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Chemoselectivity Control: Gold(I)-Catalyzed Synthesis of 6,7-Dihydrobenzofuran-4(5*H*)-ones and Benzofurans from 1-(Alkynyl)-7-oxabicyclo[4.1.0]heptan-2-ones

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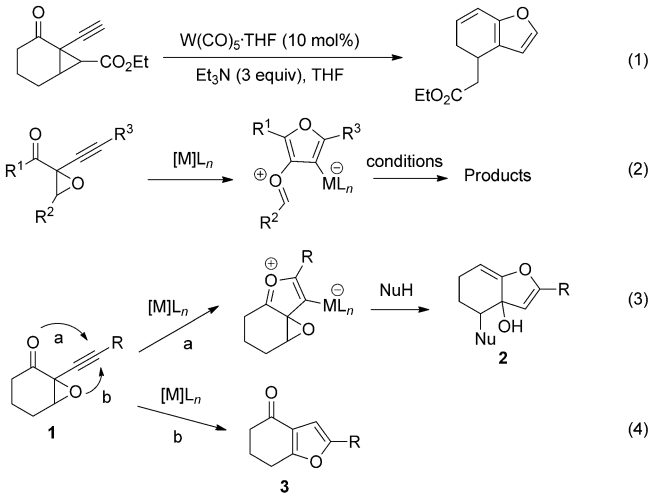
Abstract: New and chemoselective gold(I)-catalyzed transformations of 1-(arylethynyl)-7-oxabicyclo[4.1.0]-heptan-2-ones were developed. Two completely different products—6,7-dihydrobenzofuran-4(5*H*)-ones and benzofurans—could be obtained from the same starting material. The selectivity is determined by the ligand of the gold catalyst: triphenylphosphine delivers 6,7-dihydrobenzofuran-4(5*H*)-ones, and 1,3-bis(diisopropylphenyl)imidazol-2-ylidene leads to benzofurans. Eleven examples of each case are provided. The mechanistic suggestions for the pathways to both product types are supported by isotope labeling experiments.

Keywords: annulation · chemoselectivity · gold · ligand effects · synthetic methods

Introduction

It is well known that reaction pathways can be redirected by changing reaction parameters such as temperature, solvent, and catalyst. In transition-metal-catalyzed organic transformations, ligands play an important role in the control of chemoselectivity, regioselectivity, and enantioselectivity. In the past decades, gold-catalyzed transformations have become an useful tool in organic synthesis, and enormous progress has been made in this field.[1] Considering its great importance for organic synthesis, it is essential to study the influence of ligands in gold catalysis. In 2008, Toste et al. reviewed ligand effects in homogeneous gold catalysis and the development of ligands in gold catalysis.[2] As part of our efforts in gold catalysis,[3] we herein document gold-catalyzed chemoselective reactions which enable the preparation of different products from the same starting materials by variation of the ligands.

Recently, Sarpong and co-workers reported on a $W(CO)_5$·THF-catalyzed cycloisomerization of bicyclo-[4.1.0]heptane substrates to afford mono-C4-substituted 4,5-dihydrobenzo[*b*]furans [Scheme 1, Eq. (1)].[4] In this reaction, a carbon–carbon triple bond was attacked by the oxygen atom of a carbonyl group. Zhang et al. and others reported on the C–C bond cleavage of epoxide motifs [Scheme 1, Eq. (2)].[5] In these reactions, a carbonyl group and an epoxide moiety are installed in the same starting material. In analogy to the reactions with a cyclopropane unit, the carbonyl oxygen atom attacks the triple bond and then affords different products. We envisioned that the reaction pathway might be redirected by changing the reaction conditions, for example, by ligand variations. As shown in Scheme 1, by controlling the initial nucleophilic attack it should be possible to get two different products from one starting material. Attack of the carbonyl oxygen atom on the triple bond in the presence of a nucleophile could deliv-



Scheme 1. Previous work and our hypothesis.

