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Gold Catalysis: Synthesis of 3-Acylindenes from 2-Alkynylaryl Epoxides

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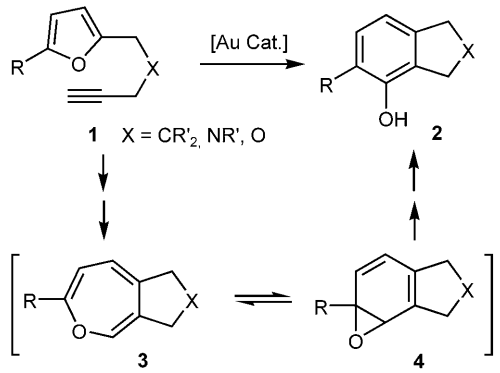
Abstract: A series of 2-alkynylaryl epoxides were prepared by a sequence of Sonogashira coupling, Wittig olefination and epoxidation or a Darzens' glycid ester synthesis. The conversion of these substrates with gold(I) catalysts furnished 3-acylindenes and, in occasional cases as side-products, the products of an isomerization of the oxirane ring to a ketone. Isotope labelling of the epoxide oxygen indicates an intramolecular oxygen transfer.

Keywords: alkynes; gold; homogeneous catalysis; indenes; isotope labelling; oxiranes

Introduction

Homogeneous gold catalysis[1] is a fast growing field, one of the most reliable transformations in this field is the phenol synthesis,[2] a special sub-type of the enyne cycloisomerization (Scheme 1). The synthetic aspects of this reaction have been explored, from easily accessible furan derivatives **1** a broad range of benzo-anellated carbo- and heterocycles **2** can be prepared by this methodology.[3] In addition, the unique mechanism was investigated,[4] experimental proof for oxepin (**3**) and arene oxide (**4**) intermediates was obtained.[3h,4c–e]



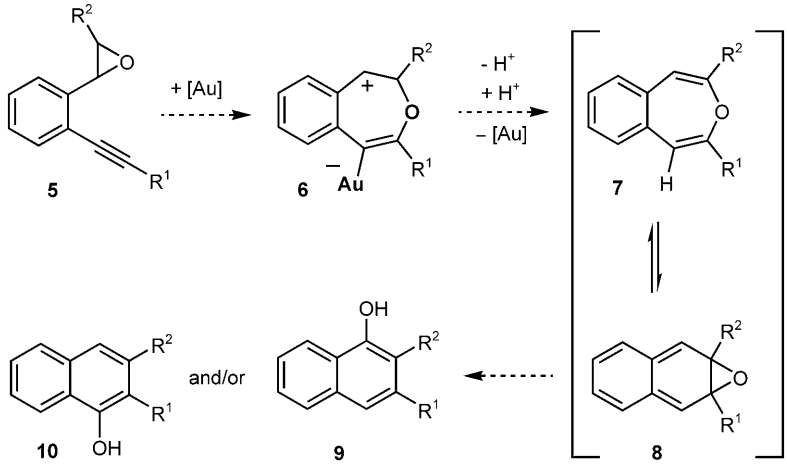
Scheme 1. Oxepines and arene oxides as intermediates in the gold-catalyzed phenol synthesis.

We then became interested in using alternative precursors for oxepines in gold catalysis. Based on our previous experience with oxiranes,[5] we assumed that an activation of the alkyne in **5** by an electrophilic gold catalyst initiates a nucleophilic attack of the epoxide oxygen, opening of the strained ring should be selective for the benzylic C–O bond to deliver the more stable benzylic cation **6**. Then elimination of a proton at the position neighbouring to the carbenium ion and a proto-desauration would lead to the benzo-anellated oxepine **7**. If the reaction would proceed from **7** in analogy to the corresponding steps of the phenol synthesis, one could ultimately expect the naphthols **9** and/or **10** as products (Scheme 2).

Here we report our observations on the gold-catalyzed conversions of substrates of type **5**.

