Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201401097

Gold(I)-Catalyzed Synthesis of Unsymmetrical Ethers Using Alcohols as Alkylating Reagents

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Received: November 22, 2014; Published online: March 13, 2015

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201401097.

Abstract: A microwave-irradiated alcohol-protecting strategy based on gold catalysis utilizing benzyl alcohol, *tert*-butyl alcohol and triphenylmethanol as alkylating reagents has been developed. This protecting strategy has wide functional group tolerance with satisfactory yields for the majority of the selected alcohols. The mechanism of this transformation was probed with oxygen-18 isotope labelled alcohols assisted by GC-MS techniques and chemical kinetic experiments. This strategy provides an efficient, straightforward and alternative approach to the preparation of benzyl, *tert*-butyl and trityl ethers in organic synthesis.

Keywords: alcohols; carbocation; gold(I) catalysts; protecting groups; unsymmetrical ether syntheses

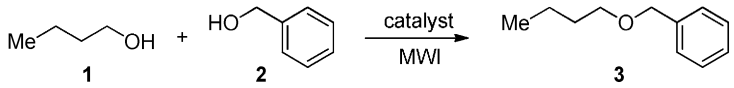
Introduction

Ethers are important compounds in organic synthesis, which are often used as protecting groups for alcohols due to their stability in the presence of: bases, active metals, dilute acids, oxidizing agents and reducing agents.[1] Various strategies have been developed to prepare ethers, including the Williamson ether synthesis,[2] the dehydration of alcohols,[3] the Ullmann condensation,[4] the Mitsunobu reaction[5] and the electrophilic addition of alcohols to alkenes.[6] Of the aforementioned strategies, the dehydration of alcohols is the most simple, green and direct method. However, the poor leaving group ability of the hydroxy group limits its application to merely the preparation of symmetrical alkyl ethers and cyclic ethers. Brønsted acids, such as sulfuric acid are often applied as catalysts to promote the formation of an ether from two alcohols.[7] Conventional Lewis acids were often less effective in the catalytic activation of alcohols to form ethers due to their sensitivity to the water generated during the etherification, especially for the synthesis of unsymmetrical ethers.[8]

The benzyl, *tert*-butyl and trityl groups are the most popular ether protecting groups for alcohols in organic synthesis. The formation of benzyl ethers can be divided into two common strategies including: (a) reaction of the alcohol with benzyl bromide/chloride and a strong base such as sodium hydride in a Williamson ether synthesis;[9] (b) reaction of the alcohol with an imidate such as benzyl trichloroacetimidate promoted by trifluoromethanesulfonic acid.[10] The introduction of the *tert*-butyl group to alcohols is performed with isobutylene and a strong acidic catalyst[11] or di-*tert*-butyl dicarbonate under the catalysis of anhydrous $Mg(ClO_4)_2$.[12] An efficient method for tritylation is achieved by treating alcohols with trityl chloride in the presence of a strong base.[13] The requirement of strong basic or acidic conditions, anhydrous solvents, irritating or non-commercially available alkylating reagents cannot be avoided in most known methodologies. It is significant and appropriate to develop a method to install benzyl, *tert*-butyl and trityl groups on to alcohols in a simple and robust way.

On the other hand, gold coordinates preferentially to alkene or alkyne bonds to promote nucleophilic attack of these substrates in numerous gold-catalyzed transformations and the conditions for gold catalysis are mild.[14] Gold(I) catalysts have the advantages of high air stability and relatively low oxophilicity and thus tolerance towards water and alcohols. These attributes have resulted in the application of gold(I) catalysts in many organic transformations by activating ketone or alcohols including some etherification reactions.[15] Herein, we describe our efforts to prepare unsymmetrical ethers from the condensation of

Table 1. Optimization of reaction conditions for the etherification of *n*-butanol (**1**) with benzyl alcohol (**2**).



Entry	Catalyst	Loading [mol%]	Ratio of **1**:**2**	Temperature [°C]	Time [min]	Yield [%][a]
1	$Ph_3PAuNTf_2$	1	1:10	120	10	31
2	$Ph_3PAuNTf_2$	1	1:10	150	10	98
3	$Ph_3PAuNTf_2$	1	1:10	170	10	98
4	$Ph_3PAuNTf_2$	0.1	1:10	150	10	24
5	$Ph_3PAuNTf_2$	0.5	1:10	150	30	97
6	$Ph_3PAuNTf_2$	0.05	1:10	150	30	95
7	$Ph_3PAuNTf_2$	0.05	1:1	150	30	57
8	**$Ph_3PAuNTf_2$**	**0.05**	**1:3**	**150**	**30**	**90**
9	$Ph_3PAuNTf_2$	0.05	1:3	150	30	87[b]
10	$HNTf_2$	0.05	1:3	150	30	21
11	$Ph_3PAuCl/AgOTf$	0.05	1:3	150	30	31
12	$Ph_3PAuCl/AgSbF_6$	0.05	1:3	150	30	10
13	$IPrAuCl/AgNTf_2$	0.05	1:3	150	30	45
14	–	–	1:3	150	30	0
15	Au nanoparticles	0.05	1:3	150	30	9
16	$NaAuCl_4$	0.05	1:3	150	30	23
17	$FeCl_3$	0.05	1:3	150	30	0
18	$SnCl_4$	0.05	1:3	150	30	46

[a] Isolated yields.
[b] Performed in the presence of 0.05 mol% 2,6-di-*tert*-butylpyridine.

alcohols with benzyl alcohol, *tert*-butyl alcohol and trityl alcohol under solvent-free conditions catalyzed by gold(I) using microwave irradiation.