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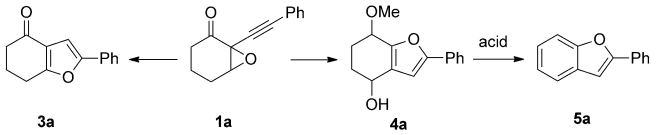
er product **2**, a valuable precursor for a subsequent isomerization reaction to give substituted benzofurans [Scheme 1, Eq. (3)]. Initial attack of the epoxide oxygen atom would afford 6,7-dihydrobenzofuran-4(5*H*)-ones, which, like benzofurans, are important motifs in natural products and building blocks for the pharmaceutical chemistry (for representative examples, see Scheme 2).[6,7]

Results and Discussion

We started our study by treating 1-(phenylethynyl)-7-oxabicyclo[4.1.0]heptan-2-one (**1a**) with $AuCl_3$ in CH_2Cl_2 at room temperature (Table 1, entry 1). However, after 2 h no conversion could be detected. Methanol was then added and 6,7-dihydrobenzofuran-4(5*H*)-one (**3a**) was obtained in moderate yield (Table 1, entry 2). Next we examined $(Ph_3P)AuCl$ in combination with different silver salts as halide scavenger (Table 1, entries 3–5). Among these $(Ph_3P)AuCl$ in combination with AgOTf gave the best result (Table 1, entry 3). The reaction yielded traces of **3a** without MeOH (Table 1, entry 6) and proceeded smoothly to afford **3a** in moderate yield on replacing MeOH with H_2O. However, water as additive resulted in a much longer reaction time (Table 1, entry 7). Further studies indicated that CH_3CN was the best solvent (Table 1, entry 10) and that MeOH was not essential for this coordinating solvent (Table 1, entry 12). Control experiments with a silver salt in the absence of a gold catalyst showed no conversion no matter whether MeOH was present or not (Table 1, entries 13 and 14).[8] When PPh_3 was replaced by 1,3-bis(diisopropylphenyl)imidazol-2-ylidene (IPr) as ligand, the desired change in chemoselectivity was achieved, and **4a** was mainly obtained as product (Table 1, entry 15; compounds **4** were always obtained as 1:1 mixtures of diastereomers). Like in the case of the phosphine ligands, AgOTf was the most efficient silver salt (Table 1, entries 15–17). Product **4a** could be easily transformed into the more valuable benzofuran **5a** in the present of an acid in a one-pot procedure. Further investigations indicated that HCl was the most suitable acid (Table 1, entry 20) and $CHCl_3$ the best solvent for this transformation (Table 1, entry 23).

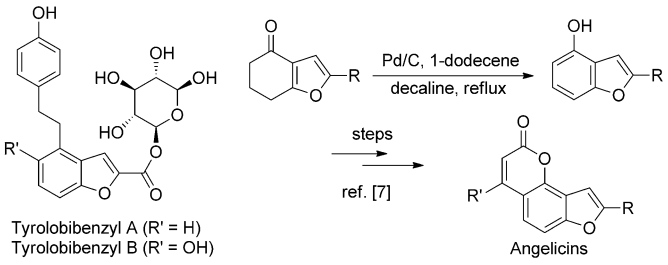
Table 1. Optimization of reaction conditions.[a,b]



