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Organohalide-catalyzed dehydrative O-alkylation between alcohols: a facile etherification method for aliphatic ether synthesis†

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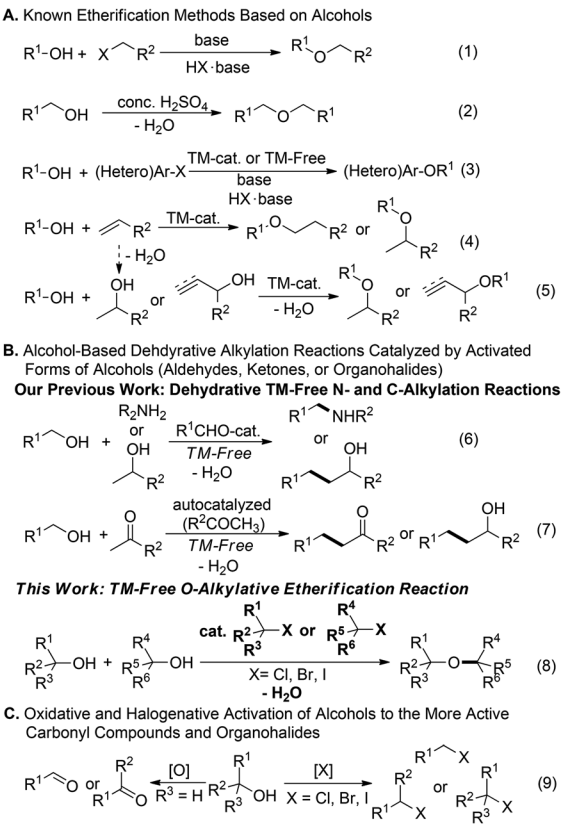
Organohalides are found to be effective catalysts for dehydrative O-alkylation reactions between alcohols, providing selective, practical, green, and easily scalable homo- and cross-etherification methods for the preparation of useful symmetrical and unsymmetrical aliphatic ethers from the readily available alcohols. Mechanistic studies revealed that organohalides are regenerated as reactive intermediates and recycled to catalyze the reactions.

Ethers are of fundamental significance in chemistry, as they can be widely used as solvents and intermediates for the synthesis of fine chemicals, pharmaceuticals, agrochemicals, polymers, materials, *etc*.[1–4] Traditionally, ethers were prepared from alcohols by the Williamson reaction (Scheme 1, eqn (1))[1a–c,5] or by strong acid-mediated dehydration methods (eqn (2)).[1a–c] Although the Williamson method is suitable for the synthesis of both symmetrical and unsymmetrical ethers, it requires strong bases and toxic and expensive organohalides, unsuitable for base-sensitive substrates, generates undesired waste salts, and may afford low yields of the products due to potential competing β-H elimination reaction and byproduct formation, especially with 2° and 3° substrates.[1a–c,5] It is thus mainly limited to primary ethers and has limited industrial applications. As for the acidic method, it uses strong and corrosive acids like sulfuric acid, unsuitable for acid-sensitive substrates and 2° and 3° alcohols due to the undesired formation of alkene byproducts.[1a–c] It is not only limited to symmetrical primary ethers, but also has the problems of harsh conditions and disposal of waste acids. During the past decades several other methodologies have also been developed, which mainly include transition metal (TM)-catalyzed improved Ullmann and Buclwald–Hartwig type coupling[2–4] and TM-free aromatic nucleophilic substitution[4] reactions of aryl halides (eqn (3)), TM-catalyzed hydroalkoxylation of alkenes (eqn (4)),[1e,6] and TM-catalyzed dehydration of the more active 2°, allylic, and propargylic alcohols (eqn (5)),[1e,7] as well as other methods including C–H activation reactions.[8]



Scheme 1 Background of research.