Results and Discussion

Optimization of the Reaction Conditions for Ether Synthesis

We started our research with a systematic optimization of catalyst species and loading, reaction times, temperatures, and ratios of model substrates: *n*-butanol and benzyl alcohol (Table 1). Temperature was examined first by utilizing commercially available [bis-(trifluoromethanesulfonyl)imidate](triphenylphosphine)gold(I), ($Ph_3PAuNTf_2$) as the catalyst[16] and a 1:10 ratio of *n*-butanol and benzyl alcohol with a 1 mol% catalyst loading. It was found that at temperatures higher than 120 °C, the yields improved until 150 °C at which point further elevation of temperatures was not helpful for improving the yield (Table 1, entries 1–3). The loading of the catalyst was successfully decreased to 0.05 mol% when the reaction time was increased (Table 1, entries 4–6). The ratio of the two alcohols has a great influence on the yield of the reaction since the formation of dibenzyl ether is the main by-product, increasing the ratio resulted in the optimal conditions to be a ratio of 1:3 *n*-butanol to benzyl alcohol with 0.05 mol% $Ph_3PAuNTf_2$,[17] whereby the dibenzyl ether by-product will be obviously suppressed (Table 1, entries 7 and 8).

In order to exclude the possibility that traces of acid are catalyzing the reaction, two control experiments were conducted. An acid scavenger, 2,6-di-*tert*-butylpyridine, was added to the optimized reaction conditions and the product can be isolated in 87% yield, furthermore, a 0.05 mol% loading of triflimide ($HNTf_2$) itself was also tested and less than 30% product was produced with a messy reaction profile. (Table 1, entries 9 and 10). A possible hidden acid influence has been also excluded by following known procedures.[18] Different gold(I) catalysts were screened with much worse isolated yields (Table 1, entries 11–13). The blank control by no addition of the catalyst was also examined and no ether product was generated, but the starting materials were recovered nearly quantitatively (Table 1, entry 14). Then gold nanoparticles[19] were also prepared to exclude the possibility of reactions catalyzed by gold nanoparticles formed at the high temperatures used (Table 1, entry 15). Gold(III) was also examined under these conditions and the yield was poor (Table 1, entry 16). Some conventional Lewis acids, such as $FeCl_3$ and $SnCl_4$ were also examined in the standard conditions, and no satisfactory results were obtained (Table 1, entries 17 and 18). We also tried to perform the ether formation reaction under conventional reflux condi-

tions with no significant loss of efficiency, only a longer reaction time (more than 24 h) was needed.

Scope of Gold(I)-Catalyzed Benzyl and *tert*-Butyl Ether Formation Reactions

With the optimal conditions in hand, we chose different kinds of alcohols as substrates to investigate the scope and toleration of functional groups for this method. To our delight, most of the selected alcohols gave satisfactory results under the standard conditions. All the selected primary alcohols, including homobenzyl alcohols, benzyl alcohols and substituted aliphatic alcohols gave excellent yields with good functional group tolerance (Table 2, **3a**–**3i**). The efficiency for the secondary alcohols was not as high as that for primary alcohols, especially for the steric hindered substrates (Table 2, **3j**–**3m**). Tertiary alcohols such as *tert*-butyl alcohol and triphenylmethanol derivatives worked well under these conditions (Table 2, **3n**–**3q**). The silanols can also be protected by the benzyl group to give the corresponding ether products with moderate yields (Table 2, **3r** and **3s**).

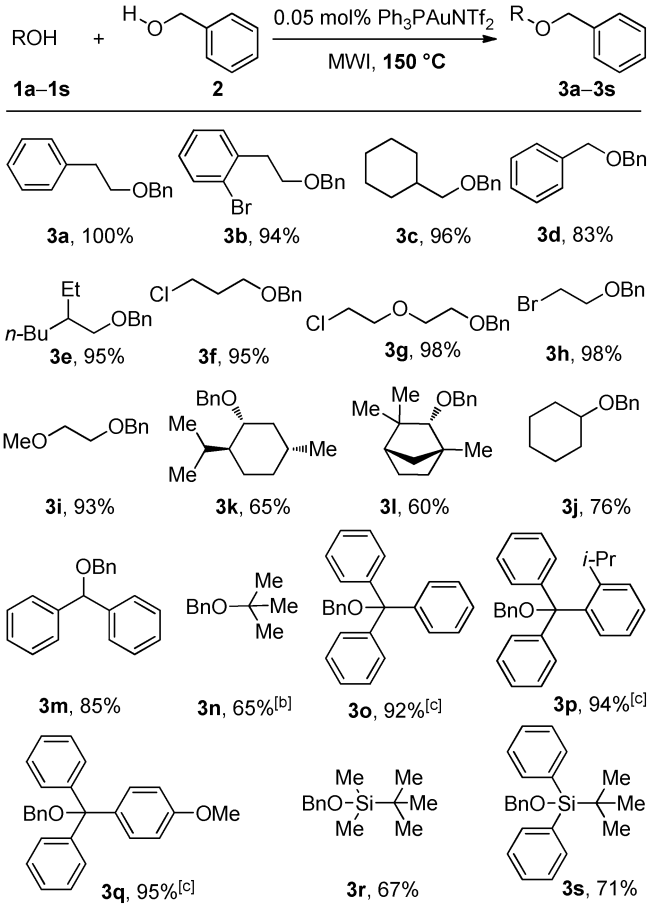
Further exploration of the scope of this method led to a study of *tert*-butyl alcohol as alkylating reagent. Much to our delight, the formation of *tert*-butyl ethers proved to be successful, but only at 1 mol% catalyst loading and 120 °C with 10 equivalents of *tert*-butyl alcohol. Excess catalyst and protecting alcohol were required due to the formation of isobutene derived from the dehydration of *tert*-butyl alcohol under the reaction conditions. All the tested primary alcohol substrates with halogen, ether, ester, amide, acetal and ketone functional groups afforded good conversions (Table 3, **4a**–**4k**). However, the formation of *tert*-butyl ethers utilizing this method is limited to relatively unhindered alcohols as evidenced by the low conversion of hindered secondary alcohols to *tert*-butyl ethers (Table 3, **4l**–**4n**).

