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Preparation of benzannulated spiroketals by gold(III) catalyzed spirocyclization of alkynyl diols

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Dedicated to Professor Jan Bergman on the occasion of his 80th birthday

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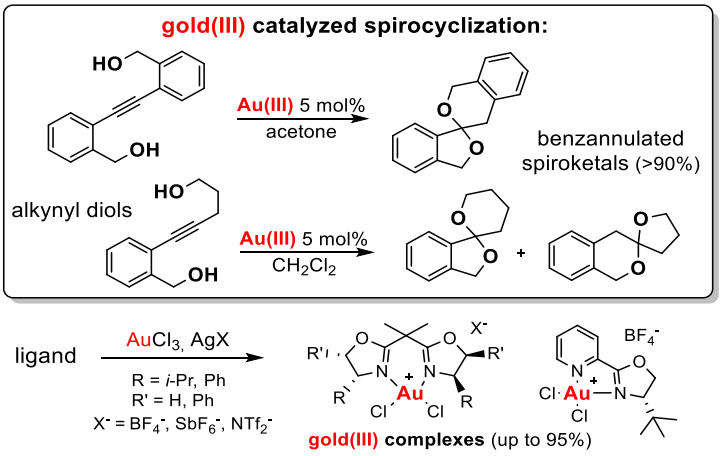
Abstract

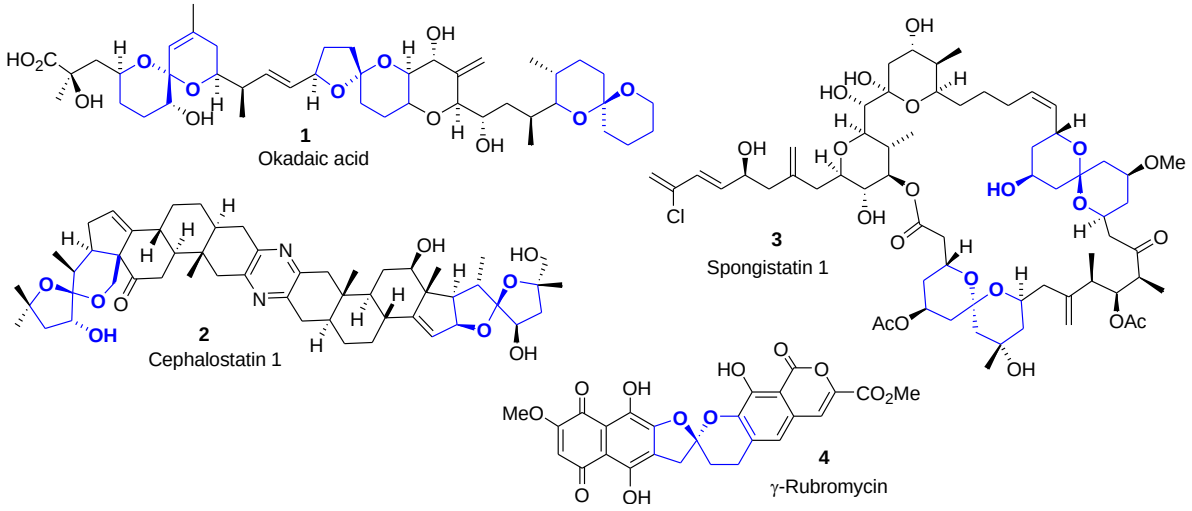
The first gold(III)-oxazoline catalysed intramolecular tandem dihydroalkoxylations of alkynyl diols to give benzannulated 5,6-spiroketal products is reported. The results showed that Au(III)-bisoxazoline (BOX) and Au(III)-pyridine-oxazoline complexes are highly efficient catalysts for such spirocyclizations. The mono- and dibenzannulated 5,6-spiroketals were obtained in high yields (> 90 %) by rapid conversion of symmetrical and nonsymmetrical alkynyl diols, respectively. The Au(III)-BOX-BF_4 catalyst generated minor spirocyclization enantioselectivity (up to 6 % ee). The choice of solvent was important for the outcome of the reactions.



Keywords: spirocyclization; alkynyl diols; gold(III) catalysis; gold(III)-BOX complexes

Introduction

Spiroketals are cyclic ketals in which two rings are joined via two ketal oxygens to a quaternary carbon, the spirocentre. The chiral spiroketal ring system is a structural motif found in a wide variety of densely functionalised natural products which exhibit a broad spectrum of biological activity. Examples of 5,5-, 5,6- and 6,6-spiroketals include okadaic acid (**1**)[1,2], cephalostatin 1 (**2**)[3,4] and spongistatin 1 (**3**)[3,5] (Scheme 1), which have all shown cytotoxic activity, as well as rutamycin which also displays antifungal behaviour.[6] The presence of the particular spiroketal fragment was correlated to increased inhibition of human telomerase by the rubromycin family of natural products. The specific chemistry of chiral benzannulated spiroketals has received much attention because they are common key substructures in bioactive natural products[7] such as γ-rubromycin (**4**), a 5,6-spiroketal comprised of an oxygenated naphthoquinone moiety linked with an isocoumarin fragment.



Scheme 1. Bioactive natural products containing spiroketal fragments.

The synthesis of spiroketals has received considerable attention. Most progress has been made on systems that include at least one six-membered ring. The synthesis of spiroketals has often been achieved by acid-catalysed condensation of either free or masked hydroxyfunctionalities on a ketone or other carbonyl surrogates.[6,8–10] However, this poses some challenges due to the reactive nature of the carbonyl group. Lately, a cycloisomerization approach by intramolecular dihydroalkoxylation of alkynyl diols catalysed by various transition metals such as Pd(II), Pt(II), Ir(I), Rh(I), Ru(II) and Au(I/III) has emerged as a more selective strategy.[11–14] This method offers specific advantages, as the alkyne acts as a masked carbonyl group, and the non-polar alkyne π-bonds being more compatible than ketones towards a number of common reaction conditions.[15]

Gold catalysis has been a rapidly emerging field within transition metal catalysis in the past decade. Gold has a high affinity towards carbon-carbon multiple bonds, especially alkynes, which may be activated towards nucleophilic attack. The combination of high functional group tolerance and usually mild reaction conditions, allow a great diversity of gold catalysed transformations, also including enantioselective reactions.[16] Due to these advantages, gold has been widely used for the synthesis of spiroketal natural products by intramolecular dihydroalkoxylation of alkynyl diols.[4,17–20] This transformation has been achieved by simple gold

salts such as AuCl[19–21] and $AuCl_3$[12], as well as Au(I) phosphine complexes[4,12,22], a Au(I) NAC complex[23] and Au(I/III) NHC complexes.[24]

