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ARTICLE

Gold(I)-Catalysed Dehydrative Formation of Ethers From Benzylic Alcohols and Phenols

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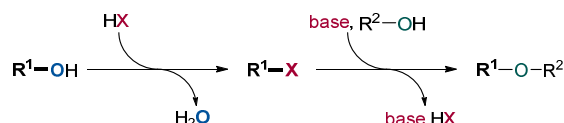
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We report the cross-dehydrative reaction of two alcohols to form unsymmetrical ethers using NHC-gold(I) complexes (NHC = *N*-heterocyclic carbene). Our progress in developing this reaction into a straightforward procedure is discussed in detail. The optimised methodology proceeds under mild reaction conditions and produces water as the sole by-product. The synthetic utility of this environmentally benign methodology is exemplified by the formation of a range of new ethers from readily available phenols bearing electron withdrawing substituents and secondary benzylic alcohols with various substituents. Finally, we present experimental results to account for the chemoselectivity obtained in these reactions.

Introduction

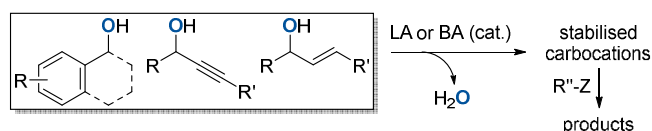
The formation of C-O bonds by means of alkylation and arylation reactions has emerged as a major objective in the construction of pharmaceutical compounds.¹ While the traditional Williamson ether synthesis represents a widely used approach, this multi-step procedure usually generates a stoichiometric amount of waste (Scheme 1).² When starting from two alcohol molecules, it requires the conversion of one alcohol into a halide or pseudo-halide leaving group. Once this group is eliminated in the substitution step, it needs to be separated from the product. These disadvantages have challenged chemists to develop novel greener procedures to effect the direct activation of alcohols for nucleophilic substitution.³ Such an approach would form water as the only by-product and would reduce the operational effort in accordance with Wender and Miller's guidelines for the "ideal synthesis" of new molecules.⁴ Consequently, hydroxide activation for nucleophilic substitution has been recognised as a key area for green chemistry research.⁵



Scheme 1 Conventional formation of ethers with poor atom-economy.

Because of the inherent difficulty of activating alcohols for S_N1 reactions, π -activated alcohols, such as propargylic and allylic alcohols were most commonly used in early reports.⁶⁻⁸ Benzylic

alcohols were later recognised as suitable substrates for this type of reaction.⁹ The structural arrangement of these alcohols eases the activation of the C-O bond, as the positively charged intermediates are stabilised by the π -electron cloud through resonance.⁹ Those substrates are now commonly used as sources of "proto-electrophiles" for substitution reactions, and various catalytic methodologies have been developed for the formation of C-C,^{10, 11} C-N,¹²⁻¹⁴ C-O,¹⁵⁻²¹ and C-S²² bonds (Scheme 2).

Scheme 2 Dehydrative bond formation from π -activated alcohols. LA = Lewis acid. BA = Brønsted acid. Z = CH, N, NH₂, OH, SH.

Although Brønsted acids have been successfully used as catalysts in both homogeneous and heterogeneous procedures,²³⁻²⁶ the use of Lewis acids as catalysts constitutes the majority of the reports in literature.^{27, 28} Cationic homogeneous gold complexes have been used as versatile catalysts for a plethora of organic transformations.^{29, 30} More specifically, their Lewis acidic nature has permitted their utilisation in dehydrative reactions with alcohols.^{31, 32} For example, simple chloride salts of gold(III)^{33, 34} or phosphine-gold(I) complexes,^{35, 36} have been used as catalysts for the formation of C-O and C-N bonds.