Mechanism Study of Benzyl Ether Formation Reaction

To gain insights about the mechanism, oxygen-18 labelled benzyl alcohol was synthesized by treatment of the corresponding benzyl chloride with $H_2{}^{18}O$ in the presence of sodium.[20] The heavy isotope substrate was then subjected to standard protection conditions for several representative alcohols which resulted in the formation of the corresponding ether products as anticipated (Scheme 1).

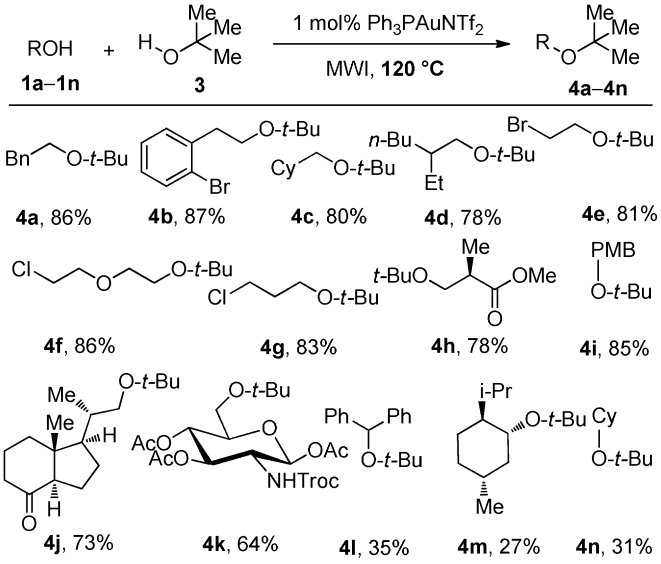
However, the oxygen-18 labelled ether products could not be detected by GC-MS (see the Supporting Information), which indicated that the carbon-oxygen bonds in the alkylating reagents could cleave prefer-

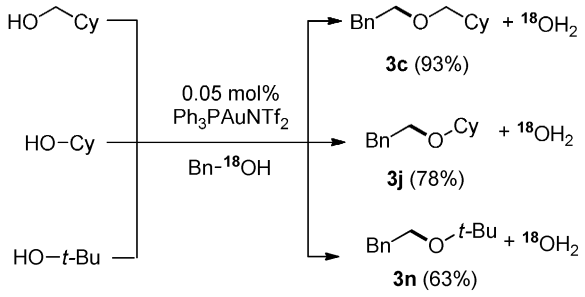
Table 2. Scope of the gold(I)-catalyzed benzyl ether formation reaction.[a]



[a] Isolated yields.
[b] Performed with 0.5 mol% catalyst.
[c] Performed at 120 °C.

Table 3. Scope of the gold(I)-catalyzed *tert*-butyl ether formation reaction.





Scheme 1. Mechanism study based on oxygen-18 isotope labelled substrates.

entially in the presence of the cationic gold catalyst. This mechanism was also supported by comparing the ^{1}H NMR spectrum of **3k**, an enantiopure benzyl ether with that reported previously (see the Supporting Information),[21] which exhibits that the chiral center of the alcohol was untouched during the formation of ethers.

To probe the mechanism further, the reaction orders of both reactants were determined by detecting the instant concentrations of them during 1 h using a benzyl ether formation reaction from 2-phenylethanol **1a** and benzyl alcohol **2** as reactants. The concentration or natural logarithm of the concentration against time graph for the reactants is shown in Figure 1.

The kinetic plot using 2-phenylethanol was a straight line in Figure 1a, indicating that the rate of the ether formation reaction was zero-order in 2-phenylethanol. The kinetic plot in Figure 1b revealed that the kinetic behaviour of benzyl alcohol was first-order, which was consistent with the results that we obtained in isotope labelled experiment. Consequently, it could be reasonably deduced that the formation of the benzyl carbocation was rate-limiting, indicating an S_N1 mechanism of the benzyl ether formation process.

