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Gold-Catalyzed Benzylation of Arenes and Heteroarenes

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Abstract: Friedel–Crafts type benzylation of arenes and heteroarenes with benzylic acetates, alcohols, and carbonates is effectively promoted under mild reaction conditions using catalytic amounts of gold salts. The resulting 1,1-diarylalkanes and 1-aryl-1-heteroarylalkanes are obtained in high yields and with high selectivity. The utility of the method is demonstrated by a short synthesis of beclobrate {ethyl 2-[4-(4-chlorobenzyl)-phenoxy]-2-methylbutyrate (**3**)}, a fibric acid derivative.

Keywords: arene functionalization; arylation; benzylation; Friedel–Crafts reaction; homogeneous catalysis; gold

The application of gold salts and complexes is an emerging area in organometallic chemistry and organic synthesis.[1] In addition to industrially important oxidation processes, which proceed in the presence of heterogeneous gold catalysts,[2] more and more organic reactions are discovered to be catalyzed by homogeneous gold complexes. So far, mainly hydrogenations,[3] isomerizations,[4] aldol reactions,[5] reactions of alkynes with nucleophiles,[6] reactions of propargyl or allenyl ketones,[7] additions of electron-rich arenes to methyl vinyl ketones,[8] and domino processes with isobenzopyrylium cation intermediates[9] have been discovered. Recently published articles include the synthesis of oxazoles,[10] domino hydroarylation and cycloisomerization reactions,[11] transformations of alkynyl epoxides to furans[12] and the benefits of N and N,O ligands in gold-catalyzed reactions.[13]

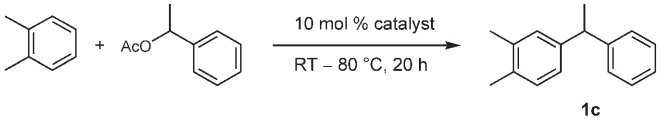
Based on our interest in the benzylation of arenes and heteroarenes,[14,15] we initiated a program to search for gold catalysts for Friedel–Crafts-like reactions. Obviously, such direct CH-functionalization reactions of arenes avoid the necessity of introducing activating groups or protection and deprotection steps. Thus, in general C–C bonds can be formed more efficiently compared to other methods, e.g., palladium-catalyzed coupling reactions of aryl halides and benzylmagnesium reagents.[16]

The direct benzylation of simple (and in general non-functionalized) arenes has been described mainly with benzyl halides (benzyl chloride, benzyl bromide) as substrates.[17] However, these reactions have drawbacks such as the necessity of drastic conditions (high temperature and strong acidic conditions). In addition, significant amounts of salt by-products (resulting from the neutralization of the by-products HCl or HBr) are formed.

Previous to our work only few transition metal catalysts based on palladium and ruthenium have been described for the benzylation of arenes.[18] While palladium complexes have been used only on a stoichiometric basis,[19] ruthenium complexes work only at higher temperature (200 °C) and gave the corresponding 1,1-diarylmethanes in low to mediocre yield (22–77%).[20] Very recently, we demonstrated that salts of precious metals, such as $IrCl_3$, $RhCl_3$, H_2PtCl_6, and even $FeCl_3$ are able to catalyze the addition of benzylic acetates to arenes and heteroarenes with high yield and selectivity under ambient conditions.

In order to improve these reactions further on, we are interested in alternative catalyst systems, which can be applied in the synthesis of all kinds of 1,1-diarylmethanes. Here, we describe the arylation reaction of benzyl alcohols and benzyl acetates leading to functionalized 1,1-diarylalkanes in the presence of gold salts. Applying this novel catalyst benzylation of activated and non-activated arenes and heteroarenes proceeds with high yield and selectivity often under mild conditions.

Looking for new catalysts, the reaction of *o*-xylene and 1-phenylethyl acetate was studied as a model reaction (see Scheme 1 and Table 1). Here, different gold salts, catalyst concentrations and solvents were tested at room temperature to 80 °C. Table 1 shows a summary of the obtained results.



Scheme 1. Reaction of *o*-xylene and 1-phenylethyl acetate.

Table 1. Screening of the model reaction.

Entry	Catalyst	mol % Catalyst	Solvent	T [°C]	Yield [%][a]	Conversion [%][b]
1	$HAuCl_4$	10	*o*-xylene	RT	99	100
2	$HAuCl_4$	10	*o*-xylene	80	99	100
3	$AuCl_3$	10	*o*-xylene	RT	95	100
4	$AuPPh_3Cl$	10	*o*-xylene	80	5	39
5	$AuPPh_3Cl$/AgOTf (1:1)	10	*o*-xylene	80	42	100
6	$HAuBr_4$	10	*o*-xylene	80	97	100
7	$HAuCl_4$	5	*o*-xylene	RT	75	100
8	$HAuCl_4$	1	*o*-xylene	RT	11	26
9	$AuCl_3$	10	CH_3NO_2	80	99	100
10	$AuCl_3$	10	ethyl acetate	80	99	100
11	$AuCl_3$	10	CH_2Cl_2	80	20	76
12	$AuCl_3$	10	CH_3CN	80	90	100

Reaction conditions: 10 mL *o*-xylene or 10 mmol *o*-xylene in 8.8 mL solvent, 0.5 mmol 1-phenylethyl acetate, 1–10 mol % catalyst, room temperature to 80 °C, 20 h.
[a] GC yield.
[b] GC conversion based on 1-phenylethyl acetate.