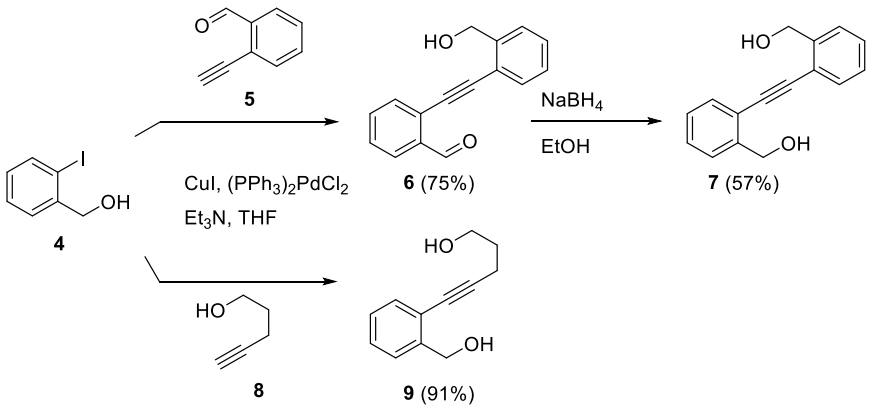
As most naturally occurring spiroketals are chiral molecules with a stereogenic spirocentre, the syntheses of chiral spiroketals has attracted attention, targeting at high yields and high diastereo- and enantioselectivities under mild conditions. It is essential to avoid epimerization of the sterogenic spirocentre, which may easily take place under mild acidic conditions. 5,6- and 6,6-Spiroketals generally equilibrate toward a particular diastereoisomer under acidic conditions, due to anomeric or substituent stabilization in the six-membered rings.[25] Despite the fact that several approaches have been developed for spiroketal synthesis, methods for direct catalytic enantioselective synthesis of chiral spiroketals by transition-metal catalysis or organocatalysis are still limited.[26–32] Highly enantioselective condensation reactions of unsaturated ketones to afford spiroketals (>99 % ee) have been performed with Ir(I) complexes of chiral phosphine–oxazoline ligands[29], while catalytic enantioselective spiroketalizations by single OH attack on cyclic enol substrates[27] are reported with both BINOL-derived chiral phosphoric acids (92 % ee)[26] and chiral BINOL-based imidodiphosphoric acid (>99 % ee).[32] Benzannulated spiroacetals are successfully formed by intramolecular tandem dihydroalkoxylation of alkynyl diols by binary systems of both gold(I) complexes with chiral Brønsted acids (up to 93 % ee)[30] and chiral gold(I)–phosphine complexes with chiral silver phosphate (74 % ee).[31]

In contrast to general broad studies based on gold(I) species, comprehensive studies of gold(III) are scarce. Thus, the limited experience of the chemistry of Au(III)-ligand species has inspired us to study the formation of new stable Au(III) complexes with a series of polydentate heterocyclic ligands. We have previously prepared and demonstrated the catalytic activity of Au(III) bisoxazoline (BOX) as well as Au(III) pyridyl/quinolinyl-oxazoline complexes in the cyclopropanation of propargyl acetates followed by *cis*-to-*trans* cyclopropyl isomerisation.[33,34] Furthermore, pyridyl-oxazoline (PYR-OX) Au(III) complexes are also catalytically active in the alkoxycyclisation reaction of 1,6-enynes.[35] Herein we report the first known study on spiroketalization based on Au(III)-BOX and -PYR-OX catalysed tandem dihydroalkoxylation of alkynyl diols to give benzannulated 5,6-spiroketal products. Regio- and stereoselectivity issues are included in the study.

Results and Discussion

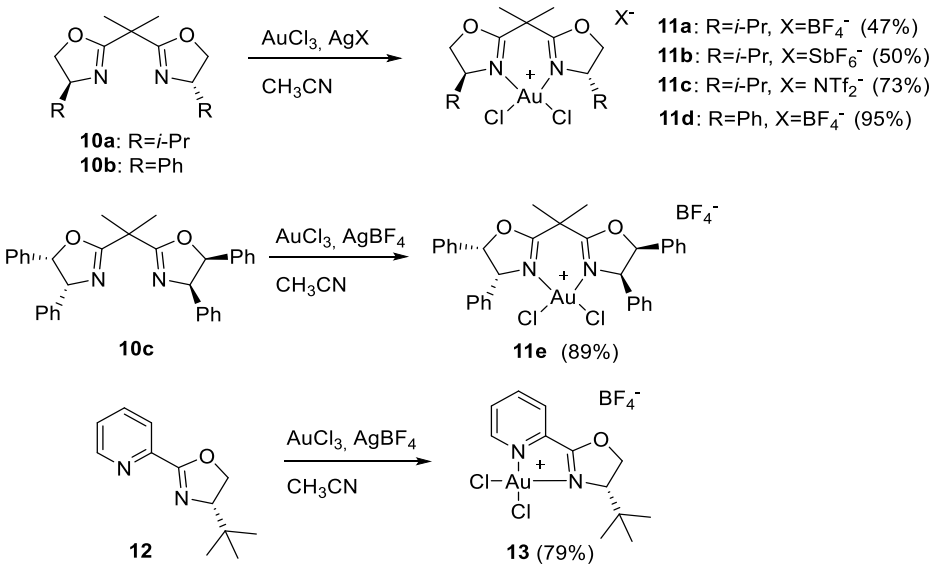
Preparation of aromatic alkynyl diols and chiral Au(III)-BOX complexes

The symmetrically substituted diarylalkynyl diol **7** was obtained by Sonogashira cross-coupling of (2-iodophenyl)methanol **4** with alkynaldehyde **5** via aldehyde **6** (75 %) and reduction (**7**, 57 %), while the non-symmetrical monoaromatic alkyne diol **9** (91 %) was readily obtained by cross-coupling of substrate **4** and alkynol **8** (Scheme 2).



Scheme 2. Synthesis of alkynyl diols **7** and **9** by Sonogashira cross-coupling.