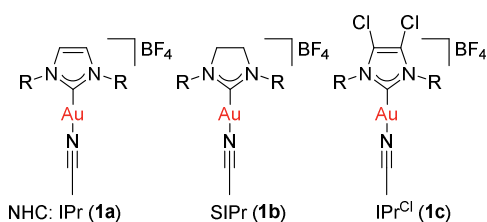
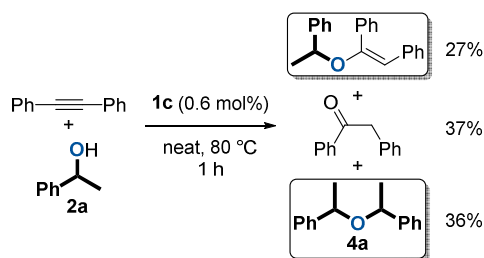


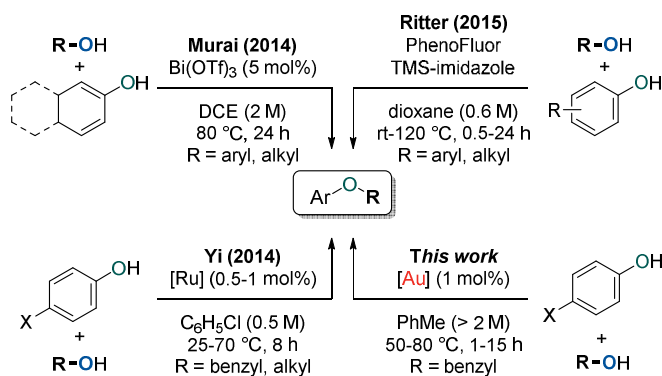
Figure 1 Complexes used as catalysts in this study. R = 2,6-diisopropylphenyl. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. IPr^{Cl} = 4,5-dichloro-1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

We previously reported that [Au(NHC)(CH₃CN)][BF₄] complexes (Figure 1) catalysed the formation of symmetrical ethers from secondary benzylic alcohols, albeit as a side-reaction (Scheme 3).³⁷ This observation prompted us to explore the capabilities of these well-defined complexes in catalysing the dehydrative formation of ethers.



Scheme 3 Formation of symmetrical ether **4a** as a side-product in hydroalkoxylation (1.1 equiv. of **2a** were used).³⁷

We herein describe that complex **1c** can be used to effectively form unsymmetrical ethers through a cross-dehydrative transformation of benzylic alcohols and phenols. These ethers are also accessible from procedures that use PhenoFluor/TMS-imidazole³⁸ or catalytic amounts of Bi,³⁹ or Ru⁴⁰ complexes (Scheme 4). These reactions proceed *via* activation of the phenol (*via* formation of an imidazolium adduct, an oxocarbenium ion, and C-H activation respectively) instead of *via* elimination of water from the benzylic alcohol.



Scheme 4 Catalytic procedures for the formation of aryl ethers. [Ru] = [Ru(C₆H₆)(PCy₃)(CO)(H)][BF₄]. [Au] = [Au(IPr^{Cl})(CH₃CN)][BF₄]. DCE = CH₂ClCH₂Cl.

Results and discussion

Optimisation studies

An initial evaluation of the reactivity of various alcohol combinations in the presence of **1c** under neat conditions revealed that unsymmetrical ether **5aa** could be formed from 1-phenylethanol (**2a**) and *p*-fluorophenol (**3a**) (see Supporting Information). This ether, however, was observed among a range of other products (Figure 2) and optimisation was essential for the selective formation of ether **5aa**.

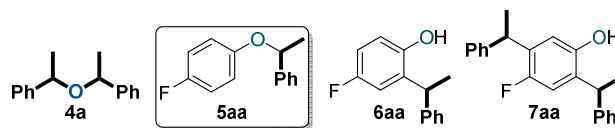


Figure 2 Products observed in the dehydrative reaction of **2a** and **3a**.

When alcohols **2a** and **3a** were heated in the absence of a catalyst and solvent, no conversion was observed after 15 minutes (Table 1, entry 1). After 96 hours, 60% of **2a** was converted into a 56/44 mixture of ethers **4a** and **5aa**. This outcome hints at an equilibrium process that is catalysed by weak Brønsted acids such as **3a**. Consequently, we continued by testing both gold complexes and Brønsted acids for catalytic activity.