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†Electronic supplementary information (ESI) available: Detailed condition screening tables, experimental details, characterization of the products, details of the mechanistic studies, and ^{1}H and ^{13}C NMR spectra of the products. See DOI: 10.1039/c5gc00284b

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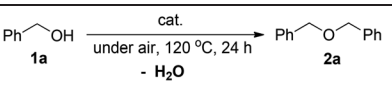
Although these methods have advantages like generality, atom-economy, and directness, they still have their respective limits such as the use of TM catalysts, ligands, excess amounts of bases or oxidants, and activated substrates, generation of waste salts, selectivity caused problems of catalyst and ligand fine tuning, harsh conditions, metal contamination problems, *etc*. The dehydration method (eqn (5))[1e,7] is in comparison a greener, more convenient, atom-economic, and preferable alternative for using the greener alcohols[9] as the substrates (many alkenes[1e,6] are in fact obtained from the alcohols *via* dehydration) and generating water as the byproduct. Recently Yi and co-workers reported an impressive Ru-catalyzed dehydration reaction of different alcohols for unsymmetrical ether synthesis.[7a] This method is advantageous for its generality, high selectivity, efficiency, and functional group tolerability, but it still requires the use of the sensitive and not readily-available cationic Ru–H complex as the catalyst and chlorinated solvents, and also requires a glove box and inert atmosphere protection for disposal of the catalyst and operation of the reactions. Therefore, developing simple and efficient etherification methods is still of great interest to date.

When studying the air-promoted TM-catalyzed dehydrative alkylation reactions[10] using alcohols as green alkylating reagents,[9] we realized that there should be more protocols for alcohol activation.[9a] Later, we accidentally found TM-free aldehyde-catalyzed (Scheme 1, eqn (6))[11] and substrate ketone-autocatalyzed (eqn (7))[12] dehydrative alkylation reactions, which were successfully employed for amine, amide, alcohol, and ketone derivative synthesis. We thus hypothesized that organohalides (RX) may also be good catalysts for certain alkylation reactions, because, analogous to aldehydes and ketones, RX should be another activated form of alcohols bearing reactive halogen groups (eqn (9)). With continuing interest in alcohol-based alkylation reactions[10–13] and useful (thio) ethers,[14] herein we report an important advance in the field by describing 1°, 2°, or 3° RX-catalyzed dehydrative O-alkylation/homo- and cross-etherification reactions between the alcohols, which led to selective, green, practical, and easily scalable methods for synthesis of the useful symmetrical and unsymmetrical aliphatic ethers from the readily available alcohols (eqn (8)). This RX-catalyzed etherification is also an O-selective alkylation reaction between the alcohols, being a good complement to our previous aldehyde-catalyzed C-selective alkylation reaction between the alcohols (eqn (6)).[11b]

To achieve a successful RX-catalyzed alkylation reaction, we initially attempted the reactions of $PhCH_2OH$ (**1a**) and various nucleophilic substrates. In spite of many failures, we found that **1a** alone could afford considerable amounts of dibenzyl ether (**2a**) in the presence of $PhCH_2Br$ (Table 1) (see ESI† for details). Thus, without $PhCH_2X$, no reaction occurred even at 120 °C (entry 1). In contrast, addition of only 1 mol% of $PhCH_2Br$ dramatically accelerated the reaction to give 41% **2a** under the same conditions (entry 2). Screening on catalyst loading, reaction temperature and time (see ESI† for details) showed that 10 mol% $PhCH_2Br$, 120 °C, and 24 h were the best conditions, ensuring complete conversion of **1a** to give a high

Table 1 Condition screening for $PhCH_2X$-catalyzed O-alkylative homo-etherification of $PhCH_2OH$[a]



Entry	Cat. (mol%), additive (mol%)	**2a**%[b]
1	—	0
2	$PhCH_2Br$ (1)	41
3	***$PhCH_2Br$ (10)***	***>99 (97)***
4	$PhCH_2Cl$ (10)	18
5[c]	$PhCH_2Br$ (10)	(93)
6[c,d]	$PhCH_2Br$ (10), toluene	(51)
7[d,e]	HBr (10), toluene	(57)
8[e]	HBr (10)	(60)
9	NaBr (10 mol%), H_3PO_4 (10–15 mol%)	(17)

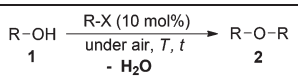
[a] Unless otherwise noted, the neat mixture of **1a** (10 mmol) and the catalyst was sealed under air in a 20 mL Schlenk tube and then heated and monitored by GC-MS and TLC. [b] GC yields (isolated yields in parenthesis) based on **1a**. [c] Dry $PhCH_2Br$ was used. [d] 4 mmol **1a** and dry toluene (0.5 mL) were used. [e] HBr (33 wt% in acetic acid) was used.