Chiral *N,N*-Au(III)-BOX and -PYR-OX ligand complexes were prepared according to our previous method[33] (Scheme 3). The respective heterocyclic bidentate BOX ligands **10a**-**10c** and PYR-OX ligand **12** were dissolved in CH_3CN before addition of $AuCl_3$ and the appropriate silver salts. Crystallization yielded Au(III) BOX complexes **11a-e** (47-95 %) and PYR-OX complex **13** (79 %) as air- and moisture stable crystals.



Scheme 3. Preparation of Au(III)-BOX complexes **11a-e** and Au(III)-PYR-OX complex **13**.

Formation of benzannulated spiroketals by Au(III) catalysed dihydroalkoxylation of alkynyl diols

1. Symmetrical alkyne substrate. With both substrates (**7, 9**) and gold(III) catalysts **11a-e, 13** in hand, the reaction conditions for the dihydroalkoxylation reaction were screened. The symmetrical alkynyl diol **7** was treated with gold(III) complexes **11a-e** and **13** (Scheme 3) in various solvents at room temperature to give the expected dibenzannulated 5,6-spiroketal **14** (spiro[isobenzofuran-1,3'-isochromane, Table 1).[13]

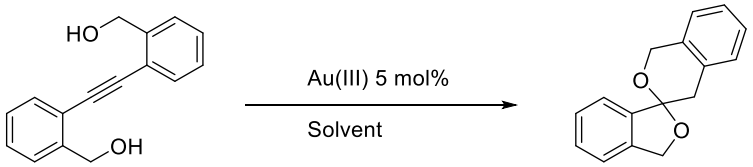
Initial solvent screening with catalyst Au(III)-BOX-BF_4 **11a** showed that the reaction of alkynyl diol **7** may take place in several solvents (CH_2Cl_2, CH_3CN, THF, toluene, CH_3NO_2, acetone) to give moderate to high yields of spiroketal product **14** (55-87 %, 1-24 h, entries 1-6). Most successful reaction by rapid conversion to spiroketal **14** in high yield was obtained in CH_2Cl_2 (84 %, 1h, entry 1). Other solvents gave slower reaction (3-24 h, entries 2-6).

Most reactions afforded racemic mixtures of spiroketal **14**. Minor enantioselectivity and high yields were only provided in acetone (5 % ee, 78 %, 5h, entry 6). Despite the faster reactions and higher yields obtained in CH_2Cl_2 and CH_3NO_2 (84-87 %, 1-3h, entries 1,5), acetone was chosen as the solvent in further experiments with the other complexes, in order to achieve possibly higher %ee values. However, nearly no enantioselectivity effect was seen with catalysts **11b-e** and **13** (0-3 % ee, entries 9-13).

Addition of a silver salt with a weakly coordinating anion is often necessary in gold catalysed reactions to abstract one or more gold bound chlorides, thus generating the catalytically active species.[36,37] The Au(III) BOX complexes have been shown to be highly active without silver salt anion exchange, presumably due to de-coordination of an oxazoline or pyridine moiety.[33] However, the addition of 10 mol% $AgBF_4$ accelerated the reaction with complex **11a** and gave increased yield, but no ee (86 %, 2h, entry 7). The formation of a black solution immediately after silver salt addition indicated decomposition of the gold catalyst and that the reaction, in this case, might be gold(0) catalysed. As gold catalysed dihydroalkoxylation of alkynyl diols with chiral phosphoric acid co-catalysts has been successful[30,38,39], a reaction with 10 mol% *S*-camphorsulfonic acid was performed. The addition of acid sped up the reaction up significantly and gave excellent yield of product **14**, but did not afford stereoselectivity (93 %, 1h, entry 8).

The effect of different Au(III) counter-anions was then explored, but catalysts **11b**,**c** with SbF_6^- and NTf_2^- anions, repectively, were less effective than Au(III)-BOX-BF_4 **11a** with regards to yields (42-58 %, 4-5h, 2-3 % ee, entries 9-10). However, both modified catalysts **11d,e**, with the 4-phenyl-BOX and the bulkier 4,5-diphenyl-BOX ligands, were more active (86 % and 70 %, 2h, entries 11, 12). The PYR-OX catalyst **13** turned out to be most active, giving almost immediate full conversion to product **14** (89 %, 30 min, 2 %ee, entry 13). However, a black precipitate was formed almost directly after addition of catalyst **13**, indicating partial decomposition to gold(0).

Table 1. Synthesis of 5,6-spiroketal **14** by gold(III) catalysed dihydroalkoxylation of alkynyl diol **7**[a]



7 **14**

Entry	Catalyst	Additive (mol%)	Solvent	Time	Yield[b]	% ee[c]
1	**11a**		CH_2Cl_2	1 h	84 %	1 %
2	**11a**		CH_3CN	3 h	76 %	0 %
3	**11a**		THF	3 h	55 %	3 %
4	**11a**		Toluene	24 h	63 %	0 %
5	**11a**		CH_3NO_2	3 h	87 %	1 %
6	**11a**		Acetone	5 h	78 %	5 %
7	**11a**	$AgBF_4$ (10 %)	Acetone	2 h	86 %	0 %
8	**11a**	*S*-Camphor-sulfonic acid (10 %)	Acetone	1 h	93 %	1 %
9	**11b**		Acetone	5 h	42 %	2 %

Table 1. Continued

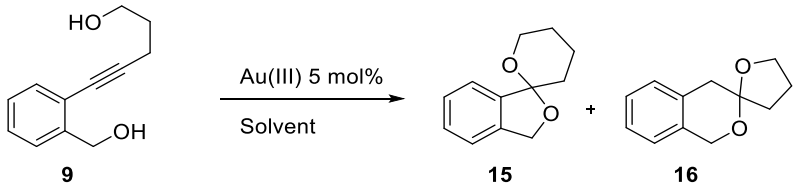
Entry	Catalyst	Additive (mol%)	Solvent	Time	Yield[b]	% ee[c]
10	**11c**		Acetone	4 h	58 %	3 %
11	**11d**		Acetone	2 h	86 %	1 %
12	**11e**		Acetone	2 h	70 %	0 %
13	**13**		Acetone	30 min	89 %	2 %

[a] All reactions were performed with 0.10 mmol substrate and 5 mol% gold(III) catalyst in 5 mL solvent at room temperature.
[b] Isolated yield.
[c] Determined by chiral HPLC.