Table 1 Catalyst screening.^a

Entry	Catalyst (mol%)	Conversion ^b (%) (4a / 5aa / 6aa)
1	none	0
2	[Au(IPr)(CH ₃ CN)][BF ₄] 1a (0.6)	0
3	[Au(SIPr)(CH ₃ CN)][BF ₄] 1b (0.6)	19 (42/58/0)
4	[Au(IPr ^{Cl})(CH ₃ CN)][BF ₄] 1c (0.6)	>95 (38/62/0)
5	[Au(IPr)(NTf ₂)] (1.0)	0
6	[Au(IPr ^{Cl})(NTf ₂)] (1.0)	0
7	[Au(PPh ₃)(NTf ₂)] (1.0)	60 (57/43/0)
8	[{Au(IPr) ₂ (μ-OH)}][BF ₄] (0.3)	0
9	[{Au(SIPr) ₂ (μ-OH)}][BF ₄] (0.3)	0
10	[{Au(IPr ^{Cl}) ₂ (μ-OH)}][BF ₄] (0.3)	0
11	[Au(IPr ^{Cl})(OH)] (0.6)	0
12	HBFA (cat.)	>95 (0/23/77)
13	H ₂ SO ₄ (cat.)	>95 (0/0/100)
14	<i>p</i> -TsOH (cat.)	>95 (0/0/100)

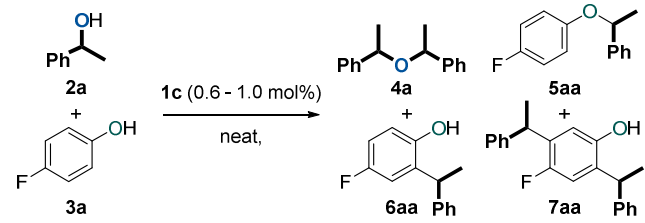
^a Reaction condition: **2a** (0.25 mmol), **3a** (0.25 mmol), neat, in air. BA = Brønsted acid, cat. = catalytic amount, approximately 1-10 mol%. ^b Determined by GC analysis, with respect to **2a**. Product distribution is given in brackets.

Among the series of gold complexes of the type [Au(NHC)(CH₃CN)][BF₄] (**1a-c**, Figure 1), those bearing NHC ligands SIPr (**1b**) and IPr^{Cl} (**1c**) were particularly active and mixtures of ethers **4a** and **5aa** were produced (Table 1, entries 2-4). Gratifyingly, the formation of styrene from **2a** was not observed despite its formation when using other catalyst systems.⁴¹⁻⁴³ No reaction occurred with NHC-bearing Gagosz-type complexes, [Au(NHC)(NTf₂)]⁴⁴ (Table 1, entries 5-6). In contrast, the reaction using [Au(PPh₃)(NTf₂)]⁴⁵ gave rapid conver-

sion of the starting alcohols (Table 1, entry 7), but ethers **4a** and **5aa** were converted to a mixture of side-products **6aa** and **7aa** (Figure 2) when the reaction was continued for another 45 minutes to reach complete conversion of **2a**. No reaction occurred with complexes $[\{\text{Au}(\text{NHC})\}_2(\mu\text{-OH})][\text{BF}_4]$ or $[\text{Au}(\text{IPr}^{\text{Cl}})(\text{OH})]$ as catalysts (Table 1, entries 8-11).^{46, 47} This lack of reactivity can be attributed to the formation of gold phenoxide complexes that are inert under the reaction conditions.⁴⁸ Reactions with catalytic amounts of different Brønsted acid led to rapid conversion of **2a**, but arylalkane **6aa** was obtained instead of the targeted ether **5aa** (Table 1, entries 12-14). Trace amounts of the corresponding di-alkylated product **7aa** were observed as well.