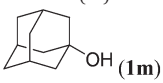
97% isolated yield of **2a** (entry 3). $PhCH_2Cl$ was also tested, only exhibiting a much lower activity (entry 4). We found that the above reactions could be readily carried out under air without affecting the results, revealing that inert atmosphere protection was not necessary. Thus, the reaction conditions and operation can be greatly simplified, revealing the high practicability of the new method.

Moreover, since the residual hydrobromic acid (HBr) in commercial $PhCH_2Br$ or from hydrolysis of $PhCH_2Br$ is also a potential factor to promote the reaction, additional control reactions were investigated to exclude or prove its influence on the reaction. Firstly, a neat reaction (entry 4) and a diluted reaction in dry toluene (entry 5) using dry $PhCH_2Br$ free of HBr were investigated, affording a high and a moderate yield of **2a**, respectively. These results showed that pure $PhCH_2Br$ is equally effective with unpretreated $PhCH_2Br$ in catalyzing the reaction. The catalytic activity of HBr (33 wt% in acetic acid) was then examined. The results revealed that HBr was less effective, giving only moderate yields of **2a** without or with a solvent (entries 7 and 8). In addition, *in situ* generated HBr from NaBr–H_3PO_4 only showed that this method is even less effective in the reaction. These results suggested that the effect of HBr (a haloid acid HX) is less important but that $PhCH_2Br$ (an organohalide RX) is highly active in catalyzing the reaction, making this method an effective etherification strategy.

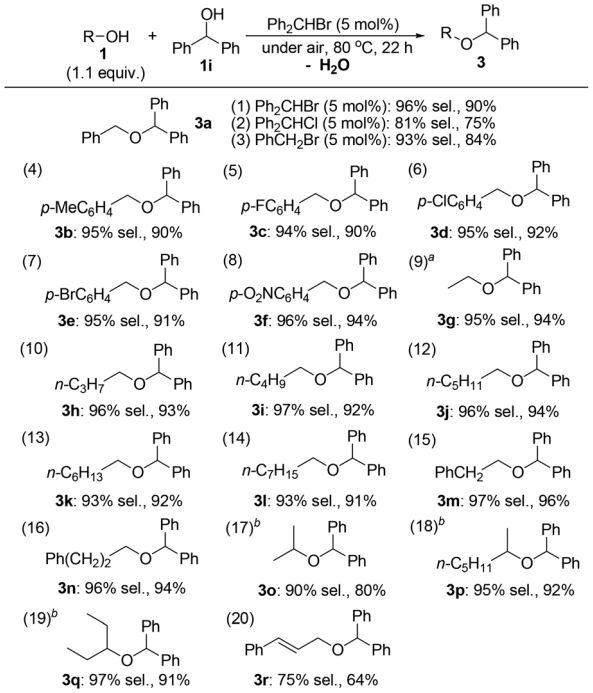
This method was then applied to other 1°, 2°, and 3° alcohols to extend the scope of the homo-etherification method (Table 2). Like **1a**, the reactions of 1° benzylic alcohols **1b–c** were readily catalyzed by the corresponding benzylic bromides to afford high yields of the target ethers under the same conditions (entries 1–3). The reactions of 1° aliphatic alcohols were less efficient. They require the use of more active alkyl iodides and a higher temperature (see ESI† for details), giving moderate yields of dialkyl ethers **2d–g** (entries 4–7). Allylic alcohol such as cinnamyl alcohol **1h** was more reactive and

Table 2 Organohalide-catalyzed O-alkylative homo-etherification of alcohols for synthesis of symmetrical ethers[a]



