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Gold-catalyzed rearrangement of substituted allyl aryl ethers

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Dedicated to Professor Thomas R. Hoye on the occasion of his 60th birthday

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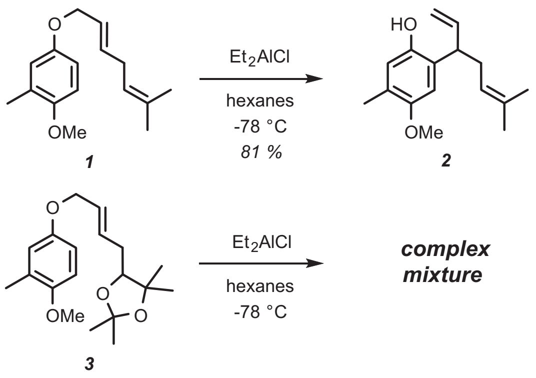
ABSTRACT

Triphenylphosphinegold(I) complexes catalyze the Claisen-type rearrangement of aryl allyl ethers to the corresponding branched and linear products. The product distribution depends on the olefin geometry of the allylic ether. Stereochemical transfer experiments support an ionic mechanism.

The [3,3]-sigmatropic rearrangement of allyl aryl ethers, more commonly known as the aromatic Claisen rearrangement, has been an important C–C bond-forming reaction for nearly a century.[1] Lewis acid catalysts,[2] most notably BCl_3[3,4] and Et_2AlCl,[5] $TiCl_4$[6] and $SnCl_4$[7] obviate the high temperatures required for the thermal rearrangement, but must be used in stoichiometric quantities and are not compatible with some functional groups. Other Lewis acids (e.g., $RuCl_3$/AgOTf/CuOTf,[8] $IrCl_3$/AgOTf,[8b] and $Bi(OTf)_3$[9]) and guanidinium hydrogen bond donors[10] may be used in sub-stoichiometric quantities but have only been examined with simple monosubstituted allyl ethers. We became interested in the aromatic Claisen rearrangement in the context of our synthesis of heliannuols C and E.[11] Although Et_2AlCl functioned well as a catalyst for the rearrangement of diene **1** to yield *ortho*-allyl phenol **2**,[11] the use of this catalyst with substrates like **3** containing more functionalized allyl side chains led to complex mixtures of products resulting from side reactions of the acetal group.[12]

The use of Au(I) complexes as carbophilic π-type Lewis acids[13] for a variety of functional group-tolerant synthetic transformations has exploded over the last decade.[14] The use of Au(I) complexes to catalyze a progargyl Claisen rearrangement[15] and the preparation of dihydrobenzofurans from simple allyl aryl ethers[16] prompted us to examine the rearrangement of *substituted* allyl aryl ethers using gold complexes.



In early experiments, we were gratified to find that treatment of ether *Z*-**4a**[17] with $Ph_3PAuOTf$ (10 mol %, prepared in situ from Ph_3PAuCl and AgOTf) in 1,2-dichloroethane resulted in good yields of [3,3]-rearrangement product **5a** along with small amounts of the regioisomeric product **6a** (Scheme 1 and Table 1, entry 1).[18,19] The constitution of **6a** was deduced through observation of an nOe between the *para*-methyl group and the benzylic methylene as shown. Reaction of *E*-**4a** under the same conditions also provided **5a** and **6a** along with the formal [1,3]-rearrangement product **7a** (Scheme 1 and Table 1, entry 2). Using the branched allyl aryl ether **8** in this reaction gave an excellent yield of **7a**.

