Gold(I)-catalysed alcohol additions to cyclopropenes†

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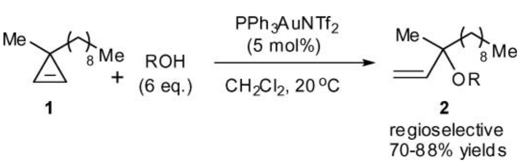
Gold(I)-catalysed addition of alcohols to 3,3-disubstituted cyclopropenes occurs in a highly regioselective and facile manner to produce alkyl *tert*-allylic ethers in good yields. The reaction is tolerant of sterically hindered substituents on the cyclopropene as well as primary and secondary alcohols as nucleophiles. In this full article, we report on the substrate scope and plausible mechanism, as well as the regioselectivity issues arising from subsequent gold(I)-catalysed isomerisation of tertiary to primary allylic ethers.

Introduction

Ethers are ubiquitous in organic chemistry and their preparation is one of the most fundamental reactions in organic synthesis. Alkyl allylic ethers, for example, are found in natural products and are versatile substrates and building blocks in organic synthesis.[1] However, the most widely used method for formation of ethers, the Williamson ether synthesis, is seldom useful for preparing tertiary ethers as elimination reactions tend to be favored when tertiary alkoxides or tertiary halides are used.[2] Despite recent advances, a mild, efficient and general method for the synthesis of alkyl *tert*-allylic ethers still remains a challenging topic for synthetic chemists.[3,4]

We recently disclosed our preliminary results on two separate methods of forming alkyl *tert*-allylic ethers: regioselective gold(I)-catalysed[5] addition of alcohols to cyclopropenes[6] (Scheme 1) and regioselective gold-catalysed hydroalkoxylation of allenes.[7] In this full article, we expand on the substrate scope, possible mechanism and regioselectivity issues of the gold-catalysed addition of alcohols to cyclopropenes as well as studies into the gold-catalysed isomerisation of *tert*-allylic ethers to primary allylic ethers.

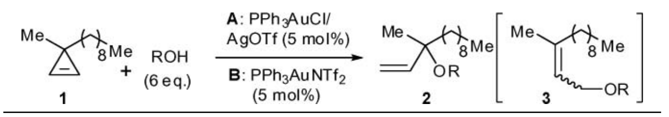


Scheme 1 Preliminary results on the regioselective gold(I) catalysed ring-opening addition of cyclopropene **1** to form *tert*-allylic ethers **2**.

Results and discussion

We recently initiated a programme to investigate gold(I) catalysed reactions of cyclopropenes[8] in the presence of nucleophiles.[9] During our initial studies, we found that Au(I) can catalyse the intermolecular addition of alcohols to 3,3-disubstituted cyclopropene **1** in a highly regioselective manner to produce alkyl *tert*-allylic ethers in good yields (Table 1).[5,10,11]

Table 1 The regioselective gold(I) catalysed ring-opening addition of cyclopropene **1** with a variety of alcohols to form *tert*-allylic ethers



Entry[a]	ROH	Method	Yield of 2[b]	Product	Ratio 2:3[c]
1	MeOH	B	86%	**2a**	>99 : 1
2	EtOH	A	64%	**2b**	>99 : 1
3	EtOH	B	83%	**2b**	>99 : 1
4	Allyl alcohol	B	88%	**2c**	>99 : 1
5	Benzyl alcohol	A	78%	**2d**	>99 : 1
6	$HOCH_2CH_2CH{=}CH_2$	B	88%	**2e**	>99 : 1
7	$HOCH_2CH_2Ph$	B	77%	**2f**	>99 : 1
8	*i*-PrOH	A	N/A[d]	**2g**	2.5 : 1
9	*i*-PrOH	B	70%	**2g**	97 : 3
10	*t*-BuOH	B	traces	**2h**	N/A
11[e]	H_2O	B	34%	**2i**	>99 : 1
12	4-methoxyphenol	B	—		N/A

[a] All reactions were carried out at 20 °C in CH_2Cl_2 for 1–2 h unless otherwise stated. [b] Isolated yield, unless otherwise stated. [c] Determined by ^{1}H-NMR analysis of the crude mixture. [d] Reaction was allowed to stir for 4 days, after which ~50% conversion was observed to **2g** and **3g** (~30%), **4** and **5** (~20%). [e] 15 eq. of *t*-BuOH was added as a co-solvent and the reaction was allowed to stir for 24 h.