Entry	R	X	*T*, *t*	2%[b]
1	$PhCH_2$ (**1a**)	Br	120 °C, 24 h	**2a:** 97
2	4-$MeC_6H_4CH_2$ (**1b**)	Br	120 °C, 24 h	**2b:** 96
3	4-$FC_6H_4CH_2$ (**1c**)	Br	120 °C, 24 h	**2c:** 88
4	*n*-C_5H_{11} (**1d**)	I	150 °C, 48 h	**2d:** 65
5	*n*-C_6H_{13} (**1e**)	I	150 °C, 48 h	**2e:** 60
6	*n*-C_7H_{15} (**1f**)	I	150 °C, 30 h	**2f:** 63
7	*n*-C_8H_{17} (**1g**)	I	150 °C, 30 h	**2g:** 64
8	$PhCH{=}CHCH_2$ (**1h**)	Br	60 °C, 16 h	**2h:** 58
9	Ph_2CH (**1i**)	Br	80 °C, 13 h	**2i:** 98
10	Ph_2CH (**1i**)	Cl	80 °C, 13 h	**2i:** 94
11	$PhCH(CH_3)$ (**1j**)	Br	90 °C, 24 h	**2j:** 89
12	$PhCH(CH_3)$ (**1j**)	Cl	90 °C, 24 h	**2j:** 71
13	*n*-$C_5H_{11}CH(CH_3)$ (**1k**)	Br	150 °C, 40 h	**2k:** 20
14	*t*-BuOH (**1l**)	Br	150 °C, 40 h	NR[c]
15	 (**1m**)	Br	150 °C, 40 h	NR[c]

[a] See Table 1 for similar conditions. [b] Isolated yields based on **1**. [c] No reaction.



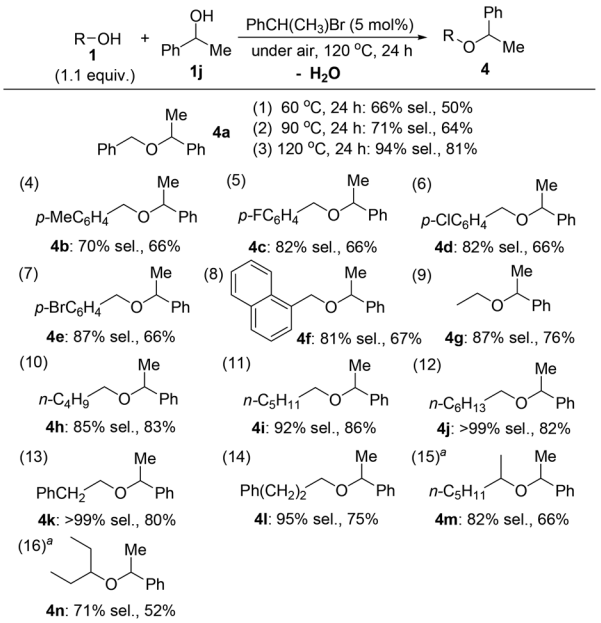
Scheme 2 Ph_2CHBr-catalyzed O-alkylative cross-etherification of Ph_2CHOH (see ESI†). Selectivities determined by GC-MS. Isolated yields based on **1i**. [a] 73 °C. [b] 3 equiv. ROH.

prone to give unknown byproducts. Thus, the reaction was carried out under a milder condition of 60 °C, affording the target dicinnamyl ether **2h** in a moderate yield (entry 8). 2° benzylic alcohols **1i–j** are also good substrates. They were readily catalyzed by the corresponding RBr or RCl, affording good to high yields of the ethers at 80–90 °C, with RBr being more active than RCl (entries 9–12). Like 1° aliphatic alcohols, 2° aliphatic ones were also less reactive, giving only a low yield of ether **2k** at 150 °C (entry 13). Contrary to the above reactions, no homo-etherification occurred with 3° alcohols such as *t*-BuOH **1l** and 1-adamantyl alcohol **1m** (entries 14 and 15), most possibly due to the large steric hindrance of the bulky 3° alkyl groups.

To further extend the scope of this etherification method for unsymmetrical ether synthesis, the same catalytic protocol was adopted in cross reactions of different alcohols by using corresponding 1°, 2°, or 3° RX as the catalyst.

