Gold(i)-catalysed dehydrative formation of ethers from benzylic alcohols and phenols†

Richard M. P. Veenboera and Steven P. Nolana,b

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.

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.10 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, C–N, C–O, and C–S bonds (Scheme 2).

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.

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

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-imidazole\(^\text{38}\) or catalytic amounts of Bi\(^\text{39}\) or Ru\(^\text{40}\) 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.

### 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 ESI\(^\text{†}\)). This ether, however, was observed among a range of other products (Fig. 2) and optimisation was essential for the selective formation of ether \(5aa\).

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.

Among the series of gold complexes of the type [Au(NHC)-
(CH3CN)][BF4]2 (1a–c, Fig. 1), those bearing NHC ligands SiPr
(1b) and IPrCl (1c) were particularly active and mixtures of
ethers 4a and 5aa were produced (Table 1, entries 3–4). Gratifyingly,
the formation of styrene from 2a was not observed despite its formation when using other catalyst systems.11–13 No reaction occurred with NHC-bearing Gagosz-type complexes, [Au(NHC)(NTf2)]44 (Table 1, entries 5 and 6). In contrast, the reaction using [Au(PPh3)(NTf2)]45 gave rapid conversion of the starting alcohols (Table 1, entry 7), but ethers 4a and 5aa were converted to a mixture of side-products 6aa and 7aa (Fig. 2) when the reaction was continued for another 45 minutes to reach complete conversion of 2a. No reaction occurred with complexes ([Au(NHC)2(μ-OH)][BF4]2)
(Table 1, entries 8–10) or [Au(IPrCl)(OH)] (Table 1, entry 11) as cata-
lysts.46–47 This lack of reactivity can be attributed to the for-

tification at 80 °C demonstrated clearly that ether 5aa transformed
to arylalkanes 6aa and 7aa upon this extended reaction time

Determination of substrate scope and limitations

The scope of this procedure was evaluated by performing reac-
tions with various secondary benzylic alcohols (2a–i) 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 pro-

ducts 5aa–ad in good yields. The etherification reaction of model substances 2a and 3a could also be performed on a
2.0 mmol scale to obtain ether 5aa again in 82% yield (355.9 mg).

<table>
<thead>
<tr>
<th>Entry</th>
<th>3a (equiv.)</th>
<th>1c (mol%)</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Conversionb (%)</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>2</td>
<td>0.6</td>
<td>80</td>
<td>0.25</td>
<td>&gt;95 (21/76/4)</td>
</tr>
<tr>
<td>2</td>
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<td>0.6</td>
<td>80</td>
<td>1</td>
<td>&gt;95 (19/74/7)</td>
</tr>
<tr>
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<td>3</td>
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<td>80</td>
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<td>&gt;95 (9/80/11)</td>
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<td>80</td>
<td>0.25</td>
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<td>0.6</td>
<td>80</td>
<td>1</td>
<td>&gt;95 (7/87/6)</td>
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<tr>
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<td>5</td>
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<td>80</td>
<td>0.25</td>
<td>&gt;95 (9/84/7)</td>
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<tr>
<td>8</td>
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<td>80</td>
<td>1</td>
<td>&gt;95 (2/87/11)</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>1.0</td>
<td>80</td>
<td>15</td>
<td>&gt;95 (0/0/100)</td>
</tr>
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<td>5</td>
<td>1.0</td>
<td>70</td>
<td>15</td>
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<tr>
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<td>1.0</td>
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<td>&gt;95 (0/19/80)</td>
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<tr>
<td>12</td>
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<td>1.0</td>
<td>50</td>
<td>15</td>
<td>&gt;95 (7/86/7)</td>
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* Reaction conditions: 2a (0.25 mmol), 3a, neat, in air. ** Determined by 1H NMR spectroscopy. Product distribution is given in brackets. † Ratio includes sum of amount of 6aa and 7aa.41
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. While secondary benzylic alcohols bearing substituents on the phenyl ring (2e–g) were reactive, we were only able to form the corresponding ethers (3ae–ag) selectively by modifying the reaction conditions slightly. Ether 3ae 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 arylalkane 6af at this temperature. Ether 5af could be formed selectively at 50 °C, but complete conversion of alcohol 2f was not obtained, even after 86 hours. The reaction of 1-(m-chlorophenyl)ethanol (2g) proceeded 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.

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.33

**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

<table>
<thead>
<tr>
<th>Entry</th>
<th>3a (equiv.)</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Conversion (%)</th>
<th>5aa/6aa</th>
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<tr>
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<td>29 (91/9)</td>
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<td>68 (79/21)</td>
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<tr>
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<td>37 (91/9)</td>
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<tr>
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<td>81 (41/59)</td>
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<td>&gt;99 (16/84)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>80</td>
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<tr>
<td>9</td>
<td>10</td>
<td>80</td>
<td>22</td>
<td>&gt;99 (0/100)</td>
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</table>

Reaction condition: 4a (0.10 mmol), neat, in air. Determined by ¹H-NMR or ¹³C(¹H)-NMR spectroscopy with respect to 4a or 3a, respectively. Product distribution is given in brackets. 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 and 2). While the reaction using 1 equivalent of 3a was particularly slow, it produced unsymmetrical ether 5aa and 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. 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 and 4). With 2 equivalents of 3a, the formation of arylalkane 7aa 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 and 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 and 9). This observation provides another hint that the Bronsted 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, entry 1). 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.

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 dehydration reactions with \( \pi \)-activated alcohols. 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 (eqn (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 eqn (1). Therefore, a control experiment was conducted in which an equal mixture of racemic and \( \textit{meso} \) isomers of 4a was subjected to the catalytic conditions (eqn (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

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 carboxilation

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Table 4: Reactions of unsymmetrical ether 5aa with phenol 3a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst [mol%]</th>
<th>3a (equiv.)</th>
<th>t (h)</th>
<th>Conversion(^a) (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>1c (1)</td>
<td>—</td>
<td>15</td>
<td>—</td>
</tr>
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<td>2</td>
<td>1c (1)</td>
<td>1</td>
<td>15</td>
<td>33 (86/14)</td>
</tr>
<tr>
<td>3</td>
<td>1c (1)</td>
<td>5</td>
<td>15</td>
<td>&gt;99 (96/4)</td>
</tr>
<tr>
<td>4</td>
<td>—</td>
<td>5</td>
<td>15</td>
<td>22 (96/4)</td>
</tr>
<tr>
<td>5</td>
<td>p-TsOH</td>
<td>—</td>
<td>1</td>
<td>93 (32/68)</td>
</tr>
</tbody>
</table>

\(^a\) Reaction condition: 5aa (0.05 mmol), neat, in air. \(^b\) Determined by \(^1\)H-NMR or \(^{19}\)F\(^{1}\)H-NMR spectroscopy with respect to 5aa. Product distribution is given in brackets.
intermediate 1 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. 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 1 or 4 to 6 via aromatic substitution seems less favourable than a Fries-type rearrangement that transforms ether 5 to arylalkane 6 instead. 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 protoelectrophiles 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]2, [[Au(NHC)]2(μ-OH)][BF4]2 (NHC = IPr, SIPr and IPrCl) and [Au(L)- (NTf2)]2 (L = IPr, IPrCl, PPh3) were synthesised according to previous reports. 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(IPrCl)(MeCN)][BF4]2 (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).

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Notes and references

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