These results demonstrate that secondary benzylic alcohols and phenols can be converted to various products (e.g. ethers **4** and **5** and arylalkanes **6** and **7**) using either cationic gold complexes or Brønsted acids as catalysts. Control over reactivity appeared to be a challenge that could most elegantly be overcome by the use of gold complex **1c**.

Table 2 Optimisation of reaction conditions.^a



Entry	3a (equiv.)	1c (mol%)	T (°C)	t (h)	Conversion (%) (4a/5aa/6aa+7aa) ^c
1	2	0.6	80	0.25	61 (21/76/4)
2	2	0.6	80	1	>95 (19/74/7)
3	3	0.6	80	0.25	90 (7/85/8)
4	3	0.6	80	1	>95 (9/80/11)
5	4	0.6	80	0.25	>95 (13/83/4)
6	4	0.6	80	1	>95 (7/87/6)
7	5	0.6	80	0.25	>95 (9/84/7)
8	5	0.6	80	1	>95 (2/87/11)
9	5	1.0	80	15	>95 (0/0/100)
10	5	1.0	70	15	>95 (0/0/100)
11	5	1.0	60	15	>95 (0/19/80)
12	5	1.0	50	15	>95 (7/86/7)

^a Reaction conditions: **2a** (0.25 mmol), **3a**, neat, in air. ^b Determined by ¹H NMR spectroscopy. ^c Ratio includes sum of amount of **6aa** and **7aa**.⁵¹

We continued our optimisation studies by evaluating product distributions from reactions in solvent (see Supporting Information), but no improvement was observed over the previous solvent-free conditions.

Next, we tested whether the use of an excess of phenol or a change in the reaction temperature could move the product distribution towards ether **5aa** (Table 2). The amount of phenol present was found to influence the rate of the reaction and we therefore evaluated the product distributions both after 15 minutes and after 1 hour. Gratifyingly, with 5 equivalents of **3a** the product distribution shifted from symmetrical ether **4aa** to the desired ether **5aa** (Table 2, entries 7-8).⁴⁹ Of note, the use of an excess of phenol should not be considered as a major disad-

vantage from an atom-economic point of view because it can be recycled.⁵⁰ Of some concern was the observation of side-products **6aa** and **7aa** when reactions were performed using an excess of phenol (Table 2, entries 3-8). Additionally, extended reaction times led to the formation of these side-products under these reaction conditions.

In an attempt to suppress the detrimental formation of **6aa** and **7aa**, reactions were examined at lower temperatures (Table 2, entries 9-12). To compensate for potentially lower reaction rates, the catalyst loading was increased to 1 mol% and the reaction time was extended to 15 hours. A control reaction at 80 °C demonstrated clearly that ether **5aa** transformed to arylalkanes **6aa** and **7aa** upon this extended reaction time (Table 2, entry 9). Reactions at 60 °C or 70 °C also led to the formation of mixtures of **6aa** and **7aa** (Table 2, entries 10-11). However, when the reaction was performed at 50 °C, the desired ether **5aa** was the major product (Table 2, entry 12).

We had thus established that the use of excess phenol was required to favour the formation of unsymmetrical ether **5aa** over symmetrical ether **4a**, but that the reaction temperature had to be lowered to suppress the formation of arylalkanes **6aa** and **7aa**. In order to simplify the procedure, slower reactions that produce the desired product predominantly were chosen over lower catalyst loadings and higher temperatures that requires the optimisation of the reaction time to give the most favourable product distribution. We concluded that ether **5aa** could thus be formed most effectively from **2a** and 5 equivalents of **3a** under solvent-free conditions at 50 °C using 1 mol% **1c** as catalyst (Table 2, entry 12). Furthermore, we considered the addition of toluene as a means to lower the rate of the reaction.⁵²