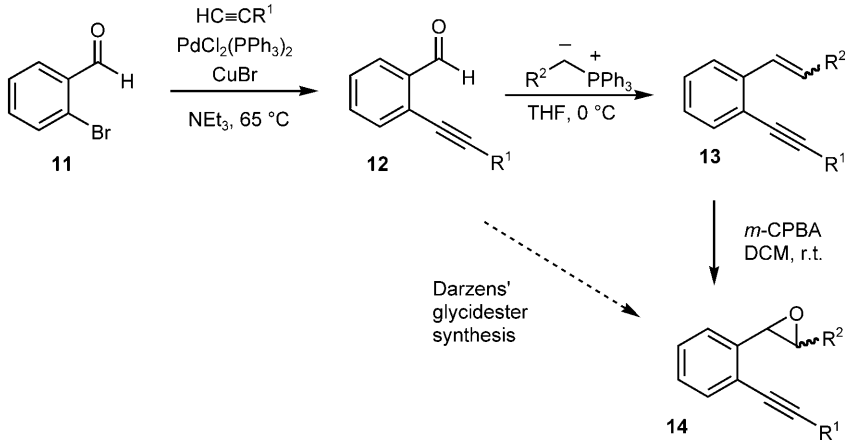
Results and Discussion

The step-wise assembly of the three components, 2-bromobenzaldehyde (**11**) with different terminal alkynes by a Sonogashira coupling and a subsequent Wittig reaction with phosphorus ylides delivered (**12**) the enynes **13** as an (*E*/*Z*) mixture. We did not address the double bond geometry in order to keep the synthetic approach as simple as possible, and we expected both diastereomers to ultimately form the same product. The alkenes were epoxidized with *m*-



Scheme 2. Substrates **5** as potential precursors for oxepines.

Table 1. A variety of substrates **14** from three components, 2-bromobenzaldehyde, a terminal alkyne and a phosphorus ylide.

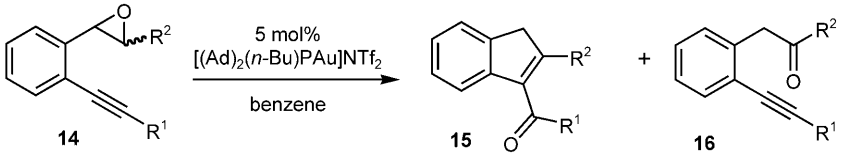


Entry	R^1	**12** (Yield)	R^2	**13** (Yield, *E*:*Z*)	**14** (Yield, *trans*:*cis*)
1	*n*-Bu	**12a** (89%)	*n*-Pr	**13a** (82%, 1:1.3)	**14a** (75%, 1:1.3)
2			H	**13b** (80%)	**14b** (51%)
3	*n*-Hex	**12b** (96%)	*n*-Pr	**13c** (92%, 1:1)	**14c** (73%, 1:0.9)
4			*i*-Pr	**13d** (46%, 1:0.6)	**14d** (86%, 1:0.5)
5			*n*-Bu	**13e** (49%, 1:0.9)	**14e** (76%, 1:0.8)
6			*n*-Pe	**13f** (51%, 1:1)	**14f** (86%, 1:0.9)
7			Me	**13g** (67%, 1:0.9)	**14g** (72%, 1:0.7)
8	Ph	**12c** (91%)	Me	**13h** (87%, 1:0.8)	**14h** (75%, 1:0.9)
9	*t*-Bu	**12d** (96%)	*n*-Pr	**13i** (59%, 1:0.7)	**14i** (95%, 1:0.5)
10	CH_2CH_2Ph	**12e** (99%)	Me	**13j** (74%, 1:0.8)	**14j** (89%, 1:0.7)
11			*n*-Pr	**13k** (79%, 1:0.9)	**14k** (76%, 1:0.8)
12	TMS	**12f** (88%)	Me	**13l** (69%, 1:0.7)	**14l** (85%, 1:0.7)
13	TBS	**12g** (99%)	*n*-Pr	**13m** (75%, 1:0.5)	**14m** (78%, 1:0.5)
14	H		Me		**14n**[a] (79%, 1:0.7)
15	Bu		CO_2Et		**14o**[b] (39%)

[a] From **14l** by desilylation.
[b] From **12a** by Darzens' glycid ester synthesis.

CPBA (Table 1), again a mixture of the *cis*/*trans* diastereomers was obtained. Compound **14n** was prepared by desilylation of the TMS-substituted alkyne **14l** (entry 14). For the ester-substitued oxirane **14o** Darzens' glycid ester synthesis was a convenient short cut (entry 15).

Table 2. Gold(I)-catalyzed conversion of **14**.