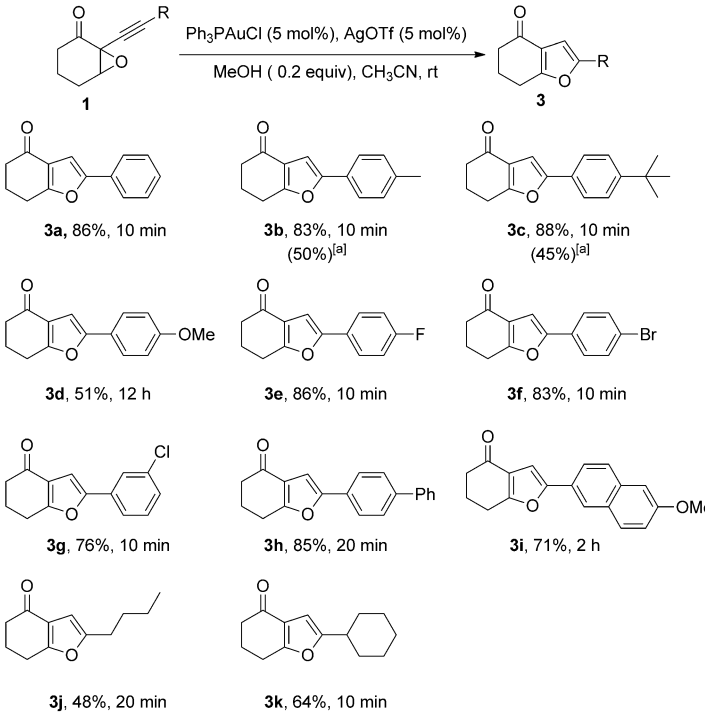
Entry	Catalyst (5 mol%)	CH_3OH [equiv]	Solvent	Acid (2 equiv)	t [min]	**1a**[c] [%]	**3a**[c] [%]	**4a**[c] [%]	**5a**[c] [%]
1	$AuCl_3$	–	CH_2Cl_2	–	120	95	–	–	–
2	$AuCl_3$	2.0	CH_2Cl_2	–	30	–	44	trace	–
3	$(Ph_3P)AuCl/AgOTf$	2.0	CH_2Cl_2	–	5	–	60	16	–
4	$(Ph_3P)AuCl/AgNTf_2$	2.0	CH_2Cl_2	–	20	–	45	17	–
5	$(Ph_3P)AuCl/AgSbF_6$	2.0	CH_2Cl_2	–	30	–	39	20	–
6	$(Ph_3P)AuCl/AgOTf$	–	CH_2Cl_2	–	600	–	<5	–	–
7	$(Ph_3P)AuCl/AgOTf$	2.0[d]	CH_2Cl_2	–	600	–	49	–	–
8	$(Ph_3P)AuCl/AgOTf$	2.0	toluene	–	20	–	65	trace	–
9	$(Ph_3P)AuCl/AgOTf$	2.0	THF	–	20	–	60	trace	–
10	$(Ph_3P)AuCl/AgOTf$	2.0	CH_3CN	–	10	–	83	–	–
11	$(Ph_3P)AuCl/AgOTf$	0.2	CH_3CN	–	10	–	86	–	–
12	$(Ph_3P)AuCl/AgOTf$	–	CH_3CN	–	10	–	85	–	–
13	AgOTf	–	CH_3CN	–	120	95	–	–	–
14	AgOTf	0.2	CH_3CN		120	92	–	–	–
15	$(IPr)AuCl/AgOTf$	2.0	CH_2Cl_2	–	5	–	–	78	–
16	$(IPr)AuCl/AgNTf_2$	2.0	CH_2Cl_2	–	5	–	–	63	–
17	$(IPr)AuCl/AgSbF_6$	2.0	CH_2Cl_2	–	5	–	–	65	–
18	$(IPr)AuCl/AgOTf$	2.0	CH_2Cl_2	PTSA	5+10[f]	–	–	n.d.[g]	51
19	$(IPr)AuCl/AgOTf$	2.0	CH_2Cl_2	MsOH	5+10[f]	–	–	n.d.[g]	trace
20	$(IPr)AuCl/AgOTf$	2.0	CH_2Cl_2	HCl[e]	5+10[f]	–	–	n.d.[g]	68
21	$(IPr)AuCl/AgOTf$	2.0	toluene	HCl[e]	5+10[f]	–	–	n.d.[g]	20
22	$(IPr)AuCl/AgOTf$	2.0	CH_3CN	–	30	50	–	30	–
23	$(IPr)AuCl/AgOTf$	2.0	$CHCl_3$	HCl[e]	5+10[f]	–	–	n.d.[g]	77

[a] For more reaction conditions tested, see Supporting Information. [b] The reactions were carried out on a 0.4 mmol scale in 2 mL of solvent. [c] Yield of isolated product. [d] 2.0 equiv of H_2O were added instead of MeOH. [e] 37% HCl aq. [f] Reaction time for the second step. [g] Not detected.