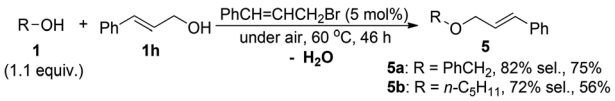
As shown in Scheme 2, in the reaction of 2° alcohol **1i** with **1a**, initial tests showed that the corresponding RX, such as $PhCH_2Br$, Ph_2CHBr, and Ph_2CHCl, all exhibited good catalytic activities to give good to high selectivities and good to high yields of the target cross ether **3a** (entries 1–3), with detection of only low amounts of homo-ether byproducts (see ESI†). Ph_2CHBr is the best catalyst, affording **3a** in the highest 96% selectivity and 90% isolated yield (entry 1). Interestingly, the $PhCH_2Br$-catalyzed reaction also gave a good result with formation of only 1% byproduct **2a** (entry 3) (see ESI†),[15] which revealed not only the high selectivity of the reaction for production of the target cross ether **3a**, but also that, in the reaction process, Ph_2CHBr rather than $PhCH_2Br$ should be selectively regenerated from the more active alcohol **1i** and then selectively reacted with the less bulky and more nucleophilic **1a** to give **3a** in high selectivity (*vide infra*).[15] Ph_2CHBr was then used as the catalyst for the reactions of **1i** and other alcohols. Thus, electron-rich and -deficient benzylic alcohols (entries 4–8), short- or long-chain aliphatic ones (entries 9–14), homo-benzylic ones (entries 15 and 16), and even the sterically more bulky 2° aliphatic alcohols (entries 17–19), all reacted efficiently with **1i** at 80 °C to give the target cross ethers in high selectivities and high yields. The reaction of cinnamyl alcohol **1h** was less selective, giving a moderate yield of the target ether **3r** (entry 20).

Similarly, cross-etherification reactions of another 2° alcohol **1j** using the more active $PhCH(CH_3)Br$ as the catalyst were also investigated (Scheme 3). In this case a slight modification of the conditions is necessary. Thus, the reactions of **1j** and **1a** at lower temperatures were less efficient, giving lower selectivities of the target cross-ether **4a** (entries 1 and 2); whereas the reaction at 120 °C afforded the best result, giving **4a** in high selectivity and a good isolated yield of 81% (entry 3). This condition was then applied to cross reactions of **1j** with electron-rich and -deficient benzylic alcohols (entries 4–8), 1° aliphatic ones (entries 9–12), and homo-benzylic ones (entries 13 and 14), all giving target ethers in good to high selectivities and good isolated yields. The reactions of **1j** with 2° aliphatic alcohols were less efficient than those of **1i**, giving moderate to good selectivities and moderate yields of the cross ethers due to formation of homo-ether byproducts (entries 15 and 16).

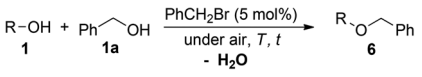


Scheme 3 $PhCH(CH_3)Br$-catalyzed O-alkylative cross-etherification of $PhCH(CH_3)OH$ (see ESI†). Selectivities determined by GC-MS. Isolated yields based on **1j**. [a] 3 equiv. of ROH; 38 h.

As for cross-etherification reactions of 1° alcohols, cinnamyl alcohol **1h** reacted with either a benzylic alcohol **1a** or an aliphatic alcohol **1d** smoothly at 60 °C in the presence of 5 mol% cinnamyl bromide, giving good selectivities and moderate to good yields of the allylic ethers **5a** and **5b** (eqn (10)). In contrast, cross reactions using **1a** as the alkylating reagent were less effective. As shown in eqn (11), the reaction of **1a** and another benzylic alcohol 4-$MeOC_6H_4CH_2OH$ give a moderate yield and selectivity of the target ether **6a** at 120 °C. Another reaction with an aliphatic alcohol n-$C_7H_{15}OH$ **1f** was even less effective. It required a higher temperature of 140 °C, and gave a low yield of the target ether **6b** in moderate selectivity.