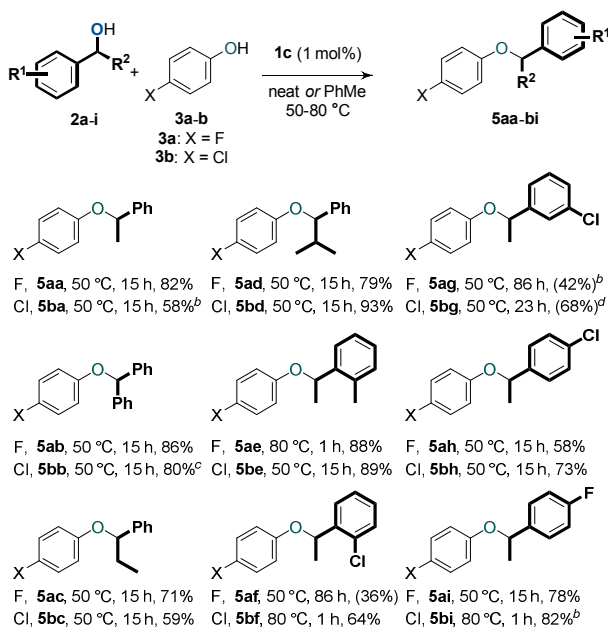
Determination of substrate scope and limitations

The scope of this procedure was evaluated by performing reactions with various secondary benzylic alcohols (**2a-g**) and phenols (**3a-b**) (Scheme 5). Reactions with *p*-fluorophenol (**3a**) and benzylic alcohols bearing alkyl or phenyl substituents in the α'-position (**2a-d**) produced the corresponding ether products **5aa-ad** in good yields. The etherification reaction of model substrates **2a** and **3a** could also be performed on a 2.0 mmol scale to obtain ether **5aa** again in 82 % yield (355.9 mg).

Benzylic alcohols bearing CO₂Me, CN or CF₃ substituents in the α'-position, did not react (even at 80 °C). This lack of reactivity can be attributed to the deactivating electron-withdrawing nature of these functional groups. 2-Furylethanol was found to decompose under the reaction conditions.³⁷ While secondary benzylic alcohols bearing substituents on the phenyl ring (**2e-i**) were reactive, we were only able to form the corresponding ethers (**5ae-ai**) selectively by modifying the reaction conditions slightly. Ether **5ae** was obtained from 1-(*o*-tolyl)ethanol (**2e**) in very high yield by performing the reaction at 80 °C, but the reaction of 1-(*o*-chlorophenyl)ethanol (**2f**) produced a mixture of ether **5af** and the corresponding aryl alkane **6af** at this temperature. Ether **5ag** could be formed selectively at 50 °C, but complete conversion of alcohol **2g** was not obtained, even after 86 hours. The reaction of 1-(*m*-chlorophenyl)ethanol (**2g**) pro-

ceeded in a similar fashion to that of alcohol **2f**, but toluene had to be added to avoid the formation of the corresponding arylalkane product at 50 °C. Unfortunately, this reaction did not reach completion, even after 86 hours. The standard reaction conditions could be applied for secondary benzylic alcohols with chloro or fluoro substituents in the *para* position of the phenyl ring (**2h-i**), and the corresponding ethers (**5ah-ai**) were obtained in modest and good yields, respectively.

Scheme 5 Scope for etherification with secondary benzylic alcohols and phenols.^a



Reactions with *p*-chlorophenol (**3b**) were then examined. Once again, reactions with secondary benzylic alcohols bearing substituents in the α' -position (**2a-d**) proceeded smoothly and the corresponding ethers **5ba-bd** were obtained in high yields. Interestingly, for the reaction of 1-phenylethanol (**2a**), toluene had to be added to the reaction mixture to avoid formation of the corresponding arylalkane. This trend in reactivity suggests that the process that converts ethers **5** to arylalkanes **6** and **7** is faster for ethers derived from *p*-chlorophenol (**3b**) compared to those derived from *p*-fluorophenol (**3a**), and that the size of the substituent in the α' -position of the benzylic alcohol has a significant influence on this process. Ether **5be** could be obtained from 1-(*o*-tolyl)ethanol (**2e**) using the standard reaction conditions, but ether **5bf** from 1-(*o*-chloro)ethanol was obtained most effectively at 80 °C. Unfortunately, reaction conditions could not be found which led to complete conversion of 1-(*m*-chlorophenyl)ethanol (**2g**) while avoiding the formation of the corresponding arylalkane. The desired ethers **5bh-bi** could be formed from alcohols **2h-i** and phenol **3b**. Finally, the formation of unsymmetrical ethers from 1-phenylethanol (**2a**) and