2. Non-symmetrical alkyne substrate. Spiroketal synthesis from alkynyl diols by transition metal catalysed dihydroalkoxylations often introduces regiochemistry concerns. Non-symmetrical substituted alkyne substrates, such as diol **9** (Table 2) may possibly form a mixture of two 5,6-spiroketal regioisomers, due to the presence of two different alkyne carbons that both potentially could become the spiroketal central carbon.[13,23,24,31] To explore the catalytic potential of our gold(III) catalysts, we therefore included a regioselectivity study of the cycloisomerization of alkynyl diol **9**, which can possibly lead to two monobenzannulated 5,6-spiroketal regioisomers. Both the spiro[isobenzofuran-1,2'-pyran] **15** and the spiro[furan-2,3'-isochromane] **16** were formed (Table 2).

Moderate to high combined yields of spiroketal regioisomers **15** and **16** were obtained with all gold(III) complexes **11a,d,e** and **13** in the tested solvent (50-91 % in acetone, CH_2Cl_2 and CH_3CN, entries 1-8). It is apparent from the study that both the nature of the catalyst and the solvent affect the product ratio **15**:**16**. Nearly equimolar mixtures of products **15** and **16** were formed with BOX catalyst **11d,e** and PYR-OX catalyst **13** in acetone (entries 4-6), while all Au(III) catalysts **11a,d,e** and **13** favored the formation of isobenzofuran **15**. However, up to 80:20 ratio of **15**:**16** was seen with both catalyst **11a** and **13** in CH_2Cl_2 (entries 2, 7). These regioselectivity results are consistent with previous studies with gold catalysts[40,41], but opposite to what is reported by Rh and Ir catalysis[13,42] where isochromane **16** is preferentially formed. Minor enantioselectivity of isobenzofuran **15** (5-6 % ee, entries 3, 8) was observed with catalysts **11a** and **13** in acetonitrile.

Table 2. Synthesis of 5,6-spiroketal regioisomers **15** and **16** by gold(III) catalysed dihydroalkoxylation of alkynyl diol **9**[a]



9 **15** **16**

Entry	Catalyst	Solvent	Time	Yield[b]	Ratio **15**:**16**	% ee[c]
1	**11a**	Acetone	2h	85 %	74:26	5 % (**15**)
						2 % (**16**)
2	**11a**	CH_2Cl_2	20 min	87 %	80:20	0 % (**15**)
						3 % (**16**)
3	**11a**	CH_3CN	1h	67 %	60:40	6 % (**15**)
						3 % (**16**)
4	**11d**	Acetone	30 min	70 %	58:42	0 %
						(**15**,**16**)
5	**11e**	Acetone	30 min	90 %	55:45	0 %
						(**15**,**16**)
6	**13**	Acetone	15 min	66 %	50:50	3 % (**15**)
						1 % (**16**)
7	**13**	CH_2Cl_2	15 min	50 %	77:23	2 % (**15**)
						2 % (**16**)
8	**13**	CH_3CN	15 min	91 %	55:45	5 % (**15**)
						3 % (**16**)

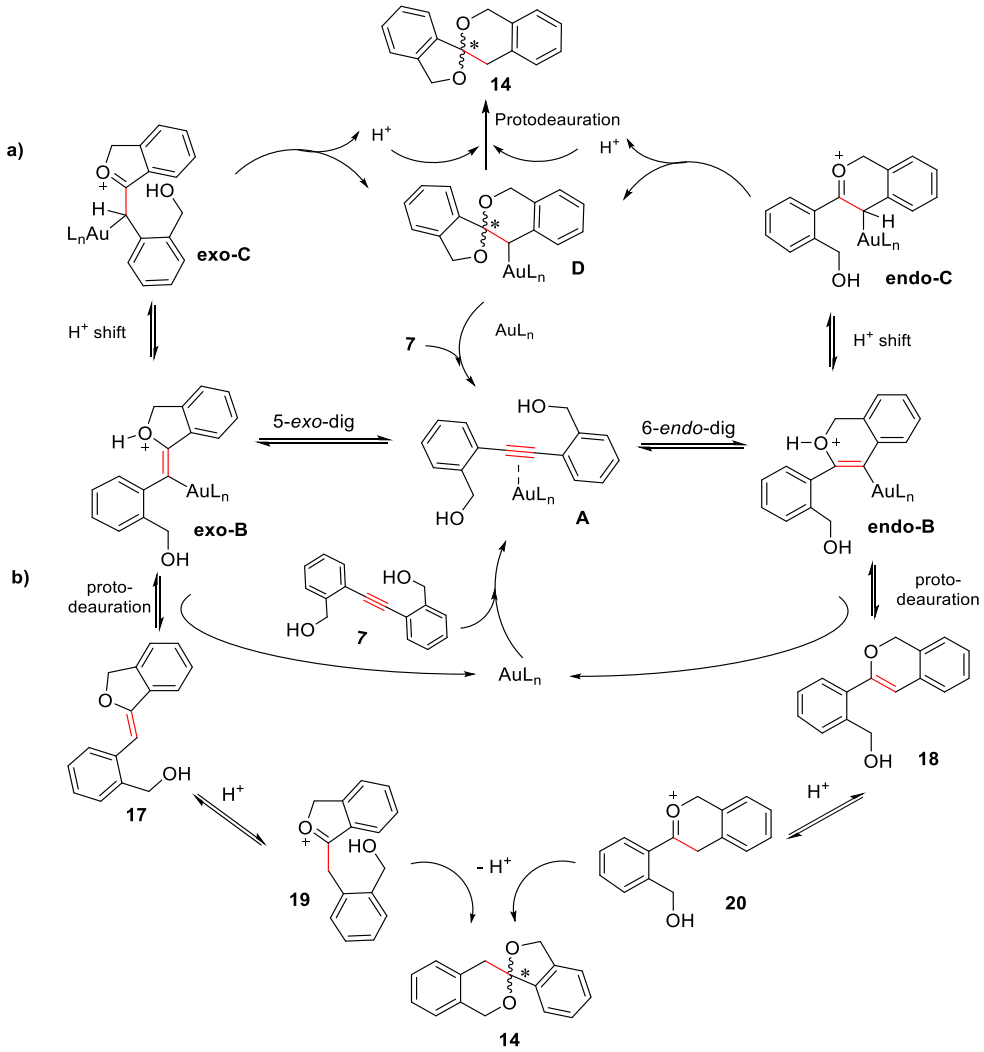
[a] All reactions were performed with 0.10 mmol substrate and 5 mol% gold(III) catalyst in 5 mL solvent at room temperature.
[b] Isolated combined yield of **15** and **16**.
[c] Determined by chiral HPLC.