Primary alcohols add in excellent regioselectivities (>99 : 1 **2**:**3**, Entries 1–7, Table 1) and secondary alcohols in very good selectivity (97 : 3 **2**:**3**, Entry 9). It is of interest to note that the employment of air stable PPh_3AuNTf_2 catalyst[12] (Entry 9) produces superior activity, regioselectivity and yield in this case compared to PPh_3AuOTf (formed *in situ* with PPh_3AuCl and AgOTf, Entry 8). Tertiary alcohols, however, do not react under these conditions (<5% conversion, Entry 10). The steric bulk of the tertiary alcohol is very likely to blame for the diminished activity. Even water can successfully act as a nucleophile to produce the corresponding tertiary alcohol **2i**, albeit in low conversion and yield (34%, Entry 11).[13] An attempt to replace the alcohol nucleophile with phenol, however, was not successful (Entry 12), presumably due to the reduced nucleophilicity of phenol.

Upon repeating the reaction shown in Entry 3 with a reduced Au(I) catalyst loading (1 mol%), complete conversion to **2b** (>99% regioselectivity) is still observed within 1.5 h. Indeed,

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† Electronic supplementary information (ESI) available: Experimental procedures, characterisation of all new compounds and copies of ^{1}H-NMR and ^{13}C-NMR spectra. See DOI: 10.1039/c0ob00085j

reactions with primary alcohol nucleophiles such as EtOH (Entry 3) are facile and often complete in <10 min with 5 mol% catalyst.

Having investigated the scope of the alcohol nucleophile, we then set out to study the scope of the cyclopropene substrates employed (Table 2).[14,15] A range of cyclopropenes reacts smoothly with alcohols to produce *tert*-allylic ethers in good regioselectivity and yields. Changing a substituent from alkyl (*e.g.* Entries 1–2) to benzyl appears to have no detrimental effect on the regioselectivity or yield (Entries 3–4). To our delight, even more sterically encumbered substituents (*i*-Pr and Bn in **9**) are tolerated with a primary alcohol nucleophile to deliver product **10** in excellent regioselectivity and good yield (>99 : 1, 73%, Entry 5). Remarkably, even the more sterically hindered cyclopropene **11** provides good regioselectivity (87 : 1) with a primary alcohol nucleophile at room temperature (Entry 6). Excellent regioselectivity (>99 : 1) can be achieved with cyclopropene **11** by cooling the reaction mixture down to 0 °C to provide **12** in 64% yield. When combining the sterically hindered cyclopropene **9** with a hindered secondary alcohol, however, the regioselectivity and yield begins to drop (92 : 8, 45%, Entry 7).

Finally, even an aryl substituent is tolerated (Entries 8 and 9). Since there is literature precedence for *intra*molecular rearrangements of aryl substituted cyclopropenes to form indenes in the presence of gold(I),[6,9] it is pleasing that intermolecular alcohol additions are viable even with substrate **14**. The regioselectivity with **14**, however, is rather surprising. Reaction with *n*BuOH under standard conditions produces a non-regioselective 1 : 1 mixture of primary and tertiary ethers. Reducing the temperature to 10 °C and increasing the alcohol to 15 equivalents successfully yields the tertiary ether **15** regioselectively with *n*BuOH (65%, Entry 8). Surprisingly, changing the alcohol nucleophile to phenethyl alcohol completely switches the regioselectivity to the primary ether **16** (Entry 9, **16** formed regio- and stereoselectively, 65%)! These results suggest that with aryl substituted cyclopropene **14**, *n*BuOH might be more effective in inhibiting the isomerisation of the *tert*-allylic ether product **15** to the primary allylic ether (*vide infra*).[16]