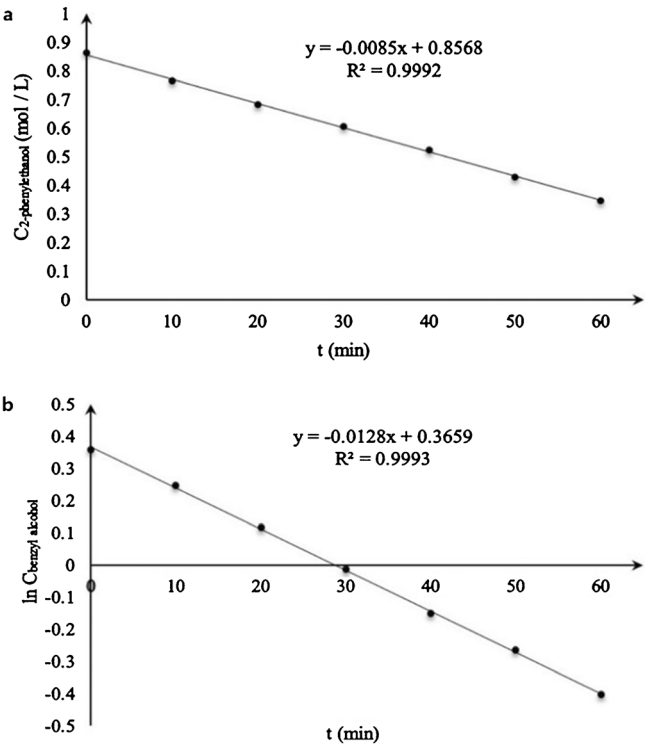


Figure 1. The kinetic plot of benzyl ether formation reaction. a) netic plot of 2-phenylethanol (with 10 equivalents of benzyl alcohol, 120 °C). b) The kinetic plot of benzyl alcohol (with 10 equivalents of 2-phenylethanol, 120 °C).

Development of the Etherification Reactions

Encouraged by the successful benzyl and *tert*-butyl etherifications of a variety of alcohols and the detailed mechanism study, we then tested the possibility of increasing the stability of carbocation by introducing an electron-donating group on the phenyl ring of the benzyl alcohol to develop more mild and useful alkylating conditions. Commercially available *para*-methoxybenzyl alcohol was first chosen as alkylating reagent to perform this etherification reaction as PMB is a popular protecting group in organic synthesis. As expected, the temperature of PMB protection of different alcohols can be reduced by 70 °C using toluene as solvent companied with a decreased efficiency, which was induced by homo-coupling of *para*-methoxybenzyl alcohol itself (Table 4).

We next envisioned the replacement of *tert*-butyl alcohol by triphenylmethanol as the alkylating reagent, which might decrease the temperature and eliminate the homo-etherification by-product. To our delight, we found that when using the triphenylmethanol not only the reaction temperature could be dropped from 120 °C to 80 °C, but also the ratio of the two alcohols could also be decreased from 10:1 to 1:1 in neat conditions or with toluene as solvent for solid alcohol substrates. Furthermore, the aliphatic alcohols gave excellent yields (Table 5, **6a**–**6e**) and halogen-substituted alcohols provided satisfactory yields (Table 5, **6f**–**6h**). Protection of substrates containing ether and silicon ethers afforded the corresponding tritylated products with satisfactory yields (Table 5, **6i** and **6j**). Substrates containing an alkyne could also afford the product accompanied by the *in situ* formation of the methyl ketone (Table 5, **6k**). The method can also selectively protect primary alcohols in the presence of secondary and tertiary alcohols (Table 5, **6m** and **6n**). The reaction exhibited good tolerance of various functional groups such as ketone, ester, amide, silyl ether and acetal (Table 5, **6l**, **6o**–**6r**). However, for secondary alcohols, the efficiency was reduced dra-

Table 4. Scope of the gold(I)-catalyzed *para*-methoxybenzyl ether formation reaction.