By way of comparison, treatment of **4a** with Et_2AlCl resulted in a much lower selectivity for **5a** (entries 3 and 4), while BCl_3[20] gave more **6a**, but in poor yield (entries 5 and 6). Using BCl_3 as catalyst also gave additional products that were not fully characterized, but appeared to be regioisomers of **6a** and **7a** based on analysis of their ^{1}H NMR spectra. Use of either Ph_3PAuCl or AgOTf alone resulted in

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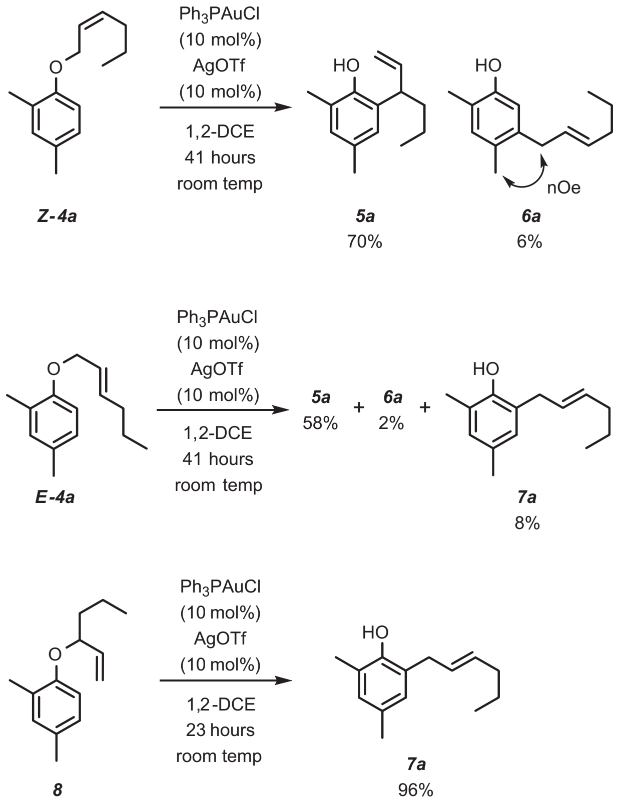

Scheme 1. Rearrangements of substituted allyl aryl ethers with $Ph_3PAuOTf$.

no conversion of *Z*-**4a** (entries 7 and 8), but treatment of *Z*-**4a** with Brønsted acids resulted in complex product mixtures containing only trace amounts of **5a** and **6a** (entries 9 and 10).[20] Combining Brønsted acids with Au(I) or Ag(I) produced complex mixtures of products that, based on analysis of ^1H NMR spectra, consisted predominantly of the cyclized dihydrobenzofuran product **9** (entries 11–14).[8,16,20]

The effect of the counter ion provided by the Ag(I) salt on the rearrangement reaction was also examined. AgOTf gave the best yield of Claisen product **5a**, with $AgNTf_2$ and $AgBF_4$ being somewhat less effective (entry 1 vs entries 15–18). It is noteworthy that in these cases, *E*-**4a** gave a higher conversion than did *Z*-**4a**, but produced more of the linear rearrangement product **7a**. Use of $AgClO_4$ with triphenylphosphine gold chloride resulted in variable reaction rates. At short reaction times, good yields of **5a** could be obtained, but at long reaction times produced only dihydrobenzofuran **9** (entry 13). We attribute this result to adventitious protons from water due to the hygroscopic nature of the silver salt.[21] In this case, addition of Proton Sponge® (3 mol %) prevented formation of **9**, but rearrangement rates were still variable. The hexafluorophosphate, acetate, trifluoroacetate, and *p*-toluenesulfonate silver salts were ineffective in promoting the rearrangement of **4a** (entries 20–26).

Although the Ph_3PAuCl/AgOTf catalyst system worked well, we also tried other gold(I) complexes as catalysts for the rearrangement reaction. Au(I) complexes based on a hindered, electron-rich biphenylbis(dialkyl)phosphine ligand (**10–12**) resulted in little or no conversion of **4** (entries 27–31).

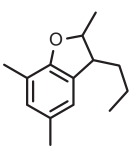

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Table 1
Rearrangements of ether **4a**[17]