3. Spirocentre enantioselectivity. Only a few asymmetric approaches are known for the preparation of chiral spiroketals.[26–32] One successful strategy has demonstrated that chiral phosphoric acids (CPAs) may serve as effective catalysts for enantioselective spiroketalizations.[43] Despite the chiral nature of the Au(III)-BOX and Au(III)-PYR-OX catalysts **11** and **13**, no enantioselectivity was obtained in our previous catalytic studies of alkoxycyclizations or in cyclopropanation reactions.[47,49] Other reports also indicate that this type of bidentate ligands does not give any enantioselectivity when a complex with a square planar geometry is involved, independently of the metal.[44–46]

On this background, our expectations to obtain asymmetric synthesis of benzannulated spiroketals using chiral Au(III)-oxazoline catalysts were limited. Therefore, the present observations of minor enantioselectivity (up to 6 %) generated with Au(III) catalysts **11a** and **13** is remarkable, being the first of our Au(III) complexes that provide detectable enantioselectivity.

Mechanism

The mechanism of the gold catalysed intramolecular tandem dihydroalkoxylation of alkynyl diol **7** to spiroketal **14** is postulated[31] to start by π-coordination of the gold catalyst to the alkyne (**7**) by forming Au(III) activated alkyne **A** (Scheme 4). The first cyclisation may proceed via either a *6-endo*-dig or a *5-exo*-dig process to give *endo*-**B** and *exo*-**B** monocyclic intermediates, respectively. Two alternative pathways a) and b) may describe the final spiroketalization. Proton shift would yield the prochiral cyclic oxocarbenium Au(III) species *endo*-**C** and *exo*-**C**, which may readily undergo spirocyclization by the second nucleophilic attack of the pendant alcohol group to form gold-coordinated spiroketal **D** from both intermediates (Scheme 4a). Formation of the stereogenic spirocentre takes place in this step and potential enantioselective ring closure may be induced by the chiral Au(III) coordinated unit. Protodeauration yields the target spiroketal product **14**.



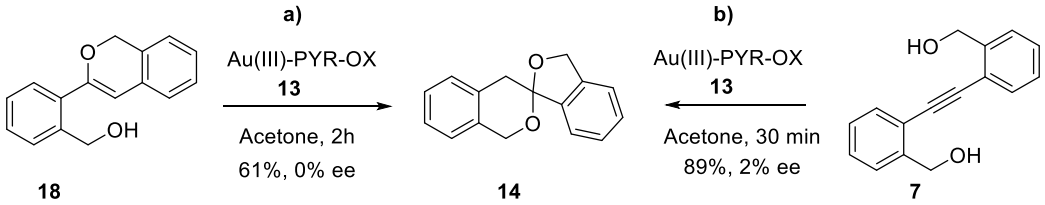
Scheme 4. Proposed mechanisms a), b) for gold catalysed dihydroalkoxylation of alkynyl diol **7** to give 5,6-spiroketal **14** (red C-C bonds represent original alkyne position).

An alternative mechanism[54] (Scheme 4b) is based on the opposite order of the two steps from intermediates **endo-/exo-B**, which may undergo direct protodeauration to form vinyl ethers **17** and **18**. Indeed, vinyl ethers **17** and **18** could be detected by NMR analysis of reaction samples and vinyl ether **18** was isolated from incomplete reaction mixtures. Protonation of the vinyl ethers leads to the oxocarbenium ions **19**

and **20**, which would quickly undergo nucleophilic attack and 6-/5-*exo*-dig spirocyclization to give spiroketal **14** with no expected enantioselectivity, due to the absence of a stereocontrolling gold moiety. In previous studies of similar Au(I)-NHC catalysed reactions, the final step is suggested to be entirely acid catalysed.[40]

The experimental results do not fully confirm either of the mechanistic pathways a), b).[40,45] Complete conversion of the alkynyl diol **7** gave a mixture of spiroketal **14** and vinyl ether **18** (NMR) within minutes for all Au(III)-BOX catalysts **11a-e**, but further conversion of vinyl ether **18** to spiroketal **14** was slow and indicates that the final cyclisation to form spiroketal **14** is the rate limiting step of these tandem reactions. No increase of reaction rate was seen by addition of more catalyst to the mixture, which could indicate that the final step might be catalysed by trace amounts of acid. Contradictory results were obtained, applying Au(III)-PYR-OX complex **13**, as full tandem conversion of the original diol substrate **7** to target product **14** was seen within 30 min (Table 1, entry 13, Scheme 5b), while, in contrast, a test cyclization reaction of purified vinyl ether **18** only gave 61 % conversion to spiroketal **14** (0 % ee, Scheme 5a) and a complex mixture of new minor products.

As the final cyclisation is the enantiodetermining cyclization step, a completely racemic spiroketal product would be expected if a gold adduct is not involved (e.g. **19**, **20**; mechanism b). The gold catalysed test reaction of the final cyclization of vinyl ether **18** did actually afford full racemization (Scheme 5a), possibly due to de-coordination of an oxazoline or pyridine moiety, as observed and discussed in our previous catalytic studies with catalyst **13**.[33] The fact that some enantioselectivity (up to 5 % ee) was observed through the complete tandem spirocyclization pathway from diol substrate **7** to target product **14**, may indicate that the spirocyclization mechanism, catalyzed by Au(III)-oxazoline complexes, is more complex than previously suggested.[31,40]



Scheme 5. Spiroketalization of vinyl ether **18** and alkynyl diol **7** to form 5,6-spiroketal **14** by a) mono- and b) dihydroalkoxylation, respectively.