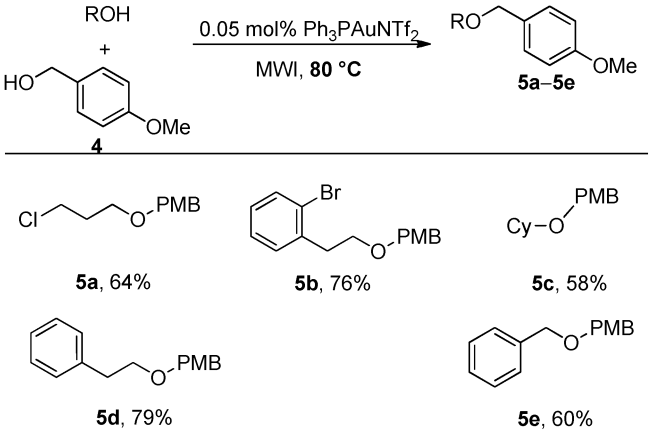
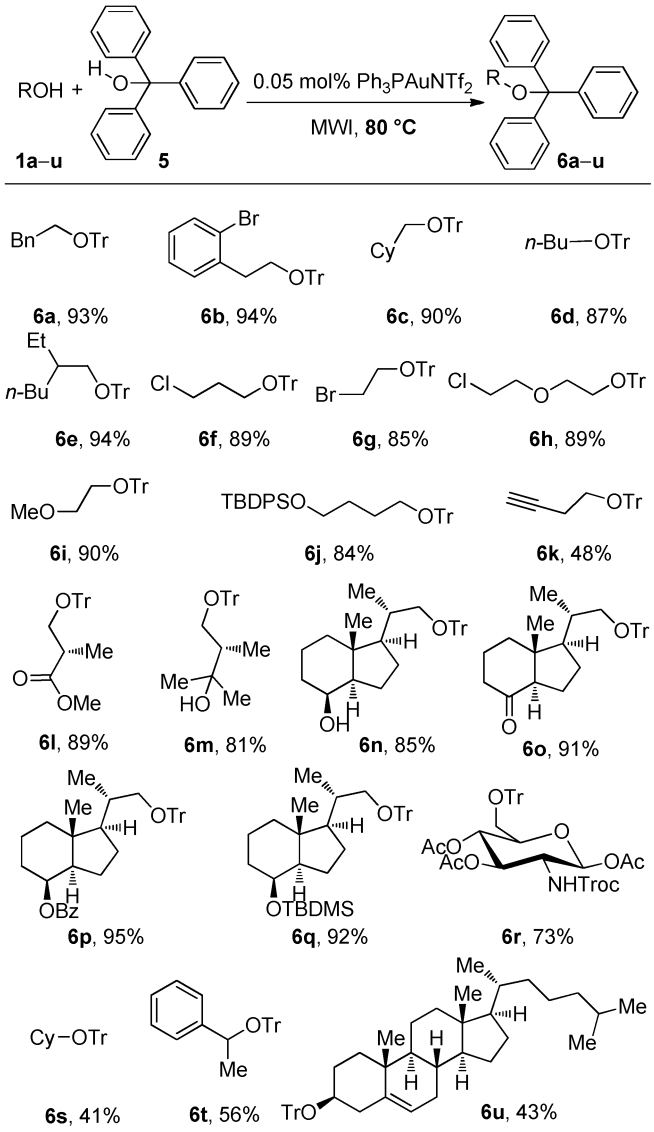
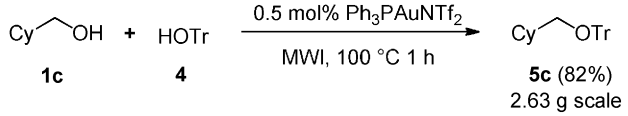


Table 5. Scope of the gold(I)-catalyzed trityl ether formation reaction.





Scheme 2. Gram-scale synthesis of **5c**.

matically due to the intrinsically hindered nature of the substrates (Table 5, **6s**–**6u**).

Importantly, the trityl ether formation reaction is not limited to the small scale used for the scope and limitation studies as it could be conveniently performed on a 2.63 g scale in 82% yield by heating **1c** and **4** in neat conditions using 0.5 mol% catalyst at 100 °C (Scheme 2).

Conclusions

In conclusion, we have demonstrated a simple, clean and alternative gold(I)-catalyzed unsymmetrical ether formation strategy which utilizes benzyl, *tert*-butyl and trityl alcohols as alkylating reagents. Furthermore, $Ph_3PAuNTf_2$ is commercially available and is efficient at very low catalyst loadings. Mechanistic investigations using oxygen-18 labelled alcohols analyzed by GC-MS and reaction kinetic data suggest that cleavage of the carbon-oxygen bond on the alkylating reagents dominated during the ether formation as evidenced by no incorporation of heavy oxygen into the ether products and the ether formation reaction proceeds *via* an S_N1 mechanism.

This method provides a rapid and straightforward access to benzyl, PMB, *tert*-butyl and trityl ethers with a wide range of substituents, which should find extensive applications as a new strategy for introducing alcohol protecting groups in organic synthesis.

Experimental Section

General Procedures

All reactions were conducted under an inert atmosphere of dry nitrogen. Unless otherwise noted, reagents were obtained commercially and used without further purification. Toluene was distilled from sodium under a nitrogen atmosphere. TLC analysis of reaction mixtures was performed on Dynamicadsorbents silica gel F-254 TLC plates. Flash chromatography was carried out on Zeoprep 60 (200–300 mesh) silica gel. ^1H and ^{13}C NMR spectra were recorded with Bruker Avance-III 600 spectrometers and referenced to $CDCl_3$ and DMSO-d_6. HR-ESI-MS were recorded on a Bruker micro-TOFQ-Q instrument. GC-MS were recorded on an Agilent 6890N/5975 instrument. IR spectra were recorded on a Bruker IFS 55 spectrometer. Melting points were determined on a Thomas Hoover capillary melting

point apparatus. Microwave reactions were performed in a CEM discover microwave reactor.

General Procedures for the Synthesis of Benzyl Ethers

To a solution of the $Ph_3PAuNTf_2$ (0.00025 mmol, 0.2 mg) in the benzyl alcohol (1.5 mmol, 162.2 mg) was added the substrate (0.5 mmol) under a nitrogen atmosphere. Then the solution was irradiated with microwaves at 150 °C for 0.5 h. The crude mixture was purified by flash column chromatography (hexanes) to afford the ether products.