Entry	Catalyst	*Z* or *E* **4a**	Conversion[b]	Yield[a] (%)		
				5a	**6a**	**7a**
1	Ph_3PAuCl/AgOTf	*Z*	100	70	6	–
2	Ph_3PAuCl/AgOTf	*E*	100	(58)	2	(8)
3	Et_2AlCl[c]	*Z*	100	(46)	10	(6)
4	Et_2AlCl[d]	*E*	100	14	10	–
5	BCl_3[d,e]	*Z*	100	Trace	10	5
6	BCl_3[d]	*E*	100	Trace	32	23
7	Ph_3PAuCl	*Z*	0			
8	AgOTf	*Z*	0			
9	TfOH	*Z*	100	Complex mixture[f]		
10	Tf_2NH	*Z*	100	Complex mixture[f]		
11	AgOTf/TfOH	*Z*	100	Complex mixture[f]		
12	$AgNTf_2$/Tf_2NH	*Z*	100	Complex mixture[f]		
13	Ph_3PAuCl/TfOH	*Z*	100	Complex mixture[f]		
14	Ph_3PAuCl/Tf_2NH	*Z*	100	Complex mixture[f]		
15	Ph_3PAuCl/$AgNTf_2$	*Z*	39	37	Trace	Trace
16	Ph_3PAuCl/$AgNTf_2$	*E*	100	(30)	5	(30)
17	Ph_3PAuCl/$AgBF_4$	*Z*	65	(50)	4	(4)
18	Ph_3PAuCl/$AgBF_4$	*E*	83	(36)	6	(31)
19	Ph_3PAuCl/ $AgClO_4$[g]	*Z*	100	65	–	–
20	Ph_3PAuCl/$AgPF_6$	*Z*	28	Trace	–	–
21	Ph_3PAuCl/$AgPF_6$	*E*	32	6	–	–
22	Ph_3PAuCl/AgOAc	*Z*	0			
23	Ph_3PAuCl/AgTFA	*Z*	0			
24	Ph_3PAuCl/AgTFA	*E*	0			
25	Ph_3PAuCl/AgOTs	*Z*	0			
26	Ph_3PAuCl/AgOTs	*E*	0			
27	**10**/AgOTf	*Z*	0			
28	**11**/AgOTf	*Z*	28	8	–	–
29	**11**/AgOTf	*E*	46	31	Trace	–
30	**12**	*Z*	0			
31	**12**	*E*	0			
32	**13**/AgOTf	*Z*	100	57	17	Trace
33	**14**/AgOTf	*Z*	66	51	6	Trace
34	**14**/AgOTf	*E*	28	16	–	Trace
35[h]	$(EtO)_3PAuOTf$	*Z*	60	35	–	–
36[h]	$(EtO)_3PAuOTf$	*E*	26	21	–	–
37[i]	$AuCl_3$/AgOTf	*Z*	100	42	–	–
38[i]	$AuCl_3$/AgOTf	*E*	100	(6)	9	(10)
39[j]	$AuCl_3$	*Z*	100	44	8	–
40[j]	$AuCl_3$	*E*	100	(25)	24	(8)

[a] Yields reported are for isolated material from silica gel chromatography. Yields in parentheses are based on integration of ^1H NMR spectrum of the inseparable mixture of **5a** and **7a**.

[b] Based on amount of recovered **4a**.

[c] 2 equiv of Lewis acid at −78 °C.

[d] 1.1 equiv of Lewis acid at −78 °C.

[e] A regioisomer of **6a** [tentatively identified as 2,4-dimethyl-3-(2-hexenyl)phenol] was also isolated (32%).

[f] Based on ^1H NMR spectrum analysis, major components of this inseparable mixture include diastereomeric dihydrobenzofurans **9** (see Refs. [16,20]).

[g] 2 h reaction time.

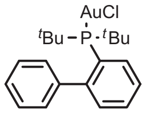
[h] Prepared in situ from $(EtO)_3P$ (10 mol %), Me_2SAuCl (10 mol %) and AgOTf (10 mol %).

[i] $AuCl_3$ (10 mol %) and AgOTf (30 mol %).

[j] $AuCl_3$ (10 mol %).

The more electron deficient tris(4-trifluoromethylphenyl) phosphine gold complex (**13**) gave good conversion of *Z*-**4a** to products (entry 32). The *N*-heterocyclic carbene gold complex **14** gave only moderate yields of **5** (entries 33 and 34). Use of a phosphite ligand for gold(I) gave incomplete conversion, but high selectivity for formation of **5a** (entries 35 and 36). Gold(III) catalysts[16] gave complete conversion of **4a**, but relatively low yields of rearrangement products (entries 37–40). Thus, the triphenylphosphine gold chloride/silver triflate system remained the catalyst of choice.

