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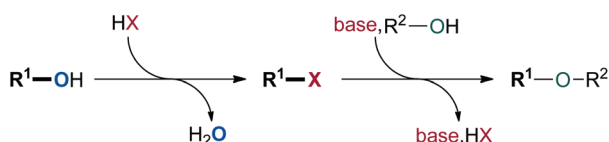
Gold(i)-catalysed dehydrative formation of ethers from benzylic alcohols and phenols†

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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.

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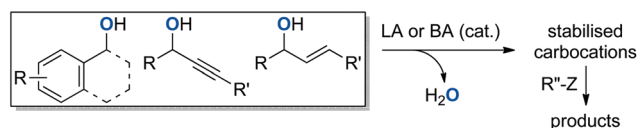
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Because of the inherent difficulty of activating alcohols for S_N1 reactions, π -activated alcohols, such as propargylic and allylic alcohols were most commonly used in early reports.^{6–8} Benzylic alcohols were later recognised as suitable substrates 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).

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



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



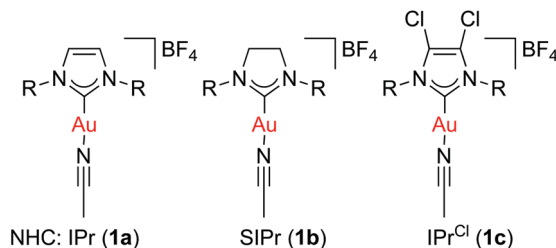
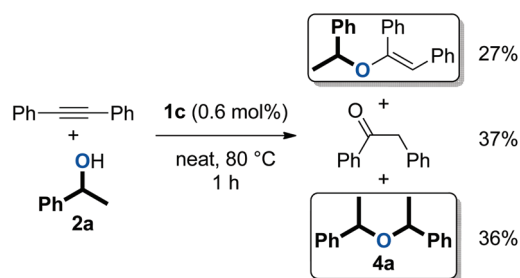


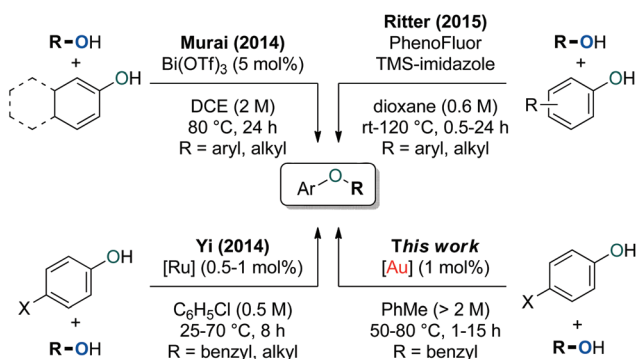
Fig. 1 Complexes used as catalysts in this study. R = 2,6-diisopropylphenyl. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene. IPr^{Cl} = 4,5-dichloro-1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene.

(Scheme 3).³⁷ 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-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 oxocarbe-



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



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.

nium 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†). 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

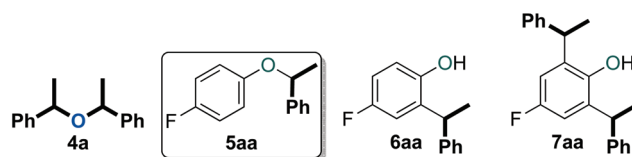


Fig. 2 Products observed in the dehydrative reaction of **2a** and **3a**.

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	HBF ₄ (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. Cat. = catalytic amount, approximately 1–10 mol%. ^b Determined by GC analysis, with respect to **2a**. Product distribution is given in brackets.



by testing both gold complexes and Brønsted acids for catalytic activity.

Among the series of gold complexes of the type $[\text{Au}(\text{NHC})-(\text{CH}_3\text{CN})][\text{BF}_4]$ (**1a–c**, Fig. 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 3–4). 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, $[\text{Au}(\text{NHC})(\text{NTf}_2)]^{44}$ (Table 1, entries 5 and 6). In contrast, the reaction using $[\text{Au}(\text{PPh}_3)(\text{NTf}_2)]^{45}$ 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 $[\{\text{Au}(\text{NHC})\}_2(\mu\text{-OH})][\text{BF}_4]$ (Table 1, entries 8–10) or $[\text{Au}(\text{IPr}^{\text{Cl}})(\text{OH})]$ (Table 1, entry 11) as catalysts.^{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 acids 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.