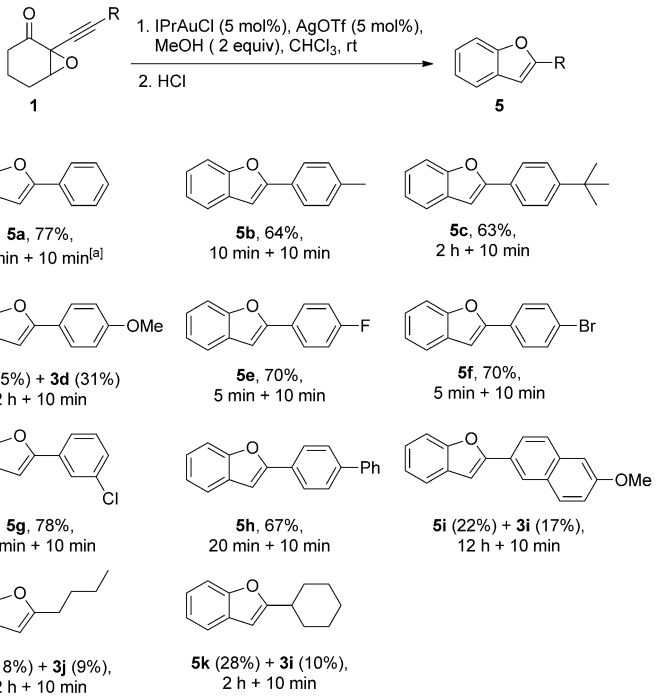
With the optimized conditions in hand, we first examined the scope of the reaction for the synthesis of 6,7-dihydrobenzofuran-4(5*H*)-ones. However, when the reactions were carried out without MeOH, complete conversion was not detected after 4 h (Scheme 3, **3b** and **3c**). Thus, 0.2 equivalents of MeOH were used in addition to the standard conditions. As shown in Scheme 3, the substituents at the acetylenic terminus could be aryl or alkyl groups. Aromatic substituents usually afforded the corresponding products in good yields. Substrate **1d**, bearing a strongly electron donating group, was an exception. It delivered only a moderate yield of product accompanied by a long reaction time (Scheme 3, **3d**). When the aromatic alkynes were replaced by alkyl alkynes, the corresponding products were only obtained in moderate yields (Scheme 3, **3j** and **3k**).



Scheme 2. Representative examples of the importance of the addressed structures: tyrolobibenzyls and the synthesis of angelicins.



Scheme 3. Scope of the reaction for the synthesis of 6,7-dihydrobenzofuran-4(5*H*)-ones. [a] The reactions were carried out without MeOH for 4 h at room temperature.



Scheme 4. Scope of the one-pot benzofuran synthesis. [a] Reaction time for the first/second step.

The one-pot transformation into benzofurans was also examined (Scheme 4). In most cases, substrates with aryl-substituted alkyne groups showed high selectivity and afforded the desired benzofurans in moderate to good yields. In accordance with the above results, a lower yield and incomplete conversion were observed with an electron-donating methoxyl group at the arene (Scheme 4, **5d**). Substrates bearing a naphthyl group or alkyl groups also showed low selectivity and partly decomposed under standard conditions (Scheme 4, **5i**–**5k**).

To obtain an unambiguous structural assignment for a compound **4**, **4f** was oxidized to ketone **6**, a solid that allowed us to grow single crystals suitable for an X-ray diffraction analysis. The solid-state molecular structure of **6** is depicted in Figure 1.[9]