Conclusions

The present first known study on gold(III)-oxazoline catalysed tandem spiroketalization shows that Au(III)-BOX (**11a-e**) and Au(III)-PYR-OX (**13**) complexes are highly efficient catalyst for intramolecular dihydroalkoxylation of alkynyl diols (**7**,**9**) to give aromatic 5,6-spiroketal products (**14** and **15/16**). The mono- and dibenzannulated spiroketals (**14** and **15/16)** were obtained in high yields (> 90 %) by rapid conversion of symmetrical and nonsymmetrical alkynyl diols, respectively (**7**,**9**). Minor enantioselectivity (up to 6 % ee) was observed with the Au(III)-BOX-BF_4 and Au(III)-PYR-OX catalysts (**11a**, **13**). The monobenzannulated 5,6-spiroketal regioisomers **15** and **16** were formed in a ratio of up to 80:20. The choice of solvent seemed to be particularly important for the yields, enantio- and regioselectivity of the reactions of alkynyl diols (**7**,**9**). The tandem mechanism for spirocyclization is discussed.

Experimental Section

General. Commercial grade reagents were used without any additional purification. Dry solvents were collected from an MB SPS-800 solvent purification system. Reactions were monitored by NMR and/or thin-layer chromatography (TLC) using silica gel 60 F254 (0.25 mm thickness). TLC plates were developed using UV-light and/or phosphomolybdic acid stain. Flash chromatography was performed with Merck silica gel 60 (0.040-0.063 mm). ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance DPX 400 MHz spectrometer. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane (TMS) as an internal standard. Accurate mass determination was performed on a "Synapt G2-S" Q-TOF instrument from Waters. Samples were ionized with an ASAP probe with no chromatography separation performed before mass analysis. Chiral HPLC was used for enantio-determination (% ee) with CHIRALPAK AD-H and OJ-H columns with *i*-PrOH:hexane eluents and flow rate 0.800 mL/min.

General procedure for Sonogashira cross-coupling

A dried two-neck flask was charged with (2-iodophenyl)methanol **4** (1 eq), the appropriate alkyne (1 eq), $(PPh_3)_2PdCl_2$ (0.05 eq) and CuI (0.10 eq) under an N_2-atmosphere. Dry, de-gassed THF was then added, followed by Et_3N (2 eq). The solution was stirred at room temperature for 16h. The reaction mixture was filtered through celite and added EtOAc. The organic phase was washed twice with sat. NH_4Cl solution, followed by brine. After drying over anhydrous Na_2SO_4 and filtration, silica gel was added to the crude product solution, followed by drying *in vacuo*. Purification by column chromatography (pentane:EtOAc) yielded the final products.

2-((2-(Hydroxymethyl)phenyl)ethynyl)benzaldehyde (6). Following the general procedure, 2-ethynylbenzaldehyde (**5,** 319 mg, 2.45 mmol) and (2-iodophenyl)methanol (**4**, 574 mg, 2.45 mmol) gave the target product **6** as an orange oil in 75 % yield (431 mg, 1.84 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 10.50 (s, 1H, CHO), 7.90 (dd, *J* 7.8, 1.3 Hz, 1H, CH_{Ar}), 7.64 (dd, *J* 7.8, 1.1 Hz, 1H, CH_{Ar}), 7.58 (td, 7.5, 1.1 Hz, 1H, CH_{Ar}), 7.55 (dd, *J* 7.6, 1.0 Hz, 1H, CH_{Ar}), 7.44-7.50 (m, 2H, CH_{Ar}), 7.38 (td, *J* 7.5, 1.4 Hz, 1H, CH_{Ar}), 7.29 (td, *J* 7.5, 1.0 Hz, 1H, CH_{Ar}), 4.90 (d, *J* 6.0 Hz, 2H, CH_2), 2.96 (t, *J* 6.2 Hz, 1H, OH). ^{1}H NMR data corresponds to previously reported data.[47]

(Ethyne-1,2-diylbis(2,1-phenylene))dimethanol (7). 2-((2-(Hydroxymethyl)phenyl)ethynyl)benzaldehyde (**6**, 242 mg, 1.02 mmol), was dissolved in ethanol (5 mL). To the solution was added $NaBH_4$ (116 mg, 3.07 mmol) and the solution was stirred for 30 min. The reaction was quenched by addition of a HCl solution (1M, 25 mL) and the product extracted into EtOAc (2x25 mL). The organic phase was washed with brine, followed by drying over anhydrous Na_2SO_4 and evaporation *in vacuo*. Purification by column chromatography (2:1 pentane:EtOAc) gave the target product **7** as a white solid in 57 % yield (139 mg, 0.581 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 7.58 (dd, *J* 7.2, 1.5 Hz, 2H, CH_{Ar}), 7.43 (dd, *J* 7.5, 1.7 Hz, 2H, CH_{Ar}), 7.30-7.38 (m, 4H, CH_{Ar}), 4.87 (d, *J* 3.5 Hz, 4H, CH_2), 2.74 (broad s, 2H, OH). ^{1}H NMR data corresponds to previously reported data.[48]

5-(2-(Hydroxymethyl)phenyl)pent-4-yn-1-ol (9). Following the general procedure, pent-4-yn-1-ol (**8,** 219 mg, 2.61 mmol) and (2-iodophenyl)methanol (**4**, 610 mg, 2.61 mg) gave the target product **9** as an orange solid in 91 % yield (450 mg, 2.38 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 7.38-7.42 (m, 2H, CH_{Ar}), 7.29 (td, *J* 7.5. 1.4 Hz, 1H, CH_{Ar}), 7.23 (td, *J* 7.5, 1.4 Hz, 1H, CH_{Ar}), 4.79 (s, 2H, CH_2), 3.84 (t, J 5.9 Hz, 2H, CH_2), 2.60 (t, *J* 6.9 Hz, 2H, CH_2), 2.33 (bs, 1H, OH), 1.88 (p, *J* 6.4 Hz, 2H, CH_2), 1.73 (bs, 1H, OH). ^{1}H NMR data corresponds to previously reported data.[13]

General procedure for the synthesis of gold(III) complexes

To a solution of the appropriate ligand (1 eq) in CH_3CN was added $AuCl_3$ (1 eq) and the appropriate silver salt (1 eq). The resulting solution was stirred at room temperature for 1 hour, followed by filtration through celite and evaporation *in vacuo*. The crude product was redissolved in DCM and the organic phase washed once each with water and brine followed by drying over anhydrous Na_2SO_4 and the volume of solvent was reduced i*n vacuo* to approx 1 mL. The complexes were precipitated out of solution by addition of Et_2O, after which filtration gave the pure complexes as crystalline solids.