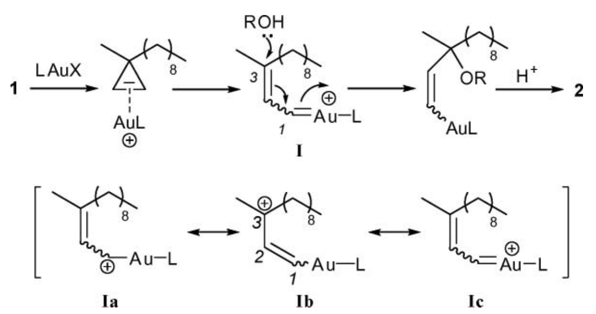
Since tertiary alcohols do not react under these conditions, we postulated that the unprotected diol **17** would react chemoselectively at the primary alcohol. Indeed, the reaction proceeds smoothly and chemoselectively to furnish **18** in 58% yield (Entry 10). Neopentyl glycol **19**, however, behaves differently and forms a 1 : 1 mixture of primary and tertiary ether products under standard conditions (room temperature, Entry 11). We postulate that the proximity of a pendant alcohol promotes the gold(I)-catalysed isomerisation of the tertiary to primary ether (*vide infra*). Cooling the reaction mixture increases the regioselectivity (>99 : 1) but the yield of **20** remains modest (33%) as oligomeric by-products are also formed.

When optically pure (*R*)-PhMeCHCH$_2$OH **21** is employed as the nucleophile, the reaction is still regioselective, but not diastereoselective (Entry 12). Employment of a secondary chiral alcohol (*R*)-PhMeCHOH **23** with cyclopropene **6** also results in good regioselectivity (96 : 4), but poor diastereoselectivity (d.r. ~1 : 1, Entry 13).

A small catalyst screen shows gold(I) catalysts to be unique in their selectivity for the tertiary allylic ether product **2** (Table 3). The gold(I) catalyst PPh$_3$AuOTf, formed *in situ* from PPh$_3$AuCl and AgOTf results in excellent selectivity for **2b** and moderately good isolated yield (64% **2b**, Entry 1).[17] Replacing the OTf$^-$ counterion with SbF$_6^-$ does not affect the selectivity, but the isolated yield is slightly lower (55% **2b**, Entry 2). Changing from PPh$_3$ to an *N*-heterocyclic carbene (NHC) ligand on Au(I) [(IPr)AuCl/AgOTf] also provides **2b** exclusively (69%, Entry 3). In all of the above cases, a hygroscopic silver salt is required as co-catalyst to generate the active catalyst *in situ*, resulting in the possibility of there being slight traces of TfOH, HSbF$_6$ or [LAu–OH$_2$]$^+$ present during the reaction. Reaction with the air stable PPh$_3$AuNTf$_2$, which does not require any hygroscopic co-catalyst, produces an even better yield of the product **2b** (83%, entry 4).

In an effort to ascertain whether the reaction is truly gold-catalysed, we carried out some control reactions (Table 3). The control reaction employing 5 mol% of TfOH as catalyst results in no reaction, suggesting that traces of acid are not catalytically active (Entry 5). Reaction with AgOTf as catalyst is also greatly inferior to gold(I), resulting in incomplete consumption of the starting material, along with a complex mixture of products (Entry 6). Next, we wanted to ascertain if Rh(OAc)$_2$, which is believed to ring-open related cyclopropenes to form the corresponding rhodium carbene intermediates, could similarly catalyse this reaction.[18] In stark contrast to Au(I), employment of Rh(OAc)$_2$ as catalyst, produces a mixture of **25**, along with traces of both **2b** and **3b** (Entry 7). Interestingly, the use of Au(III) instead of Au(I) catalyst also completely changes the outcome of the reaction, with the aldehyde **25** being the major product (Entry 8). This difference in reactivity further exemplifies the differences between Au(I) and Au(III) catalysts.[19,20]