Entry	Substrate	R^1	R^2	Amount of catalyst [mol%]	Product (yield)	
1	**14a**	*n*-Bu	*n*-Pr	5	**15a** (80%)	**16a** (7%)
2	**14b**	*n*-Bu	H	5	–	**16b** (48%)
3	**14c**	*n*-Hex	*n*-Pr	5	**15c** (85%)	**16c** (8%)
4	**14d**	*n*-Hex	*i*-Pr	5	**15d** (56%)	–
5	**14e**	*n*-Hex	*n*-Bu	5	**15e** (66%)	–
6	**14f**	*n*-Hex	*n*-Pent	5	**15f** (64%)	–
7	**14g**	*n*-Hex	Me	5	**15g** (67%)	–
8	**14h**	Ph	Me	3	**15h** (37%)	**16h** (18%)
9	**14i**	*t*-Bu	*n*-Pr	5	–	–
10	**14j**	CH_2CH_2Ph	Me	3	**15j** (90%)	–
11	**14k**	CH_2CH_2Ph	*n*-Pr	5	**15k** (68%)	–
12	**14l**	TMS	Me	5	–	–
13	**14m**	TBS	*n*-Pr	5	–	**16m** (13%)
14	**14n**	H	Me	5	–	–
15	**14o**	*n*-Bu	CO_2Et	5	–	–

Initial testing of several different gold catalysts indicated that Gagosz's catalyst[6] $[(Ad)_2(n\text{-Bu})PAu]NTf_2$ gave the best results ($AuCl_3$, $AuCl_2$[picolinate] and $\{[Mes_3PAu]_2Cl\}BF_4$ gave only an unselective reaction and low conversion). Thus the substrates **14a–o** were subjected to this gold(I) catalyst (Table 2). Interestingly, rather than the expected products, in most cases the acylindenes **15** were formed, in some examples in excellent yields. Due to the absence of stereogenic elements in **15**, both diastereomers of **14** converge to the same product.

The structure of **15**, especially the position of the carbonyl group, was initially based on spectroscopic evidence. Apart from characteristic data for the α,β-unsaturated carbonyl unit, the ^{1}H NMR nicely shows that the group R^1 is attached to the carbonyl group and R^2 is attached to the double bond. For example, in the substrates **15g**, **15h** and **15j** with R^2 = Me the methyl group shows as a singlet at 2.34, 2.08 and 2.35 ppm, respectively, typical for an allylic methyl group. For the first CH_2 group of the other side chain R^1, 2.84 ppm for the hexyl group in **15g** and 3.05 ppm for the CH_2CH_2Ph substituent in **15j** show as triplets with coupling constants of 7.3–7.5 Hz. This assignment was ultimately confirmed by a crystal structure analysis of **15j** (Figure 1).[7] It shows a planar indene skeleton (mean deviation from plane: 0.003 Å) with a coplanar keto group (angle between planes: 4.2°). There is a short intramolecular contact distance of 2.39 Å between O1 and the hydrogen atom at C8. The molecules form centrosymmetric dimers with π···π contacts of about 3.50 Å between the parallel five-membered rings. These dimers also are stabilized by additional C(methylene)–H···π(benzene) interactions. The dimers stack along the a-axis. Neighbouring stacks are connected by rather long intermolecular C–H···π interactions.

A competing process is the simple isomerization of the epoxide by initial opening of the benzylic epoxide bond (whether this is initated intermolecularly by a direct gold-oxygen interaction or intramolecularly by an interaction of the gold-alkyne complex with the epoxide, hydride shift from intermediate **18**, and elimination to re-form the alkyne, is as yet unknown). This was observed in the case of the unsubstituted epoxide **14b** (entry 2), here only **16b** was obtained. In the case of the substrates **14a**, **14c** and **14h** the ketones **16a**, **16c** and **16h** were only formed as side-products (entries 1, 3 and 8).

The limitations become visible, too. With a sterically demanding group on the alkyne, the reaction completely failed (*t*-Bu group in **14l**, entry 9) or gave only a low yield of epoxide ring opening (TBS group in **14m**, entry 13). Terminal alkynes completely fail (entry 14), another (maybe related) problem is the TMS-substituted alkyne which is easily desilylated under the electrophilic reaction conditions (entry 12). Most unfortunately, the easily accessible ester-substituted expoxide **14o** (entry 15) also does not react.

Control experiments with 5 mol% $AgBF_4$ or 5 mol% *p*-TsOH under the same conditions gave no conversion of the substrates.