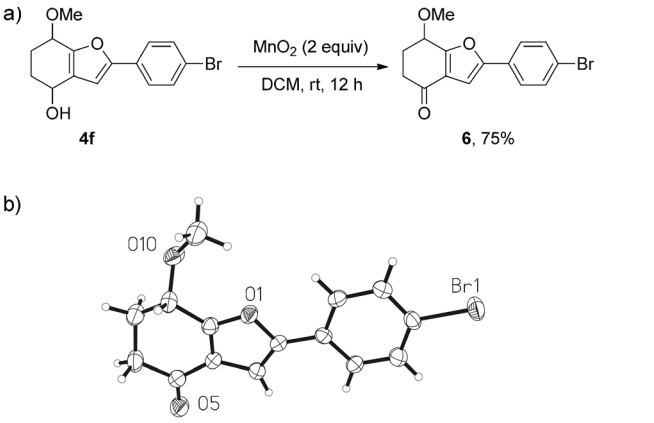
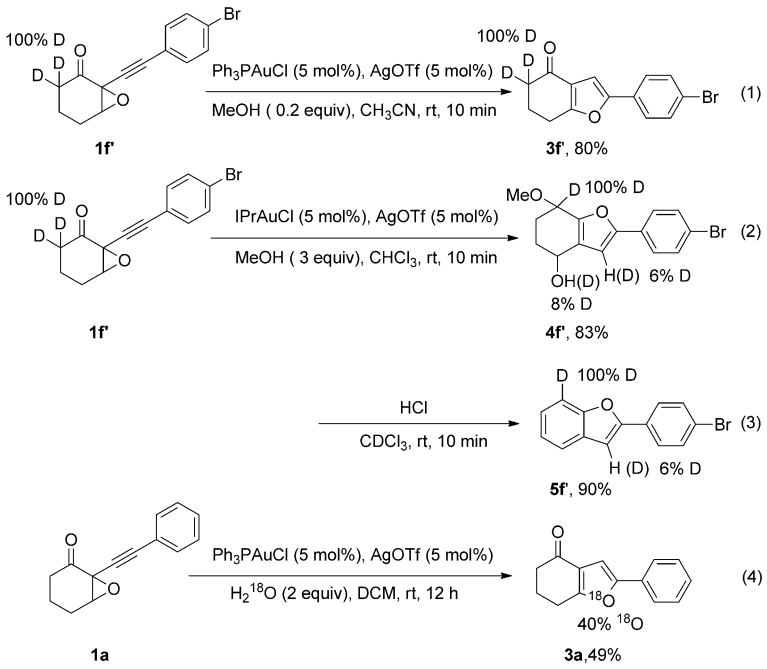


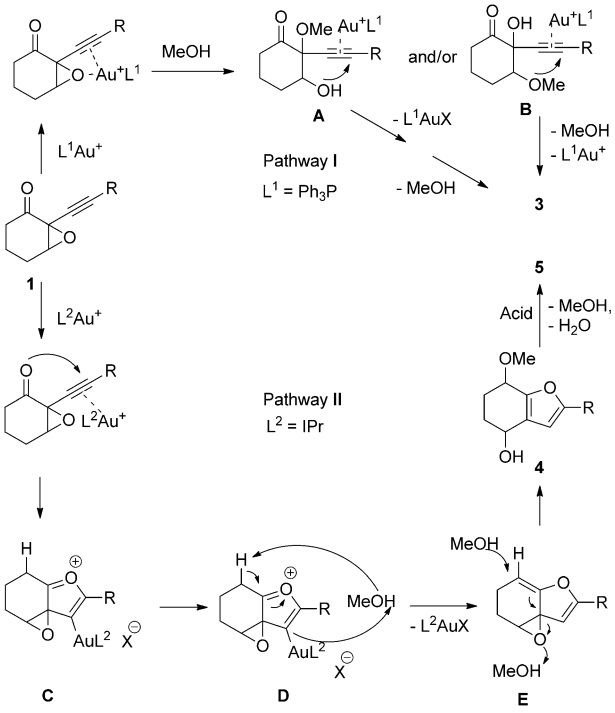
Figure 1. a) Transformation of **4f** into **6** and b) molecular structure of **6** in the solid state.

