pot two-steps approach to the preparation of cycloadducts **13** and **14** from dienynes **1**.



Ent	**1**	R^1	R^2	R^3	R^4	R^5	Product	Yield [%][a]
1	**1a**	Ph	–$(CH_2)_4$–		Me	Ph	**13aa**	69
2	**1a**	Ph	–$(CH_2)_4$–		Me	Bn	**13ab**	71
3	**1a**	Ph	–$(CH_2)_4$–		Me	Me	**13ac**	73
4	**1b**	4-$MeOC_6H_4$	–$(CH_2)_4$–		Me	Ph	**13ba**	63
5	**1c**	4-BrC_6H_4	–$(CH_2)_4$–		Me	Ph	**13ca**	57
6	**1d**	3-Th	–$(CH_2)_4$–		Me	Ph	**13da**	60
7	**1a**	Ph	–$(CH_2)_4$–		Allyl	Ph	**14aa**	53
8	**1f**	Ph	–(*o*-C_6H_4)$(CH_2)_2$–		Me	Ph	**13fa**	59
9	**1g**	Ph	*n*-Pr	*n*-Pr	Me	Ph	**13ga**	74

[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-MeO-BIPHEP ligand and $AgSbF_6$. 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.



[a] *ee* value after recrystallization. [b] The Diels-Alder reaction was conducted in CH_2Cl_2 for 48 h. [c] Carried out at –15 °C.

Scheme 5. Sequential enantioselective cycloisomerization/Diels-Alder reaction of dienynes **1**.

In conclusion, we have developed an asymmetric gold-catalyzed synthesis of cyclopentadienes by alkoxycyclization of 1,3-dien-5-ynes. 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 diastereo- and highly enantioselective way.

Experimental Section

General Remarks

All reactions involving air sensitive compounds were carried out under a N_2 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.[25a] 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. R_f 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 apparatous 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 chromatograph 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 CH_2Cl_2 (0.5 mL) was added to a solution of $XPhosAuNTf_2$ (5 mol%, 24 mg) and the appropriate nucleophile [(30 equiv, 15 mmol) or (3 equiv, 1.5 mmol, 168 mg for 1,3-cyclohexanedione)] in dry CH_2Cl_2 (0.5 mL). The reaction mixture was stirred at room temperature until complete disappearance of the dienyne 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

$AgSbF_6$ (5 mol%, 5.1 mg) was added to a solution of (*S*)-DM-MeO-BIPHEP$(AuCl)_2$ (2.5 mol%, 8.7 mg), in dry CH_2Cl_2 (0.3 mL) and the resulting reaction mixture was stirred 10–15 min under N_2. 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 ºC, –25 ºC or –15 ºC (see Table 2). Then a solution of the corresponding 1,3-dien-5-yne **1** (0.3 mmol) in dry CH_2Cl_2 (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.

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[20] Water was also checked as nucleophile by using a 4:2:1 CH_2Cl_2/acetone/H_2O 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.

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