different phenols was tested as well. Both the use of phenol, and phenols bearing substituents in either the *ortho* (Cl), *meta* (F, Cl) or *para*-position (Br, Me, OMe, CF₃) were evaluated. Unsatisfyingly, reactions with these substrates all gave mixtures of the desired unsymmetrical ethers and corresponding arylalkanes.⁵³

Catalytic conversion of symmetrical ether

The observed catalytic of the formation of both symmetrical and unsymmetrical ethers (**4** and **5**) as well as arylalkanes (**6** and **7**) prompted us to investigate the origins of these compounds. Thus, we examined whether symmetrical ether **4a** could be converted to ether **5aa** and arylalkanes **6aa** and **7aa** (Table 3).

Table 3 Reactions of symmetrical ether **4a** with phenol **3a**.^a

Entry	3a (equiv.)	T (°C)	t (h)	Conversion ^b (%) (5aa/6aa) ^c
1	1	50	22	29 (91/9)
2	2	50	22	68 (79/21)
3	1	80	0.25	37 (91/9)
4	2	80	0.25	81 (41/59)
5	10	80	0.25	>99 (16/84)
6	10	80	1	>99 (14/86)
7	10	80	22	>99 (0/100)
8 ^c	10	80	1	71 (94/6)
9 ^c	10	80	22	>99 (0/100)

^a Reaction condition: **4a** (0.10 mmol), neat, in air. ^b Determined by ¹H-NMR or ¹⁹F-NMR spectroscopy with respect to **4a** or **3a**, respectively. ^c Reaction performed in absence of catalyst.

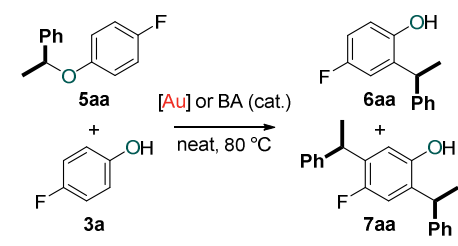
Symmetrical ether **4a** was first subjected to different amounts of phenol **3a** under the standard catalytic conditions (Table 3, entries 1-2). While the reaction using 1 equivalent of **3a** was particularly slow, it produced unsymmetrical ether **5aa** in addition to a small amount of **6aa** (Table 3, entry 1). When 2 equivalents of **3a** were used, the reaction was significantly faster and the product distribution shifted towards arylalkane **6aa** (Table 3, entry 2). These results are consistent with previous reports that describe acid-catalysed and thermal rearrangements of phenolic ethers to arylalkanes.⁵⁴⁻⁵⁶ As expected from our catalyst screening (Table 1), the transformation of **4a** to mixtures of **5aa** and **6aa** was much more rapid at 80 °C (Table 3, entries 3-4). With 2 equivalents of **3a**, the formation of arylalkane **7aa** (Figure 2) was also observed. The influence of phenol **3a** in this transformation was further evaluated by using a ten-fold excess with respect to **4a** (Table 3, entry 5). Ether **4a** showed complete conversion to arylalkane **6aa** upon extended reaction time (Table 3, entries 6-7). In this case, only trace amounts of arylalkane **7aa** could be observed. When the experiment was repeated in

the absence of **1c**, we obtained similar results (Table 3, entries 8-9). This observation provides another hint that the Brønsted acidity of phenol **3a** enables its role as a catalyst in this transformation.