[(Benzyloxy)(2-isopropylphenyl)methylene]dibenzene (3p): Colorless oil; yield: 94% (EtOAc/petroleum ether = 1:80); mp 100.6–101.9 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.57 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 7.7 Hz, 4H), 7.41 (d, J = 7.5 Hz, 2H), 7.37–7.29 (m, 4H), 7.25–7.20 (m, 5H), 7.12 (t, J = 7.3 Hz, 3H), 4.20 (s, 2H), 3.20 (hept, J = 6.7 Hz, 1H), 0.75 (d, J = 6.7 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 150.39, 145.64, 139.33, 139.27, 130.17, 128.62, 128.51, 128.40, 128.10, 127.87, 127.28, 126.92, 126.62, 124.77, 87.76, 66.71, 29.50, 24.09; IR (thin film, cm^{-1}) 3451, 3083, 3061, 3028, 2999, 2956, 2922, 2887, 2852, 1484, 1446, 1383, 1087, 1065, 761, 741, 711; HR-MS (ESI): m/z = 415.2030, calcd. for $C_{29}H_{28}ONa$: 415.2032.

General Procedures for the Synthesis of *tert*-Butyl Ethers

The substrate (0.5 mmol), $Ph_3PAuNTf_2$ (0.005 mmol, 3.7 mg) and *tert*-butyl alcohol (5 mmol, 370 mg) were added in a dried vessel under a nitrogen atmosphere. Then the solution was irradiated with microwavea at 120 °C for 0.5 h. The crude mixture was purified by flash column chromatography (hexanes) to afford the products.

(1*R*,3a*R*,7a*R*)-1-[(*S*)-1-(*tert*-Butoxy)propan-2-yl]-7a-methylhexahydro-1*H*-inden-4(2*H*)-one (4j): Colorless oil; yield: 75% (EtOAc/petroleum ether = 1:20); ^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.24 (dd, J = 8.6, 3.4 Hz, 1H), 2.97 (dd, J = 8.3, 7.6 Hz, 1H), 2.36–2.28 (m, 2H), 2.16 (dt, J = 15.1, 5.7 Hz, 1H), 2.04 (m, 1H), 1.90–1.83 (m, 1H), 1.73 (dt, J = 12.7, 4.3 Hz, 2H), 1.68 (d, J = 9.2 Hz, 2H), 1.46 (m, 2H), 1.36–1.27 (m, 1H), 1.27–1.21 (m, 1H), 1.09 (s, 9H), 1.00 (s, 3H), 0.92 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 212.09, 71.64, 65.55, 59.97, 48.16, 46.82, 35.65, 35.26, 27.33, 27.14, 22.60, 20.64, 19.70, 17.52; IR (thin film): ν = 3422, 2922, 2852, 3345, 1708, 1632, 1460, 1384, 1328, 1271, 1129, 878, 840, 780, 702, 669, 645, 619, 516 cm^{-1}; HR-MS (ESI): m/z = 289.2136, calcd. for $C_{17}H_{30}O_2Na$: 289.2138.

(2*S*,3*R*,4*R*,5*S*,6*R*)-6-(*tert*-Butoxymethyl)-3-{[(2,2,2-trichloroethoxy)carbonyl]amino}tetrahydro-2*H*-pyran-2,4,5-triyl triacetate (4k): Colorless oil; yield: 75% (EtOAc/petroleum ether = 1:6); ^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.18 (d, J = 9.1 Hz, 1H), 6.02 (d, J = 3.4 Hz, 1H), 5.22–5.10 (m, 1H), 5.06 (t, J = 9.8 Hz, 1H), 4.94 (d, J = 12.5 Hz, 1H), 4.72 (d, J = 12.5 Hz, 1H), 3.99–3.91 (m, 2H), 3.39 (td, J = 10.6, 3.4 Hz, 2H), 2.15 (s, 3H), 1.96 (s, 3H), 1.90 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 169.70, 169.24, 168.99, 154.78, 96.10, 89.64, 73.52, 72.54, 70.61, 70.45, 68.52, 59.65, 52.62, 40.04, 27.00, 20.86, 20.44; IR (thin film): ν = 3425, 2922, 2852, 2344, 1753, 1632, 1540, 1448, 1384, 1218, 1128, 778, 705, 619, 477 cm^{-1}; HR-MS (ESI): m/z = 560.0825, calcd. for $C_{19}H_{30}Cl_3NO_{10}Na$: 560.0828.

General Procedure for the Synthesis of *para*-Methoxbenzyl Ethers

To a solution of the substrate (0.5 mmol) in anhydrous toluene (0.5 mL), $Ph_3PAuNTf_2$ (0.005 mmol, 0.2 mg) and *para*-methoxybenzyl alcohol (1.5 mmol, 207.2 mg) were added under a nitrogen atmosphere. Then the solution was irradiated with microwaves at 80 °C for 0.5 h. The crude mixture was purified by flash column chromatography to afford the products.

General Procedures for the Synthesis of Trityl Ethers

To a dried vessel the substrate (0.5 mmol), $Ph_3PAuNTf_2$ (0.00025 mmol, 0.2 mg) and triphenylmethanol (0.5 mmol, 130.1 mg) were added under a nitrogen atmosphere. The reaction mixture was irradiated with microwaves at 80 °C for 0.5 h. The crude mixture was purified by flash column chromatography to afford the products.