At room temperature excellent results are obtained in the presence of 10 mol % $HAuCl_4$ (99% of **1c**) and $AuCl_3$ (95% of **1c**) (Table 1, entries 1 and 3). In addition, also $AuPPh_3Cl$ gave a significant yield of the desired product (42%), but only with added silver triflate (Table 1, compare entries 4 and 5). The use of 5 mol % (1 mol %) $HAuCl_4$ at room temperature afforded 75% (11%) yield of **1c** (Table 1, entries 7 and 8).[21] Noteworthy, the benzylation of *o*-xylene can be carried out in excellent yield in polar solvents like CH_3NO_2, ethyl acetate, and CH_3CN (Table 1, entries 9, 10, and 12).

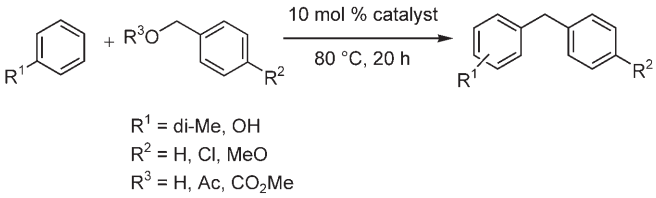
Having reliable catalysts for the benzylation of *o*-xylene in hand, we were interested in the benzylation of other arenes and heteroarenes (Table 2) and in the use of different benzylating agents (Table 3).

Due to its easier handling most of the reactions were performed by applying $HAuCl_4$ as catalyst. As expected a variety of electron-rich arenes such as *o*-xylene (99%, Table 2, entry 3), anisole (99%, Table 2, entry 4), 1,4-dimethoxybenzene (99%, Table 2, entry 5), 4-chloroanisole (99%, Table 2, entry 6), 2-chloroanisole (99%, Table 2, entry 7), and 2-iodoanisole (90%, Table 2, entry 8) gave the corresponding products in good to excellent yields. The reaction of 2-anisaldehyde (63%, Table 2, entry 9) illustrates that activation occurs chemoselectively at the benzyl position and not at the formyl group.

In addition, heteroarenes such as 3-methylthiophene (82%, Table 2, entry 10), 2,5-dimethylfuran (87%, Table 2, entry 11) and 2-acetylfuran (82%, Table 2, entry 12) react well.

In general, the regioselectivity of the reaction is good to excellent (86 to >99%). However, in the case of 3-methylthiophene three isomers (2-/4-/5-positions) were obtained in a ratio of 62/7/3 (Table 2, entry 10).

Next, we set out to study the scope and limitations of the benzylating agent in more detail (Scheme 2; Table 3). As shown in Table 3 in addition to 1-phenylethyl acetate also *sec*-phenylethanol, benzyl alcohol, benzyl acetate, benzyl methyl carbonate, 4-methoxybenzyl acetate, 4-methoxybenzyl alcohol, 4-methoxybenzyl methyl carbonate, and 4-chlorobenzyl alcohol react with *o*-xylene in the presence of $HAuCl_4$ or $AuCl_3$ at 80 °C to give the corresponding benzylated products.

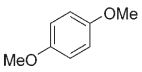
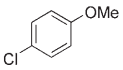


Scheme 2. Benzylation of *o*-xylene with different benzylating reagents.

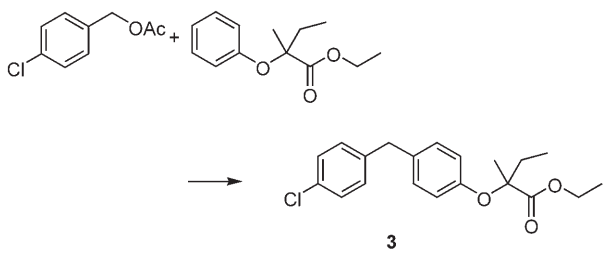
There is no general trend observed for the different benzylating reagents. While benzyl alcohol gave the best result (60%) among the simple benzyl derivatives (Table 3, entries 2–4), 1-phenylethyl acetate (99%) and 4-methoxybenzyl methyl carbonate (59%) proved to be superior in case of the substituted benzylation reagents (Table 2, entry 3, Table 3, entries 1, 5–7).

Since many biologically active substances and current pharmaceuticals such as piritrexim, trimethoprim, avrainvilleol, papaverine, beclobrate or letrozole contain a 1,1-diarylmethane motif, we attempted to apply our benzylation method to the synthesis of an actual drug. Indeed, the reaction of ethyl 2-methyl-2-phenoxybutyrate[22] with commercially available 4-chlorobenzyl acetate in the presence of $HAuCl_4$ gave compound **3** in 90% yield (see Scheme 3). This product is known as beclobrate, a fibric acid derivative with potent hypolipidemic activity. Noteworthy, it is not necessary to apply a large excess of the arene in this reaction.