Catalytic conversion of unsymmetrical ether

Finally, we evaluated the stability of unsymmetrical ether **5aa** (Table 4). This product did not transform to arylalkanes **6aa** and **7aa** in the absence of phenol **3a** (Table 4, entries 1-2). In the presence of 1 equivalent of phenol **3a**, however, slow conversion to arylalkane **6aa** was observed (Table 4, entry 2). This reaction reached completion when 5 equivalents of phenol **3a** were used (Table 4, entry 3). Repeating the latter reaction in the absence of catalyst gave a much lower conversion (Table 4, entry 4), thereby demonstrating that gold complex **1c** assists this transformation.

Table 4 Reactions of unsymmetrical ether **5aa** with phenol **3a**.^a



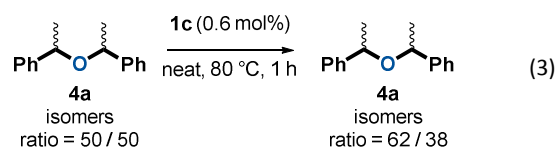
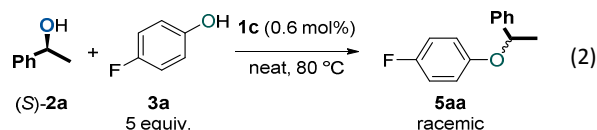
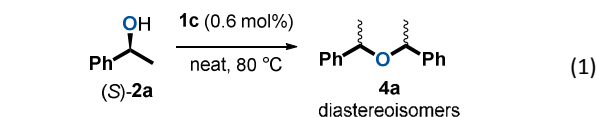
Entry	Catalyst (mol%)	3a (equiv.)	t (h)	Conversion ^b (%) (6aa / 7aa)
1	1c (1)	-	15	-
2	1c (1)	1	15	33 (86/14)
3	1c (1)	5	15	>99 (96/4)
4	-	5	15	22 (96/4)
5	<i>p</i> -TsOH	-	1	93 (32/68)

^a Reaction condition: **5aa** (0.05 mmol), neat, in air. ^b Determined by ¹H-NMR or ¹⁹F-NMR spectroscopy with respect to **5aa**.

The formation of mixtures of **6aa** and **7aa**, especially in the reaction with 1 equivalent of phenol **3a** (Table 4, entry 2) is intriguing. This result suggests the existence of a pathway that delivers a benzyl-fragment from **5aa** that subsequently reacts with **6aa** to form **7aa**.

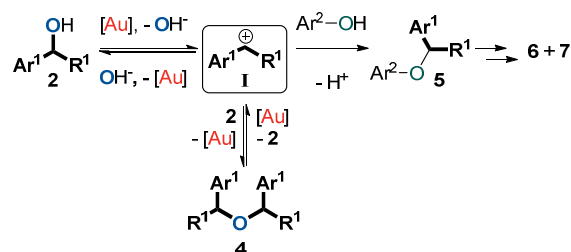
Reactions with enantiopure alcohol

Various mechanistic proposals have suggested the formation of a carbocation intermediate in dehydrative reactions with π -activated alcohols.³³⁻³⁵ This planar intermediate should give racemic products upon reaction with a nucleophile. Thus, the observation of racemic products from reactions with enantiopure alcohols would support such a mechanism. To test this, (*S*)-1-phenylethanol ((*S*)-**2a**) was subjected to the catalytic conditions with and without the addition of 5 equivalents of phenol **3a** (Eq. 1 and 2). As expected, only racemic **4a** and **5aa** were observed by chiral HPLC analysis.



The ratio of isomers of **4a** evolved upon extended reaction time in the reaction depicted in Eq. 1. Therefore, a control experiment was conducted in which an equal mixture of racemic and meso isomers of **4a** was subjected to the catalytic conditions (Eq. 3). The ratio of isomers evolved also in this reaction, indicating that an equilibrium process was operative. Of note, this phenomenon was not observed in the absence of a catalyst under otherwise identical conditions. This result is consistent with our observations that symmetrical ether **4** is not merely a side-product in our targeted etherification reaction, but rather a kinetic intermediate that can be converted to the more stable ether **5**. The need for an excess of phenol (**3**) in our procedure can then be justified by the necessity to displace this equilibrium and to drive the reaction to the desired unsymmetrical ether (**5**).