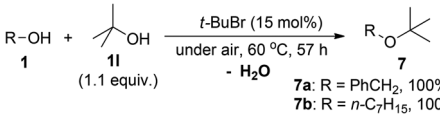


(10)

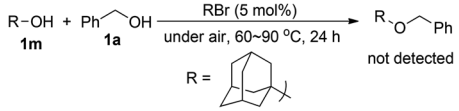


(11)

Although 3° alcohols are not good substrates in homo-etherification reactions (*vide supra*), we still investigated their cross reactions with other alcohols using the corresponding RX as the catalyst. As shown in eqn (12), both the reactions of a benzylic and an aliphatic alcohol with *t*-BuOH (**1l**) in the presence of *t*-BuBr successfully afforded moderate yields of the useful *t*-butyl ethers **7a–b** in high selectivity under mild conditions of 60 °C. By contrast, the reaction of 1-adamantyl alcohol (**1m**) with **1a** still gave no target cross ether (eqn (13)).

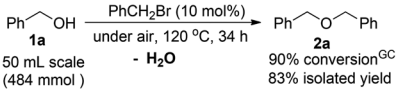


(12)



(13)

The scalability of the etherification method was then investigated because this is significant to the practical preparation of the target ethers. Thus, in a round-bottomed flask equipped with a water separator and a condenser open to air (see ESI† for details), 50 mL **1a** (~484 mmol) and 10 mol% $PhCH_2Br$ were heated at 120 °C. Byproduct water gradually formed and was collected in the water separator. Then, vacuum distillation of the residue readily afforded 83% isolated yield of **2a** (eqn (14)). This simple procedure shows the high scalability and practicability of the large scale etherification reaction, and also its potential for industrial scale preparation of useful ethers.



(14)

Meanwhile, the use of catalytic amounts of RX to successfully catalyze the reactions also suggested that the reaction mechanism should be interesting. Like aldehydes and ketones, RX is another activated form of the alcohols (Scheme 1C). Besides, we frequently observed in GC or NMR spectra that the added RX still remained in considerable quantities in the reaction mixtures (see ESI†). As shown in Fig. 1, ^{1}H NMR analysis of the reaction of **1a** and **1i** indicated that, as the conversion of **1i** and yield of **3a** increased greatly, catalyst Ph_2CHBr did not disappear, gradually reaching a steady value in the reaction mixture (see ESI†). We thus hypothesized that, similarly to previous aldehyde-catalyzed and substrate ketone-autocatalyzed N- and C-alkylation reactions,[11,12] this etherification reaction may also involve an RX-participated, -regenerated,

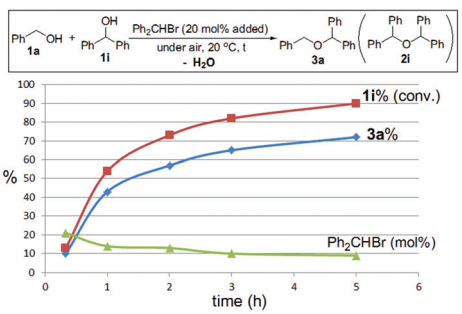
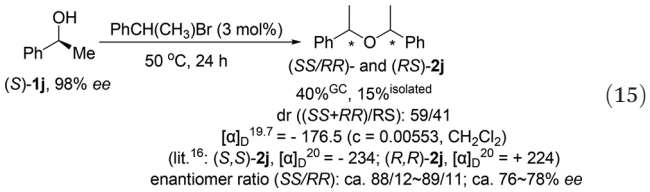


Fig. 1 Results for ^{1}H NMR analysis on variation of the components in the Ph_2CHBr-catalyzed cross-etherification reaction of **1a** and **1i** (see ESI†).

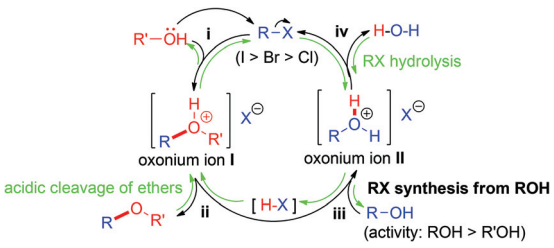
-recycled, and consequently-catalyzed dehydrative O-alkylation type mechanism.