Regarding the mechanism, we prepared the ^{18}O-labelled derivative of **14j**. The product **15j** still con-

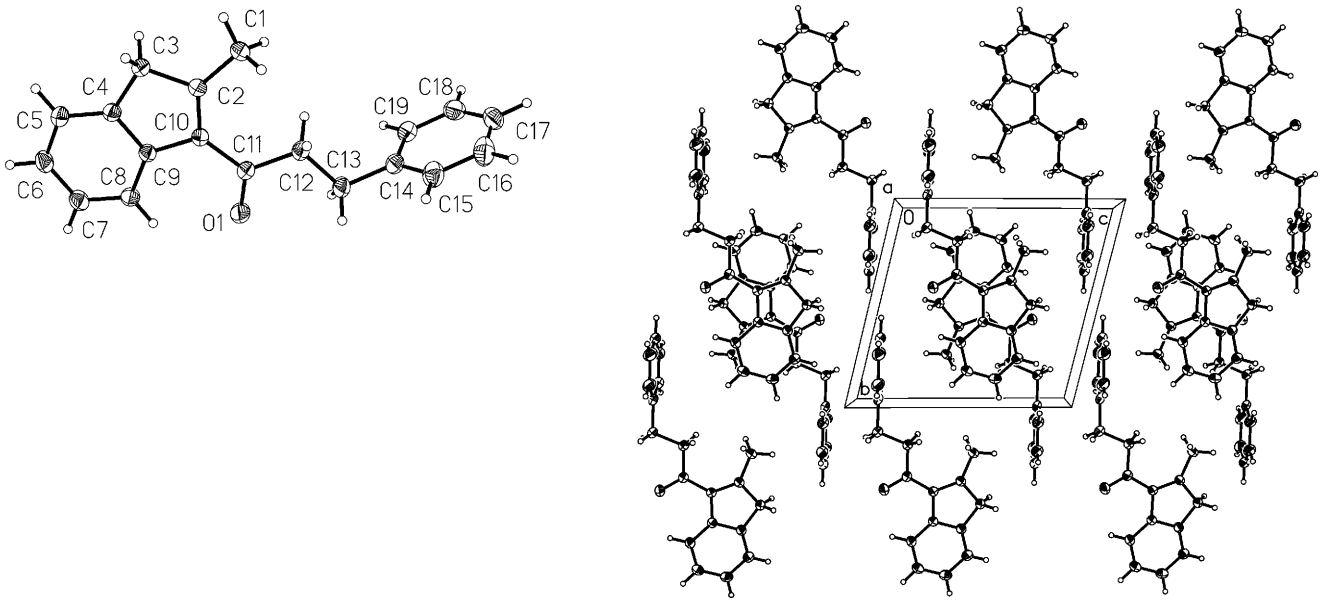


Figure 1. The X-ray crystal structure analysis of **15j** confirmed the structural assignment.

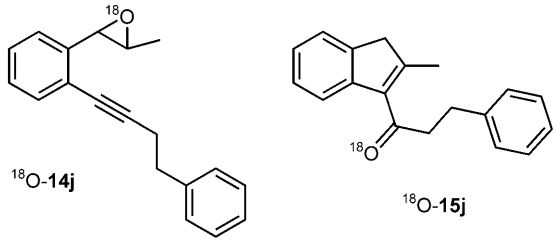


Figure 2. Labelling studies suggest an intramolecular transfer of the oxygen atom.

tained the ^{18}O-label (Figure 2), which proves an intramolecular oxygen transfer and excludes external water molecules as nucleophiles. For example, the possibility of an epoxide isomerization to **16**, a hydratation of the triple bond to the benzyl ketone, as discussed in work by Liu,[8] and a final intramolecular condensation of the two carbonyl side-arms, can be ruled out. The same is true for a potential hydratation to a vinylgold intermediate and a reaction of the latter with the epoxide. Similarly, a cross-over experiment of a mixture of ^{18}O-**14j** and **14a** gave ^{18}O-**15j** and **15j** and no evidence for ^{18}O-**15j** (MS detection).

Furthermore, the fact that internal alkynes react, excludes the participation of vinylidene-metal species as suggested by Liu et al. for related reactions of similar substrates with ruthenium catalysts (leading to different products).[9]

A mechanistic proposal is shown in Scheme 3. After coordination of the alkyne to the catalyst (**17**) and electrophilic attack at the oxirane oxygen atom, the benzylic cation **18** could be generated. Then, the remaining C–O bond of the former epoxide ring is broken and an even more delocalized carbenium ion **19** can be formed. In Scheme 3 the pentadienyl cation structure of **19** is emphasized, and in analogy to the gold-catalyzed Rautenstrauch rearrangement[10] a ring closure to the allyl cation **20** could follow. Here the allyl cation in **20** would be part of a well-stabilized benzylic cation. Elimination of the gold catalyst to **21** and isomerization of the double bond finally would deliver the product **15**.