A brief survey of solvents showed that weakly polar solvents like 1,2-dichloroethane and dichloromethane gave the best yields of rearranged products **5–7**. Nonpolar solvents such as hexanes and toluene gave only trace amounts of the rearranged products even after extended reaction times at room temperature. Polar



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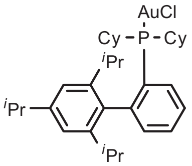

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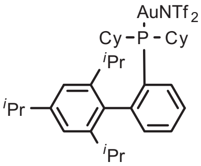

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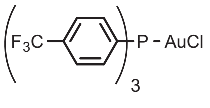

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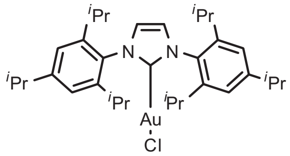

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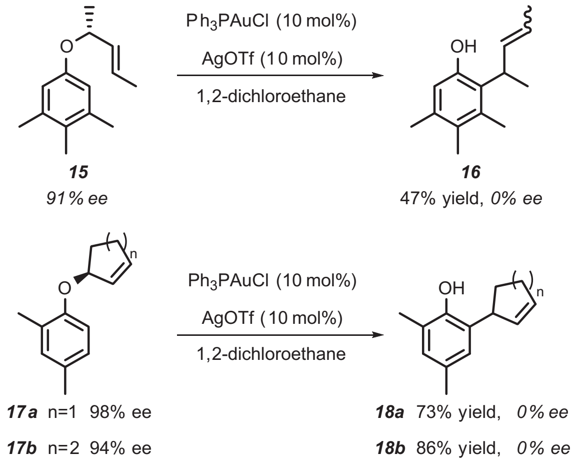
solvents like nitromethane were ineffective and only the starting ether **4** was recovered. Catalyst loading was also examined briefly using substrate *E*-**4a**. Use of 10 mol % Ph_3PAuCl + AgOTf gave complete conversion after 36 h, but reducing the amount of catalyst to 5 mol % gave only 71% conversion after 72 h. Further reducing the catalyst loading to 2 mol % gave 65% conversion after 72 h.

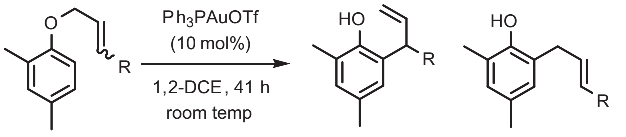
From these results, it was clear that the Au(I)-catalyzed rearrangement of **4** cannot follow an entirely concerted mechanism. At minimum, a competing ionic pathway is needed to explain the isolation of **6** and the formal [1,3]-rearrangement product **7** from some reactions. The observation that the *Z*-isomers of **3** produce higher percentages of the formal [3,3]-rearrangement product **5** than the corresponding *E*-isomers suggested that the olefin geometry is important in dictating the reaction path. We next conducted several experiments to refine our mechanistic understanding of the reaction. When purified **5a** was resubjected to the reaction conditions, a very slow conversion to cyclic product **9** was observed by ^1H NMR analysis, but no **6** or **7** was observed, indicating the reaction is not reversible and that **5** is not an intermediate that produces **6** or **7**.

Stereochemical transfer experiments were conducted using optically active substrates **15** and **17** (Scheme 2).[22] When **15** and **17** were subjected to the rearrangement conditions, modest to good yields of rearranged products **16**[22] and **18** were obtained, but in all cases the products were racemic according to chiral GC analysis, ruling out any possibility of a competing concerted rearrangement pathway. Thus, it seems clear that this transformation proceeds via a solvent separated ion pair mechanism.



Scheme 2. Rearrangements of optically active allyl aryl ethers with $Ph_3PAuOTf$.