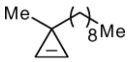
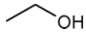
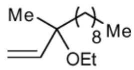
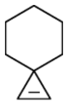
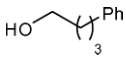
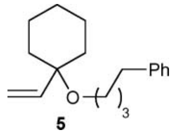
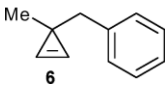
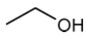
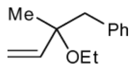
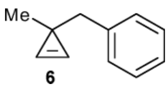
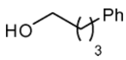
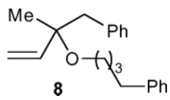
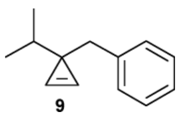
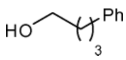
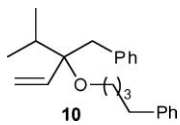
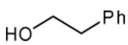
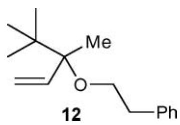
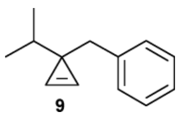
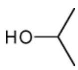
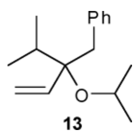
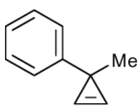
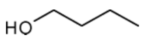
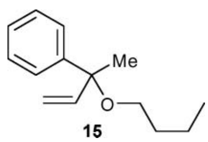
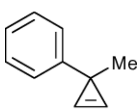
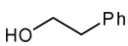
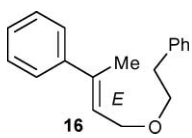
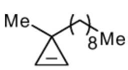
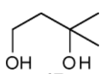
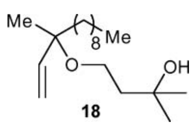
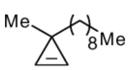
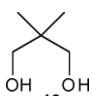
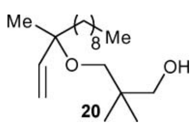
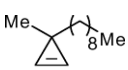
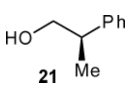
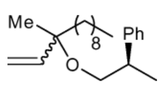
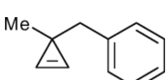
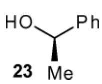
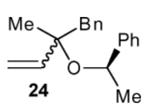
Our proposed mechanism for the regioselective gold(I) catalyzed ring-opening addition of cyclopropene **1** with alcohols is shown in Scheme 2. Activation of the strained cyclopropene double bond by gold(I) results in ring-opening to produce the proposed intermediate **I**, which can be represented as mesomeric structures **Ia**, **Ib** or **Ic**.[21,22] Attack of the alcohol at the C-*3* position followed by protodemetallation thus furnishes the *tert*-allylic ether **2**. In order to probe the validity of our proposed mechanism, the reaction was carried out with CD$_3$OD as the nucleophilic alcohol (Scheme 3). Deuterium is indeed incorporated at the C-*1* position (90%), lending support to our proposed mechanism.



Scheme 2 Proposed mechanism for the regioselective gold(I)-catalysed ring-opening addition of **1** with alcohols.

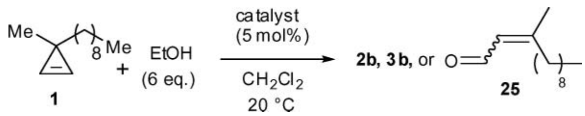
It is of interest to note that an excess of alcohol is necessary to ensure good regioselectivity (Scheme 4). When the alcohol nucleophile is reduced from excess to 1 equivalent, the regioselectivity of **2b**:**3b** drops from >99 : 1 to 2 : 1. However, when the reaction is carried out with 1 equiv. of EtOH and 5 equiv. of

Table 2 The regioselective gold(I) catalysed ring-opening addition of alcohols to a variety of cyclopropenes[a]

Entry	Cyclopropene	ROH	Product	Yield (%)[b]	Regioselectivity[c]
1	 **1**		 **2b**	83%	>99 : 1
2	 **4**		 **5**	87%	>99 : 1
3	 **6**		 **7**	80%	>99 : 1
4	 **6**		 **8**	86%	>99 : 1
5	 **9**		 **10**	73%	>99 : 1
6	 **11**		 **12**	64%[d]	>99 : 1 (0 °C) 87 : 1 (20 °C)
7	 **9**		 **13**	45%	92 : 8
8[e]	 **14**		 **15**	65%	>99 : 1
9[e]	 **14**		 **16**	65%	>1 : 99
10[f]	 **1**	 **17**	 **18**	58%	>99 : 1
11	 **1**	 **19**	 **20**	16%, 16% 33%	1 : 1 (20 °C) >99 : 1 (10 °C)
12	 **1**	 **21**	 **22**	65%	>99 : 1 dr~1 : 1
13	 **6**	 **23**	 **24**	46%	96 : 4 dr~1 : 1

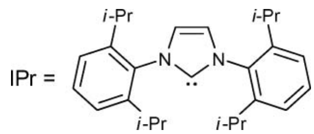
[a] All reactions carried out with PPh_3AuNTf_2 (5 mol%) and 6 equiv. ROH at 20 °C in CH_2Cl_2 for 1–2 h unless otherwise stated. [b] Isolated yield, unless otherwise stated. [c] Determined by ^1H-NMR analysis of the crude mixture. Regioselectivity of the tertiary:primary allylic ether product. [d] Reaction was carried out at 0 °C for 16 h. [e] 15 Equiv. ROH, 10 °C, 4 h. [f] Reaction carried out with 2 equiv. diol for 16 h.