[(2-Bromophenethoxy)methanetriyl]tribenzene (5b): White solid; yield: 94% (EtOAc/petroleum ether = 1:80); mp 137.9–139.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.55 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 7.7 Hz, 6H), 7.29 (t, J = 7.5 Hz, 7H), 7.26–7.19 (m, 4H), 7.10 (t, J = 7.3 Hz, 1H), 3.36 (t, J = 6.8 Hz, 2H), 3.09 (t, J = 6.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 144.41, 138.83, 132.87, 131.79, 128.88, 128.13, 127.93, 127.43, 127.07, 125.00, 86.88, 63.22, 37.01; IR (thin film); ν = 3056, 2946, 2918, 2874, 1959, 1757, 1489, 1471, 1447, 1221, 1198, 1084, 1064, 766, 758, 751, 659, 647, 632 cm^{-1}; HR-MS (ESI): m/z = 467.0935, calcd. for $C_{27}H_{25}BrONa$: 467.0981.

{[(2-Ethylhexyl)oxy]methanetriyl}tribenzene (5e): Colorless oil; yield: 94% (EtOAc/petroleum ether = 1:80); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.47 (d, J = 7.5 Hz, 6H), 7.30 (t, J = 7.7 Hz, 6H), 7.23 (t, J = 7.3 Hz, 3H), 2.99 (qd, J = 9.0, 5.3 Hz, 2H), 1.52–1.48 (m, 1H), 1.46 (dd, J = 13.7, 6.6 Hz, 1H), 1.42–1.35 (m, 2H), 1.32 (dd, J = 13.7, 7.9 Hz, 1H), 1.27 (dd, J = 15.7, 7.8 Hz, 2H), 1.15 (dd, J = 15.7, 7.8 Hz, 2H), 0.87 (t, J = 7.3 Hz, 3H), 0.79 (t, J = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 144.83, 129.02, 127.83, 126.96, 86.24, 65.39, 40.51, 30.96, 29.28, 24.39, 23.26, 14.32, 11.38; IR (thin film): ν = 3058, 3022, 2957, 2927, 2871, 1759, 1597, 1490, 1447, 1066, 762, 745, 705, 661, 648, 632 cm^{-1}; HR-MS (ESI): m/z = 395.2350, calcd. for $C_{27}H_{32}ONa$; 395.2345.

***tert*-Butyldiphenyl[4-(trityloxy)butoxy]silane (5j):** Colorless oil; yield: 84% (EtOAc/petroleum ether = 1:80); ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.57 (d, J = 7.6 Hz, 4H), 7.44 (t, J = 6.9 Hz, 2H), 7.38 (t, J = 7.5 Hz, 4H), 7.34 (d, J = 8.0 Hz, 6H), 7.30 (t, J = 7.6 Hz, 6H), 7.23 (t, J = 7.1 Hz, 3H), 3.60 (t, J = 6.2 Hz, 2H), 2.96 (t, J = 6.2 Hz, 2H), 1.66–1.60 (m, 2H), 1.60–1.54 (m, 2H), 0.96 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 144.02, 134.93, 133.26, 129.69, 128.09, 127.75, 126.84, 85.74, 63.18, 62.69, 28.89, 26.60, 25.78, 18.70; IR (thin film): ν = 3447, 2922, 2852, 1640, 1448, 1384, 1112, 746, 703, 617, 486 cm^{-1}; HR-MS (ESI): m/z = 593.2846, calcd. for $C_{39}H_{42}O_2SiNa$: 593.2862.

(*R*)-2,3-Dimethyl-4-(trityloxy)butan-2-ol (5m): Colorless oil; yield: 81% (EtOAc/petroleum ether = 1:10); ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.37 (d, J = 7.4 Hz, 6H), 7.33 (t,

J=7.7 Hz, 6H), 7.25 (t, J=7.2 Hz, 3H), 4.04 (s, 1H), 3.26 (dd, J=8.9, 4.1 Hz, 1H), 2.74 (t, J=8.5 Hz, 1H), 1.82–1.61 (m, 1H), 0.96 (s, 3H), 0.95 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6): δ=144.12, 128.21, 127.77, 126.84, 85.90, 70.14, 65.02, 44.04, 27.64, 26.74, 13.25; IR (thin film): ν=3458, 3086, 3058, 3032, 2970, 2927, 2882, 1958, 1727, 1631, 1597, 1490, 1449, 1384, 1176, 1154, 1060, 776, 766, 705, 648, 633, 510 cm^{-1}; HR-MS (ESI): m/z=383.1978, calcd. for $C_{25}H_{28}O_2Na$: 383.2019.

(1*R*,3a*R*,4*S*,7a*R*)-7a-Methyl-1-[(*S*)-1-(trityloxy)propan-2-yl]octahydro-1*H*-inden-4-yl benzoate (5p): white solid; yield: 95% yield (EtOAc/petroleum ether=1:50); mp 89.5–90.9 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ=7.95 (d, J=7.9 Hz, 2H), 7.64 (t, J=7.3 Hz, 1H), 7.52 (t, J=7.6 Hz, 2H), 7.37 (d, J=8.0 Hz, 6H), 7.33 (t, J=7.6 Hz, 6H), 7.24 (t, J=7.1 Hz, 3H), 5.26 (d, J=1.9 Hz, 1H), 3.06 (dd, J=8.8, 2.9 Hz, 1H), 2.70–2.65 (m, 1H), 1.98 (d, J=12.6 Hz, 1H), 1.84 (d, J=14.0 Hz, 1H), 1.71 (dt, J=13.7, 8.5 Hz, 1H), 1.60–1.45 (m, 4H), 1.39–1.31 (m, 2H), 1.26–1.16 (m, 4H), 1.10 (d, J=6.5 Hz, 3H), 0.94 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6): δ=165.45, 144.06, 133.11, 130.13, 128.95, 128.73, 128.18, 127.75, 126.84, 85.56, 71.51, 67.28, 52.59, 50.38, 41.33, 36.39, 29.82, 25.90, 22.13, 17.50, 13.14; IR (thin film): ν=3450, 3059, 3021, 2920, 2851, 1958, 1640, 1596, 1493, 1447, 1384, 1133, 1078, 1031, 759, 735, 700, 619, 606, 494, 468 cm^{-1}; HR-MS (ESI): m/z=581.3023, calcd. for $C_{38}H_{52}O_2SiNa$: 581.3026.