Table 2. Benzylation of arenes and heteroarenes.

Entry	Educt	Product	Yield [%][a]	Conversion [%][b]	Regioselectivity (*o/p*)
1		**1a**	52	100	14/86
2		**1b**	47	96	–
3		**1c**	99	100	< 1/99
4		**1d**	99	100	13/87
5[d]		**1e**	99	100	–
6		**1f**	99	100	< 1/99
7		**1g**	99	100	< 1/99
8[d]		**1h**	90	100	< 1/99
9		**1i**	63	100	< 1/99
10		**1j**	82	100	62/7/31[c]
11		**1k**	87	100	–
12[d]		**1l**	82	100	> 1/99

Reaction conditions: 10 mL educt, 0.5 mmol 1-phenylethyl acetate, 10 mol % $HAuCl_4$, 80 °C, 20 h.
[a] GC yield.
[b] GC conversion based on 1-phenylethyl acetate.
[c] 2-/4-/5-isomer.
[d] 10 mmol educt in 8 mL $MeNO_2$.



3
90% (o/p 42:58)

Reaction conditions: 1 mmol ethyl 2-methyl-2-phenoxybutyrate, 0.5 mmol 4-chlorobenzyl acetate, 2 mL $MeNO_2$, 10 mol% $HAuCl_4 \cdot n\,H_2O$, 80 °C, 20 h.

Scheme 3. Synthesis of beclobrate.

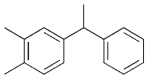
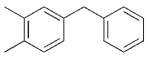
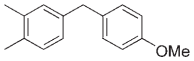
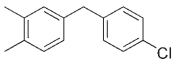
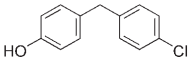
In conclusion, we have developed the first gold-catalyzed arylation of benzyl alcohols and carboxylates. Using Au catalysts an easy and general synthesis of 1,1-diarylmethanes and 1-aryl-1-heteroarylmethanes is possible. Typically reactions proceed under mild conditions (room temperature to 80 °C; no strong acid or base). The practical utility of this benzylation protocol is shown by the synthesis of the fibric acid derivative beclobrate.

Experimental Section

General Remarks

All reactions were carried out without any special precautions in air. ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX 400 spectrometer. Chemical shifts (δ) are given in ppm and refer as internal standard to the residual solvent ($CDCl_3$: 7.26 ppm) or TMS: 0.00 ppm. Gas chromatography was performed on a Hewlett Packard HP 6890 chromatograph with an HP5 column. Mass spectra were recorded on a AMD 402/

Table 3. Variation of the benzylating agent.

Entry	Product		R^3	Yield [%][a]	Conversion [%][b]	Regioselectivity (*o/p*)
1		**1c**	H	83	100	1/99
2		**2a**	Ac	30	39	1/99
3			H	60	100	1/99
4			CO_2Me	38	68	1/99
5[c]			Ac	58	100	1/99
6		**2b**	H	52	100	1/99
7			CO_2Me	59	100	1/99
8		**2c**	H	41	77	36/64
9[d]		**2d**	H	99	100	38/62

Reaction conditions: 10 mL educt, 0.5 mmol benzylating agent, 10 mol % $HAuCl_4$, 80 °C, 20 h.
[a] GC yield.
[b] GC conversion based on benzylating agent.
[c] $AuCl_3$ as catalyst.
[d] 10 mmol phenol in 8 mL $MeNO_2$.

3 mass spectrometer. Chemicals and solvents were purchased from Fluka and Aldrich and used as received.

General Procedure for the Benzylation of *o*-Xylene

In a pressure tube, 1-phenylethyl acetate (0.5 mmol) and catalyst (10 mol %, 0.05 mmol) were dissolved in *o*-xylene (5 mL). Then decane (50 μL) was added as internal GC standard. After stirring for 20 h aliquots were taken from the reaction mixture and subjected to GC analysis for determination of yield and conversion. For isolation of the products the reaction was quenched with water. The water phase was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and the solvents were distilled off. The product was purified by column chromatography on silica gel (70–230 mesh), eluent: *n*-heptane/ethyl acetate (50:1).

Characterization data for **1a**–**l**, **2a**–**d**, and **3** are listed in the Supporting Information.

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[21] For comparison: 1 mol % (10 mol % HBF_4 at room temperature leads to 3% (99%) of **1c**. The use of HBF_4 in polar solvents leads to lower yields compared to gold catalysts. For example the reaction of *o*-xylene with 1-phenylethyl acetate in the presence of 10 mol % HBF_4 in ethyl acetate (80 °C, 20 h) gives 23% yield of **1c** (with $AuCl_3$: 99% yield of **1c**, see Table 1, entry 10). In addition the reaction of phenol with 4-chlorobenzyl alcohol in the presence of 10 mol % HBF_4 in $MeNO_2$ (80 °C, 20 h) results in 38% yield of **2d** (with $HAuCl_4$: 99% yield of **2d**, see Table 3, entry 9).

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