***i*-Pr-BOX-Au-BF_4 (11a).** Following the general procedure, ligand **10a** (39.2 mg, 0.147 mmol), $AuCl_3$ (44.6 mg, 0.147 mmol) and $AgBF_4$ (28.6 mg, 0.147 mmol) gave complex **11a** as yellow crystals in 47 % yield (43.4 mg, 0.0691 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.00 (dt, *J* 9.3, 3.2 Hz, 2H, CH), 4.88 (t, *J* 9.2 Hz, 2H, CH_2), 4.71 (dd, *J* 9.2, 3.3 Hz, 2H, CH_2), 2.62 (m, 2H, CH), 1.85 (s, 6H, CH_3), 0.97 (d, *J* 7.2 Hz, 6H, CH_3), 0.87 (d, *J* 6.8 Hz, 6H, CH_3). ^{1}H NMR data corresponds to previously reported data.[33]

***i*-Pr-BOX-Au-SbF_6 (11b).** Following the general procedure, ligand **10a** (69.0 mg, 0.259 mmol), $AuCl_3$ (78.6 mg, 0.259 mmol) and $AgSbF_6$ (89.0 mg, 0.259 mmol) gave complex **11b** as yellow crystals in 50 % yield (100.4 mg, 0.130 mmol). ^{1}H NMR (400 MHz, CD_3CN) δ (ppm) 4.92 (dt, *J* 9.4, 2.9 Hz, 2H, CH), 4.86 (dd, *J* 9.6, 3.1 Hz, 2H, CH_2), 4.67(t, *J* 9.5 Hz, 2H, CH_2), 2.49 (ds, *J* 7.0, 2.6 Hz, 2H, CH), 1.76 (s, 6H, CH_3), 0.94 (d, J 7.0 Hz, 6H, CH_3), 0.82 (d, *J* 7.0 Hz, 6H, CH_3). ^{1}H NMR data corresponds to previously reported data.[33]

***i*-Pr-BOX-Au-NTf_2 (11c).** Following the general procedure, ligand **10a** (53.1 mg, 0.199 mmol), $AuCl_3$ (60.5 mg, 0.199 mmol) and $AgNTf_2$ (77.3 mg, 0.199 mmol) gave complex **11c** as yellow crystals in 73 % yield (118.1 mg, 0.146 mmol). ^{1}H NMR (400 MHz, CD_3CN) δ (ppm) 4.93 (dt, J 9.3, 2.6 Hz, 2H, CH), 4.86 (dd, J 9.8, 3.2 Hz, 2H, CH_2), 4.70 (t, J 9.6 Hz, 2H, CH_2), 2.49 (ds, *J* 7.0, 2.8 Hz, 2H, CH), 1.76 (s, 6H, CH_3), 0.95 (d, *J* 7.0 Hz, 6H, CH_3), 0.82 (d, *J* 6.9 Hz, 6H, CH_3). ^{13}C NMR (100 MHz, CD_3CN) δ (ppm) 175.2 (C=N), 73.1 (CH_2), 71.4 (CH), 30.9 (CH), 25.7 (CH_3), 18.0 (CH_3), 13.7 (CH_3). HRMS (ESI) *m/z* [M^+]: calcd. for $C_{15}H_{26}AuCl_2N_2O_2$ 533.1037, found 533.1046.

Ph-BOX-Au-BF_4 (11d). Following the general procedure, ligand **10b** (44.9 mg, 0.134 mmol), $AuCl_3$ (40.7 mg, 0.134 mmol) and $AgBF_4$ (26.1 mg, 0.134 mmol) gave complex **11d** as yellow crystals in 95 % yield (88.2 mg, 0.128 mmol). ^{1}H NMR (400 MHz, CD_3CN) δ (ppm) 7.41-7.49 (m, 6H, CH_{Ar}), 7.33-7.36 (m, 4H, CH_{Ar}), 6.05 (dd, *J* 10.1, 4.9 Hz, 2H, CH), 5.18 (t, *J* 9.5 Hz, 2H, CH_2), 4.74 (dd, *J* 9.3, 4.8 Hz, 2H, CH_2), 2.03 (s, 6H, CH_3). ^{1}H NMR data corresponds to previously reported data.[33]

4,5-diPh-BOX-Au-BF_4 (11e). Following the general procedure, ligand **10c** (25.5 mg, 0.0524 mmol), $AuCl_3$ (15.9 mg, 0.0524 mmol) and $AgBF_4$ (10.2 mg, 0.0524 mmol) gave complex **11d** as yellow crystals in 89 % yield (39.4 mg, 0.468 mmol). ^{1}H NMR (400 MHz, CD_3CN) δ (ppm) 7.13-7.22 (m, 16H, CH_{Ar}), 7.03-7.06 (m, 4H, CH_{Ar}), 6.60 (d, *J* 9.8 Hz, 2H, CH), 6.47 (d, *J* 9.8 Hz, 2H, CH), 2.26 (s, 6H, CH_3). ^{13}C NMR (100 MHz, CD_3CN) δ (ppm) 176.9 (C=N), 134.4 (C_{Ar}), 132.1 (C_{Ar}), 130.1 (CH_{Ar}), 129.6 (CH_{Ar}), 129.4 (CH_{Ar}), 129.1 (CH_{Ar}), 128.5 (CH_{Ar}), 127.8 (CH_{Ar}), 91.2 (CH), 73.6 (CH), 44.0 (C), 26.1 (CH_3). HRMS (ESI) *m/z* [M^+]: calcd. for $C_{33}H_{30}AuCl_2N_2O_2$ 753.1350, found 753.1360.