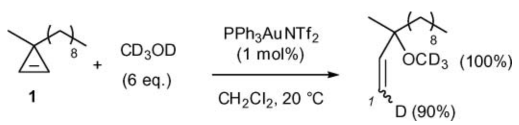
Table 3 Transition metal-catalysed reaction of **1** with EtOH



Entry	Catalyst	Time/h	Result
1	$PPh_3AuCl/AgOTf$	1.5[a]	**2b** [b]only, 64% yield
2	$PPh_3AuCl/AgSbF_6$	1.5	**2b** [b]only, 55% yield
3	(IPr)AuCl/AgOTf	1.5	**2b** [b]only, 69% yield
4	PPh_3AuNTf_2	1.5	**2b** [b]only, 83% yield
5	HOTf	24	No reaction[c]
6	AgOTf	24	7 : 4 ratio of **1**:**2b** along with traces of **3b**, **25** and other unidentified by-products[c]
7	$Rh(OAc)_2$	24	Major product: **25** (with traces of **2b** and **3b** and other unidentified by-products)[c]
8	$AuCl_3$	24	Complex mixture of products: **25** (with traces of **2b** and **3b** and other unidentified by-products)[c]

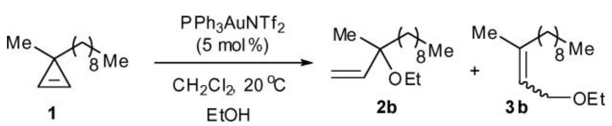
[a] No change in yield or selectivity is observed if the reaction is allowed to stir for 24 h. [b] Isolated yield; **3b** and **25** were not detected by ^{1}H-NMR analysis of the crude mixture. [c] By ^{1}H-NMR analysis of the crude mixture. (IPr = NHC ligand *bis*-2,6-diisopropylphenyl imidazolylidinene) .





Scheme 3 The regioselective gold(I) catalyzed ring-opening addition of **1** with CD_3OD.

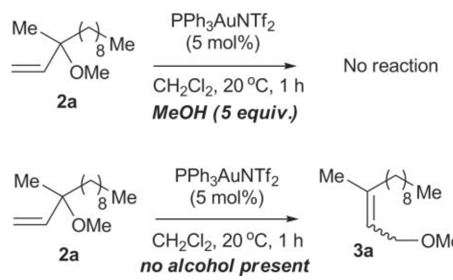
t-BuOH, as an additive, the regioselectivity is retained (>99% **2b**, 64% yield). Thus the alcohol nucleophile need not be in excess, as long as a non-reactive alcohol such as *t*-BuOH is present in excess to help maintain good regioselectivities. This approach of having a cheap, non-reacting alcohol additive may be useful if the nucleophilic alcohol employed is expensive.[23]



Equivalents of EtOH	Ratio **2b**:**3b**
6 equiv.	>99:1
3 equiv.	>99:1
1 equiv.	2:1
1 equiv. + 5 equiv. *t*BuOH	>99:1

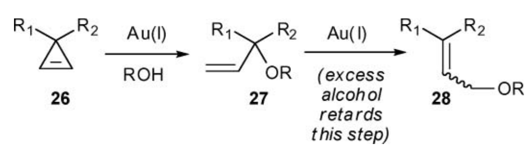
Scheme 4 Dependence of regioselectivity on excess alcohol

Next, we sought to explain the need for excess alcohol to ensure good regioselectivity. As shown in Scheme 5, the *tert*-allylic ether product **2a** was isolated and resubjected to the reaction conditions in the absence and presence of excess methanol. The tertiary ether **2a** isomerises to the primary ether **3a** under gold(I)-catalysis, but addition of excess alcohol appears to stop this isomerisation (Scheme 5). The isomerisation **2a**→**3a** is not reversible (both in the absence and presence of excess MeOH). The isomerisation appears catalyst dependent: subjection of **2b** to NHC-gold catalyst (IPr)AuCl/AgOTf (5 mol%) in CH_2Cl_2 at room temperature results in no reaction whereas $PPh_3AuCl/AgOTf$ (5 mol%) results in a mixture of **2b**, **3b** and other unidentified by-products after 1 h at room temperature. Possible explanations for the inability of (IPr)AuOTf to isomerise *tert*-allylic ethers are the steric bulk of the IPr ligand,[24] or the less electrophilic gold(I) centre caused by the more σ-donating NHC catalyst.[25]