To investigate the mechanism of the transformations, deuterated substrate **1f′** was prepared and converted under the two reaction conditions; **3f′** was obtained in 80% yield and with complete preservation of the labeling in the position α to the carbonyl group [Scheme 5, Eq. (1)]. Treatment of **1f′** with (IPr)AuOTf and three equivalents of MeOH in $CHCl_3$ for 10 min afforded **4f′** in 83% yield, in which part of the deuterium had migrated to the hydroxyl group and to the 2-position of the furan [Scheme 5, Eq. (2)]. Compound **4f′** was subsequently treated with HCl, and deuterated benzofuran **5f′** was obtained in 90% yield [Scheme 5, Eq. (3)]. By treating **1a** with $H_2{}^{18}O$ in the present of (PPh_3)AuOTf, **3a** was obtained with 40% ^{18}O labeling [Scheme 5, Eq. (4)].

According to the results of the labeling experiments together with related transformation in the literature,[10] two plausible pathways are reasonable (Scheme 6). On pathway I, Ph_3P acts as the ligand. The epoxide coordinates to the catalyst and is attacked by MeOH, which affords intermediate **A** and/or intermediate **B**. After cyclization and subsequent elimination, the final product **3** is obtained. The second pathway can be addressed by changing the ligand from Ph_3P to IPr. On this pathway, the triple bond coordinates to the activated catalyst but, instead of the epoxide opening, the carbonyl oxygen atom acts as a nucleophile which generates intermediate **C**. A subsequent 1,2-hydride shift then affords vinyl gold intermediate **D**. In the presence of MeOH, the catalyst is regenerated and, at the same time, intermediate **E** is formed, which subsequently undergoes rearrangement to compound **4**.[11] After aromatization by elimination of MeOH and H_2O, benzofuran **5** is obtained as final product.



Scheme 5. Deuterium labeling experiments. D/H ratio was determined by NMR analysis and ^{18}O by HRMS analysis.



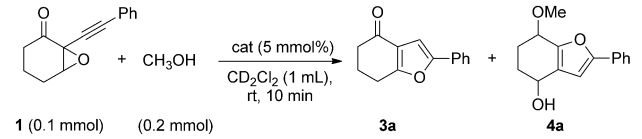
Scheme 6. Plausible pathways for the transformations.

To gain insight into the ligand properties,[12] different ligands were then examined. The ratios of **3a** to **4a** in dependence on the ligands are summarized in Table 2. Several trends can be readily identified: 1) electron-withdrawing ligands decrease the electron density at the metal center, and the thus-formed harder Lewis acids prefer epoxide opening to coordinating to the softer triple bond. This mode leads to furan product **3a** (Table 2, entries 1 and 2), while soft acids (electron-donating ligands) mainly afford product **4a** (which is transformed into **5a** under the reaction condition) by activating the triple bond through π activation rather than epoxide opening (Table 2, entry 3). 2) All of the P-coordinated gold catalysts, including that with a secondary phosphine oxide,[13] tend to be less alkynophilic, and therefore epoxide opening is the initial reaction step, which delivers mainly furan product **3a** (Table 2, entries 4–11), while C-coordinated gold catalysts tend to activate the triple bond as initial reaction step, which leads to **4a** as main product (Table 2, entries 12–16). 3) In line with the above observations, among the P-coordinated gold catalysts, electron-deficient ones show high selectivity for the furan synthesis (Table 2, entries 8, 10, and 11), while electron-rich ones deliver only a mixture of the two compounds (Table 2, entries 4–7). The only exception is the tris(-pentafluorophenyl)phosphine (**L6**)-ligated gold catalyst, which gave a mixture of **3a** and **4a** in a ratio of 1/0.8 despite its electron-withdrawing nature (Table 2, entry 9). This might be rationalized by the special effect of fluoride. The ratio of **3a** to **4a** (which was transformed into **5a** under the reaction conditions) was dramatically increased by addition of catalytic amounts of *p*-toluenesulfonic acid in combination with the IPr ligand (Table 2, entry 16). The added Brønsted acid can activate the epoxide, which changes the **3a/4a** ratio significantly. This further indicates that, in the absence of an additionally added acid, (IPr)AuOTf tends to active the triple bond in preference to the epoxide.