PYR-OX-Au-BF_4 (13). Following the general procedure, ligand **12** (25.0 mg, 0.122 mmol), $AuCl_3$ (37.1 mg, 0.122 mmol) and $AgBF_4$ (23.8 mg, 0.122 mmol) gave complex **13** as yellow crystals in 79 % yield (54.1 mg, 0.0965 mmol). ^{1}H NMR (400 MHz, CD_3CN) δ (ppm) 9.42 (dd, *J* 5.8, 0.8 Hz, 1H, CH_{Ar}), 8.64 (td, *J* 7.7, 1.1 Hz, 1H, CH_{Ar}), 8.29 (dd, *J* 7.8, 1.5 Hz, 1H, CH_{Ar}), 8.24 (ddd, *J* 7.6, 5.8, 1.4 Hz, 1H, CH_{Ar}), 5.43 (dd, *J* 10.0, 2.7 Hz, 1H, CH_2), 5.11 (dd, *J* 9.9, 8.9 Hz, 1H, CH_2), 4.54 (dd, *J* 8.9, 2.7 Hz, 1H, CH), 1.06 (s, 9H, CH_3). ^{1}H NMR data corresponds to previously reported data.[35]

General procedure for the dihydroalkoxylation of alkynyl diols

Alkynyl diol **7/9** (1 eq) was dissolved in the appropriate solvent and the gold catalyst (0.05 eq) was added. The reaction was monitored either by TLC chromatography or by ^{1}H NMR of reaction mixture aliquots. When the reaction was complete, the solvent was evaporated *in vacuo*. Purification by column chromatography (pentane:EtOAc) yielded the spiroketals **14-16**.

3H-Spiro[isobenzofuran-1,3'-isochromane] (14). Results are as shown in Table 1. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.39 (dq, *J* 6.9, 1.9 Hz, 1H, CH_{Ar}), 7.30-7.36 (m, 3H, CH_{Ar}), 7.21-7.24 (m, 2H, CH_{Ar}), 7.16-7.20 (m, 1H, CH_{Ar}), 7.08-7.10 (m, 1H, CH_{Ar}), 5.25 (d, *J* 12.7 Hz, 1H, CH_2), 5.15 (d, *J* 14.7 Hz, 1H, CH_2), 5.07 (d, *J* 12.7 Hz, 1H, CH_2), 4.86 (d, *J* 14.8 Hz, 1H, CH_2), 3.57 (d, *J* 16.2 Hz, 1H, CH_2), 3.07 (d, *J* 16.3 Hz, 1H, CH_2). HPLC: CHIRALPAK AD-H, UV-detector: 210 nm eluent: *i*-PrOH:hexane 97:3, retention time: 10.64 min, 13.39 min. ^{1}H NMR data corresponds to previously reported data.[13]

3',4',5',6'-Tetrahydro-3*H*-spiro[isobenzofuran-1,2'-pyran] (15). Results are as shown in Table 2. Isolated as a mixture of spiroketals **15** and **16**. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.13-7.17 (m, 2H, CH_{Ar}), 7.07-7.10 (m, 1H, CH_{Ar}), 6.99-7.02 (m, 1H, CH_{Ar}), 4.92 (d, *J* 14.8 Hz, 1H, CH_2), 4.67 (d, *J* 14.8 Hz, 1H, CH_2), 3.98-4.01 (m, 2H, CH_2), 3.23 (d, *J* 16.4 Hz, 1H, CH_2), 2.82 (d, *J* 16.4 Hz, 1H, CH_2), 2.17 (m, 1H, CH_2), 2.13 (m, 1H, CH_2), 1.97 (m, 1H, CH_2), 1.88 (m, 1H, CH_2). HPLC: CHIRALPAK OJ-H, UV-detector: 210 nm, eluent: *i*-PrOH:hexane 90:10, retentiom time: 9.84 min, 18.60 min. ^{1}H NMR data corresponds to previously reported data.[13]

4,5-Dihydro-3H-spiro[furan-2,3'-isochromane] (16). Results are as shown in Table 2. Isolated as a mixture of spiroketals **15** and **16**. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.13-7.17 (m, 2H, CH_{Ar}), 7.07-7.10 (m, 1H, CH_{Ar}), 6.99-7.02 (m, 1H, CH_{Ar}), 4.92 (d, *J* 14.8 Hz, 1H, CH_2), 4.67 (d, *J* 14.8 Hz, 1H, CH_2), 3.98-4.01 (m, 2H, CH_2), 3.23 (d, *J* 16.4 Hz, 1H, CH_2), 2.82 (d, *J* 16.4 Hz, 1H, CH_2), 2.17 (m, 1H, CH_2), 2.13 (m, 1H, CH_2), 1.97 (m, 1H, CH_2), 1.88 (m, 1H, CH_2). HPLC: CHIRALPAK OJ-H, UV-detector: 210 nm, eluent: *i*-PrOH:hexane 90:10, retention time: 11.05 min, 15.34 min. ^{1}H NMR data corresponds to previously reported data.[13]

(2-(1H-isochromen-3-yl)phenyl)methanol (18). Performed according the general procedure, with the reaction being terminated after 10 min. ^{1}H NMR (600 MHz, CD_2Cl_2) δ (ppm) 7.56 (dd, *J* 7.7, 0.9 Hz, 1H, CH_{Ar}), 7.52 (apparent d, *J* 7.6 Hz, 1H, CH_{Ar}), 7.44 (td, *J* 7.7, 1.3 HZ, 1H, CH_{Ar}), 7.37 (td, *J* 7.5, 1.1 Hz, 1H, CH_{Ar}), 7.31 (apparent t, *J* 7.6 Hz, 1H, CH_{Ar}), 7.24 (td, *J* 7.6, 1.0 Hz, 1H, CH_{Ar}), 7.13-7.15 (m, 2H, CH_{Ar}), 6.23 (s, 1H, C=CH), 5.29 (s, 2H, CH_2), 4.75 (d, *J* 6.6 Hz, 2H, CH_2OH), 2.40 (t, *J* 6.6 Hz, 1H, OH). ^{13}C NMR (150 MHz, CD_2Cl_2) δ (ppm) 155.5 (C=C), 139.8 (C_{Ar}), 134.4 (C_{Ar}), 131.6 (C_{Ar}), 129.5 (CH_{Ar}), 129.3 (CH_{Ar}), 128.9 (CH_{Ar}), 128.3 (CH_{Ar}), 127.7 (CH_{Ar}), 127.6 (C_{Ar}), 126.8 (CH_{Ar}), 123.9 (C_{Ar}), 123.5 (CH_{Ar}), 105.2 (C=CH), 68.8 (CH_2), 64.0 (CH_2OH).

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Supplementary Material

^{1}H and ^{13}C NMR spectra of novel compounds **11c,e, 18** and ^{1}H NMR spectra of known compounds **6, 7, 9, 11a,b,d, 13-16** and **18**, as well as chiral HPLC chromatograms, can be found in the Supplementary Material file.

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