Mechanistic proposal



Scheme 6 Plausible reaction mechanism. Ar² = 4-X-phenyl. X = F, Cl.

Altogether, we propose a plausible mechanism to account for our observations (Scheme 6). It must be noted that while the gold catalyst is likely to serve as Lewis acid, we have not established its exact role in these transformations. The carbocation intermediate **I** that forms from formal gold-assisted elimination of hydroxide from **2** can be trapped by either the benzylic alcohol (**2**) or the phenol (**3**) to give symmetrical ether **4** or unsymmetrical ether **5**. Since dehydration of **2** via protonation would be more favourable than the direct release of hydroxide, phenol **3** is likely to be involved in this step.⁶ The formation of **4** is reversible under the reaction conditions employed, while **5** can be subsequently converted to thermodynamic products **6** and **7**. Because of the low electron density on the arenes (**3**) used in this study, direct transformation from **I** or **4** to **6** via aromatic

substitution seems less favourable than a Fries-type rearrangement that transforms ether **5** to arylalkane **6** instead.^{56, 57, 58} As such, a pathway might be operative in which the ether is converted to the starting alcohols which then form the side-products *via* a Friedel-Crafts reaction.

Conclusions

In summary, we have demonstrated that ethers can be prepared from readily available benzylic alcohols and phenols under mild and environmentally benign conditions. Besides giving access to new products, it provides another example of remarkable chemoselectivity that can be obtained by employing an appropriate NHC-gold(I) complex as catalyst. Investigations to use secondary benzylic alcohols as proto-electrophiles to react with nucleophiles other than phenols are currently ongoing in our laboratories.

Experimental

General information

All reagents were obtained through commercial suppliers and were used as received. Unless otherwise stated, all alcohols were used as their racemate. [Au(NHC)(CH₃CN)][BF₄], [{Au(NHC)}₂(μ-OH)][BF₄] (NHC = IPr, SIPr and IPr^{Cl}) and [Au(L)(NTf₂)] (L = IPr, IPrCl, PPh₃) were synthesised according to previous reports.^{44, 46, 47, 59, 60} All reactions were set up on the benchtop in screw cap vials with Teflon seal inserts and carried out under an atmosphere of air. Flash column chromatography was performed using silica gel.

General procedure for formation of ethers

To [Au(IPr^{Cl})(MeCN)][BF₄] (**1c**) (1.0 mol%) were added benzylic alcohol **2** (0.25 mmol), phenol **3** (1.25 mmol, 5 equiv.) and toluene (0–100 μL). The reaction mixture was stirred at 50 °C or 80 °C. After the reaction mixture was cooled down, the crude product was purified by flash column chromatography on silica gel (petroleum ether/diethyl ether = 9/1).⁶¹

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Notes and references

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49. When this reaction was repeated without catalyst, no conversion was observed after 1 hour. This result demonstrates phenol **3a** is no effective in catalyst for the targeted etherification reaction (*c.f.* Table 1, entry 1).
50. The phenol could be recycled after recovery from the products by flash column chromatography on silica gel.
51. The ratio of **6aa** and **7aa** can be determined by ¹⁹F NMR spectroscopy or GC analysis. In these reaction, the amount of **7aa** constitutes <10% of the total amount of product. As such, the exact amount can not be determined with high accuracy and the data is omitted.
52. The addition of toluene could potentially enhance the homogeneity of reaction mixtures of substrates with high melting points or retard the formation of side-products from reactions with activated substrates.
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61. Alternative to flash column chromatography, excess phenol can be removed from the crude reaction mixture by filtration after crystallisation from pentane and cooling to -20 °C.

A well-defined NHC-gold(I) complex has been shown highly effective in the formation of ethers from secondary benzylic alcohols and phenols under mild reaction conditions.