Conclusion

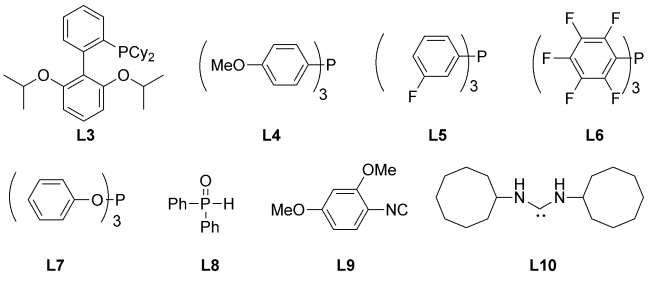
We have developed new chemoselective gold(I)-catalyzed transformations of 1-(arylethynyl)-7-oxabicyclo[4.1.0]-heptan-2-ones. Two different products can be obtained from the same starting material, namely, 6,7-dihydrobenzofuran-4(5*H*)-ones and benzofurans, both of which are potent building blocks for synthetic chemistry. In this intramolecular competition the two potential nucleophiles are the carbonyl and epoxide oxygen atoms. Changing the ligand of the gold catalyst enables complete control of the selectivity, which is an important aspect for selectivity control in homogeneous gold catalysis.

Table 2. Investigation of the ligand effect.



Entry	Catalyst[a] (5 mol%)	Conversion [%][b]	NMR yield (**3a**+**4a**) [%][b]	**3a**/**4a**[b]
1	$AuCl_3$ (5 mol%)/ AgOTf (15 mol%)	100[c]	75	>1/0.01
2	AuCl/AgOTf	60[c]	30	1/0.08
3	AuCl	30	25	1/1.9[e]
4	(Ph_3P)AuCl/AgOTf	100	91	1/0.3
5	Cy_3PAuCl/AgOTf	100	88	1/0.3
6	**L3**AuCl/AgOTf	100	88	1/0.8
7	**L4**AuCl/AgOTf	100[c]	76	1/0.4
8	**L5**AuCl/AgOTf	100	95	1/0.04
9	**L6**AuCl/AgOTf	100[c]	73	1/0.8
10	**L7**AuCl/AgOTf	100[c]	80	1/0.01
11	**L8**AuCl/AgOTf[f]	100[c]	70	>1/0.01
12	**L9**AuCl/AgOTf	40[c]	10	1/3.9
13	**L10**AuCl/AgOTf	100[c]	75	1/2
14	(IPr)AuCl/AgOTf	100	90	<1/40
15	(IMes)AuCl/AgOTf[g]	100[c]	78	1/3
16	(IPr)AuCl/AgOTf/ PTSA[d]	100	88	1/6.4[e]

[a] Ligands **L3**–**L10**.



[b] The conversion and **3a**/**4a** ratio were determined by NMR analysis, and dibromomethane was used as internal standard. [c] Some undetermined byproducts were observed. [d] 5 mol% *p*-toluenesulfonic acid (PTSA) was added. [e] **3a**/**5a** ratio. [f] **L8**AuCl[14] was generated in situ by stirring diphenylphosphine oxide and (Me_2S)AuCl in CD_2Cl_2 for 15 min. [g] IMes = 1,3-dimesitylimidazol-2-ylidene.

Acknowledgements

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[8] Silver salts can catalyze the reaction with or without MeOH in CH_2Cl_2 with lower yields. See Supporting Information for more reaction conditions examined.

[9] CCDC-936447 (**6**) 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.

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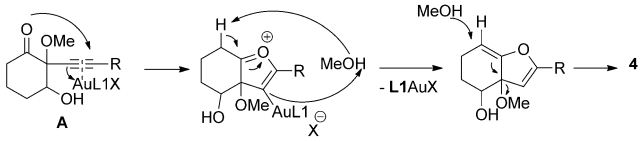
[11] As one of the referees suggested, **4** can also be formed via intermediate **A**:



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