Table 2
Effect of olefin geometry and steric bulk on the Au(I)-catalyzed rearrangement of substituted allyl aryl ethers **4**

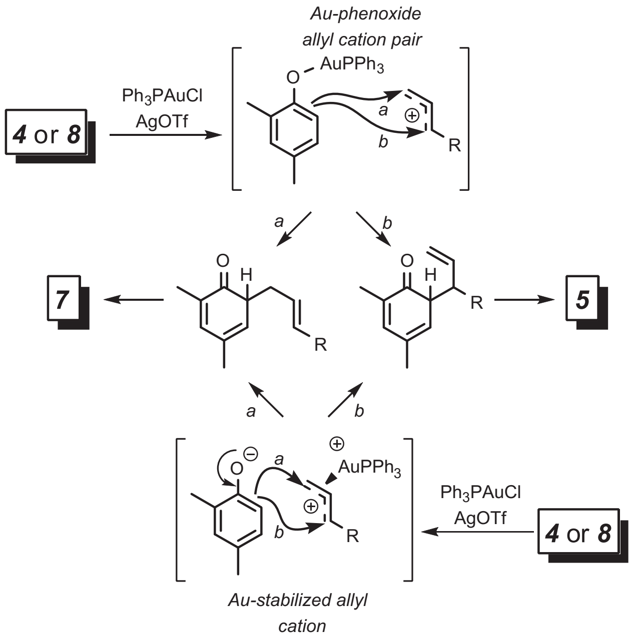


4 **5** **7**

Entry	Substrate	R	Conversion[b]	Yield (%)[a]	
				5	**7**
1	*Z*-**4b**	n-C_5H_{11}	100	56	—
2	*E*-**4b**	n-C_5H_{11}	100	57	—
3	*Z*-**4c**	Ph	100	(21)	(42)
4	*E*-**4c**	Ph	100	—	69
5	*Z*-**4d**	*t*-Bu	0[c]		
6	*E*-**4d**	*t*-Bu	100[d]	—	56

[a] Yields reported are for isolated material from silica gel chromatography. Yields in parentheses are based on integration of ^1H NMR spectrum of the inseparable mixture of **5** and **7**.
[b] Based on amount of recovered **4**.
[c] *Z*-**4d** was recovered quantitatively after 72 h. Reaction time = 120 h.
[d] Reaction time = 65 h; 2,4-dimethylphenol (31%) also isolated.

We have found that the steric bulk of the allyl substituent and the stereochemistry of the olefin has significant effects on the product distribution in the Au(I)-catalyzed rearrangement of allyl aryl ethers **4** (Table 2). Good yields of branched products were obtained from straight chain-substituted substrates **4b** (entries 1 and 2). The phenyl-substituted substrates **4c** gave good yields of rearranged products, but relatively little branched product **5c** was formed from *Z*-**4c**, and *E*-**4c** produced only the linear product **7c** (entries 3 and 4). The *tert*-butyl substrate *Z*-**4d** failed to produce any rearrangement products, allowing the starting material to be recovered quantitatively (entry 5). Conversely, ether *E*-**4e** reacted completely, but produced only the linear rearrangement product **7d** along with a significant amount of 2,4-dimethylphenol (entry 6).



Scheme 3. Mechanistic hypotheses for Au(I)-catalyzed rearrangement of allyl aryl ethers.

We have two mechanistic hypotheses with respect to the role of the gold catalyst.[23] It is possible that the gold cation coordinates to the electron-rich aryl ring, promoting cleavage of the allyl group and formation of a gold phenoxide that traps the allylic cation (Scheme 3, top).[24] Alternatively, the gold cation may coordinate to the olefin of the allyl aryl ether and lead to a gold-stabilized allylic cation, that is subsequently trapped by the phenoxide (Scheme 3, bottom). If the gold catalyst coordinates to the ether oxygen to form a 'free' allylic carbocation intermediate, then substrates *Z*-**4a**, *E*-**4a**, and **8** should all give the same products in similar ratios.[25] Thus, we favor a mechanism that involves interaction between the gold catalyst and the allyl cation intermediate.

In summary, Au(I) complexes catalyze the rearrangement of allyl aryl ethers to produce both formal [3,3] and [1,3]-rearrangement products through an ionic mechanism. Further investigation of the reaction mechanism with respect to the role of the gold catalyst is on going, as well as studies aimed at determining the scope and limitations of this reaction, particularly with respect to functional group tolerance.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.078.

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