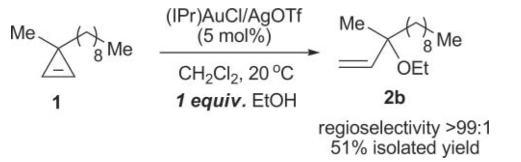
Scheme 5 Gold(I)-catalysed isomersation of *tert*-allylic ethers to primary allylic ethers[26]

With these results in hand, we propose that the gold(I)- catalysed addition of alcohols to 3,3-disubstituted cyclopropenes **26** occurs regioselectively to produce the kinetic *tert*-allylic ether product **27**. In the absence of excess alcohol, this kinetic product can be isomerised by gold(I) to the more stable primary allylic ether **28** (Scheme 6).[27] In the presence of excess alcohol, we postulate that the gold(I) catalyst PPh_3AuNTf_2 is deactivated such that it is no longer able to isomerise **27**→**28**,[28] thus excellent regioselectivity for the tertiary ether **27** is observed.



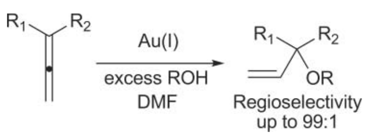
Scheme 6 Effect of excess alcohol on the gold(I)-catalysed addition of alcohols to cyclopropenes

Since the NHC catalyst (IPr)AuOTf does not isomerise tertiary ether **2b** to primary ether **3b** even in the absence of excess alcohol (*vide supra*) excess alcohol should in principle not be necessary in order to achieve good selectivities with this catalyst system.[25] The alcohol addition to cyclopropene **1** was thus repeated with (IPr)AuCl/AgOTf (5 mol%) with only 1 equiv. of alcohol and indeed, only the tertiary ether **2b** is observed (Scheme 7). The isolated yield, however, is not as high as with PPh_3AuNTf_2 as catalyst under our standard conditions (51% *vs.* 83%).



Scheme 7 Excess alcohol is *not* required for good regioselectivity with the NHC–Au catalyst (IPr)AuOTf, as the catalyst does not isomerise **2b** to **3b**.

These observations have recently helped us to switch the regioselectivity of the gold(I)-catalysed hydroalkoxylation of allenes to form *tert*-allylic ethers,[7] compared to the previously reported primary allylic ethers (Scheme 8).[29] The major benefit of utilising the hydroalkoxylation method shown in Scheme 8 is that 1,1-disubstituted allenes are more readily accessible [commercial (R_1=R_2=Me), or two steps from commercially available material *vs.* three steps for 3,3-disubstituted cyclopropenes].[30] On the other hand, the hydroalkoxylation method is much more sensitive to steric hindrance than the gold(I)-catalysed addition of alcohols to cyclopropenes described in this paper. For example, secondary alcohols provide poor regioselectivity (**27**:**28** 3 : 1) in the allene hydroalkoxylation reaction but are still excellent nucleophiles in the cyclopropene addition reaction (**27**:**28** 97 : 3, Entry 9, Table 1). We believe the two methods are thus complementary approaches towards alkyl *tert*-allylic ethers. Future work will focus on the extension of these reactions to enantioselective methods.



Scheme 8 Gold(I)-catalysed hydroalkoxylations of allenes[7]

Conclusions

Gold(I)-catalysed addition of alcohols to 3,3-disubstituted cyclopropenes occurs in a highly regioselective manner to produce alkyl *tert*-allylic ethers in good yields. The reaction is facile (as quick as <10 min), mild (20 °C), efficient (as low as 1 mol% catalyst loading can be used to no detrimental effect), and inert atmosphere and distilled solvents are not required. The reaction is tolerant of sterically hindered substituents on the cyclopropene as well as primary and secondary alcohols as nucleophiles. Excess alcohol is crucial for achieving high regioselectivities as it retards any subsequent isomerisation of the tertiary allylic ether products to primary allylic ethers.

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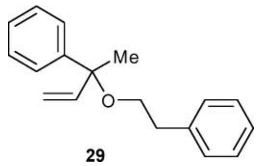

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