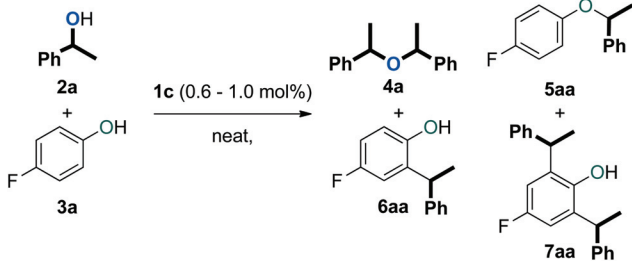
These results demonstrate that secondary benzylic alcohols and phenols can be converted to various products (e.g. ethers **4** and **5** and arylalkanes **6** and **7**) using either cationic gold complexes or Brønsted acids as catalysts. Control over reactivity appeared to be a challenge that could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

We continued our optimisation studies by evaluating product distributions from reactions in solvent (see ESI†), 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 shift 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 and 8).⁴⁹ Of note, the use of an excess of phenol should not be considered as a major disadvantage 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 1–8). 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 Optimisation of reaction conditions^a



Entry	3a (equiv.)	1c (mol%)	<i>T</i> (°C)	<i>t</i> (h)	Conversion ^b (%) (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. Product distribution is given in brackets. ^c Ratio includes sum of amount of **6aa** and **7aa**.⁵¹

(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 and 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–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 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).





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.^{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 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 Brønsted acidity of phenol **3a** enables its role as a catalyst in this transformation.

Catalytic conversion of unsymmetrical ether

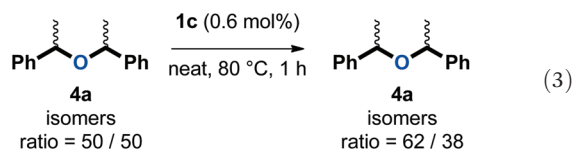
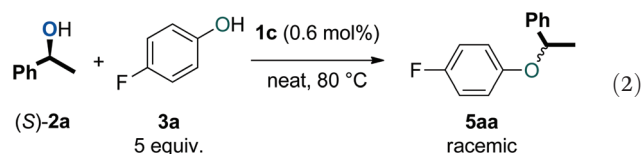
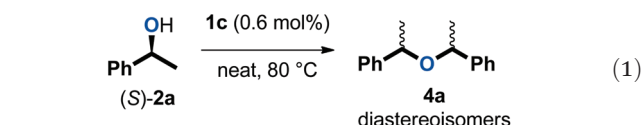
Finally, we evaluated the stability of unsymmetrical ether **5aa** (Table 4). This product did not transform to arylalkanes **6aa** and **7aa** in the absence of phenol **3a** (Table 4, entry 1). In the presence of 1 equivalent of phenol **3a**, however, slow conversion to arylalkane **6aa** was observed (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 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** (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 *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

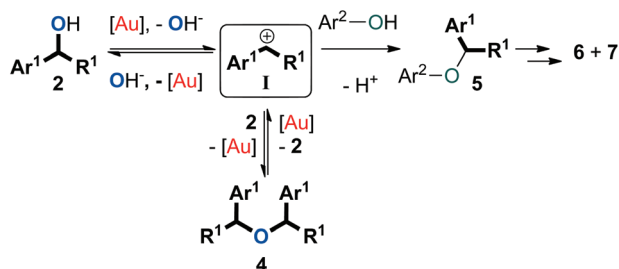
Altogether, we propose a plausible mechanism to account for our observations (Scheme 6). It must be noted that while the gold catalyst is likely to serve as Lewis acid, we have not established its exact role in these transformations. The carbocation

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

Entry	Catalyst (mol%)	3a (equiv.)	<i>t</i> (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{¹H}-NMR spectroscopy with respect to **5aa**. Product distribution is given in brackets.





Scheme 6 Plausible reaction mechanism. $\text{Ar}^2 = 4\text{-X-phenyl}$. $\text{X} = \text{F}, \text{Cl}$.

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.^{56–58} 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. $[\text{Au}(\text{NHC})(\text{CH}_3\text{CN})][\text{BF}_4]$, $[\{\text{Au}(\text{NHC})\}_2(\mu\text{-OH})][\text{BF}_4]$ ($\text{NHC} = \text{IPr}, \text{SIPr}$ and IPr^{Cl}) and $[\text{Au}(\text{L})\text{NTf}_2]$ ($\text{L} = \text{IPr}, \text{IPrCl}, \text{PPh}_3$) 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 $[\text{Au}(\text{IPr}^{\text{Cl}})(\text{MeCN})][\text{BF}_4]$ (**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 $^\circ\text{C}$ or 80 $^\circ\text{C}$. 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

Acknowledgements

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- 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.
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