***tert*-Butyldimethyl{[(1*R*,3a*R*,4*S*,7a*R*)-7a-methyl-1-[(*S*)-1-(trityloxy)propan-2-yl]octahydro-1*H*-inden-4-yl]oxy}silane (5q):** Colorless oil; yield: 92% (EtOAc/petroleum ether=1:50); ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.45 (d, J=7.6 Hz, 6H), 7.29 (t, J=7.7 Hz, 6H), 7.22 (t, J=7.3 Hz, 3H), 3.97 (d, J=1.9 Hz, 1H), 3.12 (dd, J=8.7, 3.2 Hz, 1H), 2.74–2.69 (m, 1H), 1.97 (d, J=12.4 Hz, 1H), 1.80 (dt, J=13.8, 3.7 Hz, 1H), 1.69–1.59 (m, 2H), 1.51–1.40 (m, 2H), 1.40–1.33 (m, 2H), 1.25–1.15 (m, 2H), 1.15–1.05 (m, 5H), 1.04–0.95 (m, 1H), 0.95–0.85 (m, 12H), 0.00 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=144.86, 129.04, 127.82, 126.94, 86.25, 69.62, 68.22, 53.91, 53.06, 42.39, 40.86, 37.16, 34.68, 26.86, 26.04, 23.32, 18.25, 17.99, 17.88, 13.92, −4.58, −4.94; IR (thin film): ν=3449, 3059, 3023, 2927, 2853, 1643, 1490, 1471, 1449, 1385, 1165, 1129, 1093, 1070, 1024, 775, 704, 619 cm^{-1}; HR-MS (ESI): m/z=591.3624, calcd. for $C_{38}H_{52}O_2SiNa$: 591.3629.

(2*S*,3*R*,4*R*,5*S*,6*R*)-3-{[(2,2,2-Trichloroethoxy)carbonyl]-amino}-6-[(trityloxy)methyl]tetrahydro-2*H*-pyran-2,4,5-triyl triacetate (5r): White solid; yield: 73% (EtOAc/petroleum ether=1:6); mp 107.9–109.2 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ=8.21 (d, J=9.1 Hz, 1H), 7.40–7.30 (m, 12H), 7.26 (t, J=6.5 Hz, 3H), 6.13 (d, J=3.4 Hz, 1H), 5.25 (t, J=9.9 Hz, 1H), 5.16 (t, J=10.2 Hz, 1H), 4.97 (d, J=12.5 Hz, 1H), 4.75 (d, J=12.5 Hz, 1H), 4.17–4.07 (m, 1H), 3.99 (d, J=10.1 Hz, 1H), 3.19 (d, J=9.9 Hz, 1H), 2.88 (dd, J=10.8, 3.2 Hz, 1H), 2.13 (s, 3H), 1.90 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=171.65, 168.85, 154.29, 145.47, 143.68, 129.89, 128.92, 128.13, 128.02, 127.97, 127.92, 127.23, 95.50, 90.89, 86.79, 74.88, 71.41, 71.18, 68.18, 61.61, 53.62, 21.16, 20.92, 20.83, 20.62; IR (thin film): ν=3437, 3060, 2921, 2851, 1756, 1643, 1450, 1384, 1218, 1129, 1034, 821, 746, 705, 633, 619, 477 cm^{-1}; HR-MS (ESI): m/z=744.1181, calcd. for $C_{34}H_{34}ClNO_{10}Na$: 744.1210.

Preparation of ^{18}O-Labelled Benzyl Alcohol

Sodium (0.05 g) was added to ^{18}O-labelled water (0.75 mL, 98% $^{18}OH_2$) in a flask, and then 1-chloromethylbenzene (0.5 mL) was added into the flask. The mixture was heated to 95 °C and refluxed for 48 h with continuous stirring. The product was purified by flash column chromatography and $C_6H_5CH_2{}^{18}OH$ (0.25 g) was obtained. The ^{18}O enriched benzyl alcohol was examined by GC-MS, and the abundance of $C_6H_5CH_2{}^{18}OH$ was determined to be 98%.

Acknowledgements

We thank the following for financial support: the National Natural Science Foundation of China (Grants 21202103), the Natural Science Foundation of Liaoning Province of China (Grants 2014020080). We acknowledge the program for innovative research team of the Ministry of Education and program for Liaoning innovative research team in university. We thank Prof. Ping Gong (Shenyang Pharmaceutical University) for facilities support and Mr. Patrick Michael Barbour (University of Colorado at Boulder) for the assistance in manuscript preparation.

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