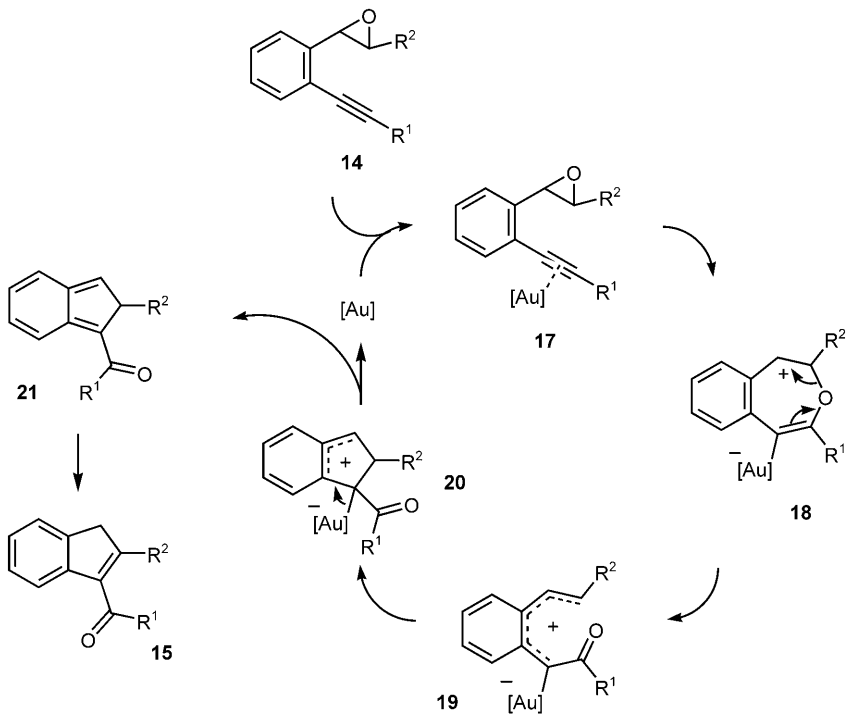
Conclusions

This new conversion nicely complements the few known routes to 3-acylindenes.[11] Furthermore, the mechanistic study proofs an intramolecular oxygen transfer and points towards a pentadienyl cation to cyclopentenyl cation cyclization as a key step and not a hydrative carbocyclization or the participation of vinylidene-metal species. Future optimization of the catalyst and the reaction conditions is necessary to completely suppress the side product **16**.

Experimental Section

General Procedure A: Sonogashira Coupling

1.2 equivalents alkyne, 1 equivalent bromobenzaldehyde **11** and $PdCl_2(PPh_3)_2$ were dissolved in degassed triethylamine, and after 1 min, copper(I) iodide was added. The mixture was stirred at 65 °C for 16 h and was then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel.



Scheme 3. Possible reaction mechanism for the gold-catalyzed conversion of **14** to **15**.

General Procedure B: Wittig Reaction B

1.3 equivalents *n*-butyllithium were added slowly to a solution of 1.5 equivalents Wittig reagent in THF at 0 °C. At this temperature the mixture was stirred for 30 min. Then the substituted benzaldehyde **12** was added and the mixture again stirred at 0 °C for 4 h. Afterwards the mixture was hydrolyzed with brine, extracted three times with diethyl ether, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel.

General Procedure C: Epoxidation with *m*-CPBA

To a solution of 1 equivalent alkene **13** in dichloromethane, 1.3 equivalents *m*-CPBA were added at 0 °C and the mixture stirred for 5 h at room temperature. Then the reaction mixture was hydrolyzed with saturated $NaHCO_3$, extracted three times with diethylether, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel.

General Procedure D: Gold Catalysis

The epoxyalkyne **14** was dissolved in benzene, then the gold(I) catalyst was added. The mixture was stirred at room temperature. After the reaction was completed, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel.

Supporting Information

Details regarding the individual reactions and the spectroscopic data can be found in the Supporting Information

Acknowledgements

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[7] CCDC 692173 (**15j**) contains 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 (or from Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44)1223-1336-1033; deposit@ccdc.cam.ac.uk).

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