In addition, to gain more insight into the stereochemistry of the reaction, we investigated the homo-etherification of optically enriched (*S*)-**1j** (98% ee) catalyzed by racemic PhCH(CH$_3$)Br (eqn (15)) (see ESI†). After heating at 50 °C for 24 h, 15% isolated yield of **2j** with a (*SS* + *RR*)/*RS* ratio of 59/41 was obtained (see ESI†). Optical rotatory power measurement (α = −0.977) suggested that (*S*,*S*)-**2j** is the major isomer. Then, the specific optical rotatory power ($[\alpha]_D^{19.7}$ = −176.5) and its comparison with the literature data ((*S*,*S*)-**2j**, $[\alpha]_D^{20}$ = −234; (*R*,*R*)-**2j**, $[\alpha]_D^{20}$ = +224)[16] also suggested that the *SS*/*RR* enantiomer ratio should be *ca.* 88/12–89/11 (*ca.* 76–78% ee). These results indicated that S_N2 pathways should have been involved in the reaction, but S_N1 pathways still cannot be excluded since the diastereomer selectivity is not high.



(15)

Based on all the above results, a simplified mechanism for the etherification reaction was proposed. As shown in Scheme 4, under base-free neutral conditions, RX (reactivity: RI > RBr > RCl, *vide supra*) may firstly react selectively with the less bulky and more nucleophilic R′OH (step i) to form oxonium ion **I** and afford the ether product (step ii), which is in fact the counter-reaction of the well documented ether's acidic cleavage with strong acids.[1a–c] In this step, both the selective S_N2 paths and the non-selective S_N1 paths with formation of carbon cation species are possible, since the reaction is not a stereospecific one but a not very selective reaction (eqn (15)). Besides, although possible formation of gaseous HX of low boiling points in this step and loss of X in the reaction can not be excluded completely, **I** may also undergo proton exchange directly with the more active ROH to produce another oxonium ion **II** (step ii–iii) to prevent the loss of X,[17] since considerable amounts of RX were always detected in the reaction mixtures and RX is found to be catalytically more effective than HX (*vide supra*) (see ESI†).[17] Upon formation, **II** may lose water to give RX (step iv), which is the well-known organohalide preparation reaction from alcohols and also the counter-reaction of organohalide hydrolysis.[1a–c] Finally, upon regeneration, RX should selectively react with R′OH again and then catalyze the whole reaction to give the target homo- or cross-ethers in high selectivities, producing water as the byproduct.



Scheme 4 Possible mechanism for organohalide-catalyzed etherification reaction of alcohols.

In conclusion, based on our previous work[11,12] and by a rational design of the dehydrative alkylation reactions, organohalides are now found to be effective catalysts for dehydrative O-alkylation/homo- and cross-etherification reactions between the alcohols. This new method provided a selective, practical, green, and easily scalable method for preparation of the useful symmetrical and unsymmetrical aliphatic ethers from the readily available alcohols, with water generated as the byproduct. More importantly, the present results showed that addition of organohalides can indeed be an effective method for alcohol activation, which not only leads to a complementary O-selective alkylation method using the same alcohols,[11b] but also suggests that alcohols can also be activated *via* halogenation reactions to give more reactive organohalides and further work as the alkylating reagents. Further application and extension of the organohalide-catalyzed dehydrative alkylation reactions and deeper mechanistic insights are underway.

Acknowledgements

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Notes and references

1 (*a*) J. McMurry, *Organic Chemistry*, Thomson, Brooks/Cole, 7th edn, 2008; (*b*) J. March, *Advanced Organic Chemistry, Reactions, Mechanisms and Structure*, Wiley, New York, 4th edn, 1992; (*c*) H. Feuer and J. Hooz, in *The Chemistry of the Ether Linkage*, ed. S. Patai, Interscience Publishers, London, 1967; (*d*) T. George, R. Mabon, G. Sweeney, J. B. Sweeney and A. Tavassoli, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2529; (*e*) J. Muzart, *Tetrahedron*, 2005, **61**, 5955.

2 (*a*) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400; (*b*) K. Kunz, U. Scholz and D. Ganzer, *Synlett*, 2003, 2428; (*c*) I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337; (*d*) D. Ma and Q. Cai, *Acc. Chem. Res.*, 2008, **41**, 1450; (*e*) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054; (*f*) F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, **48**, 6954.

3 (*a*) J. F. Hartwig, *Angew. Chem., Int. Ed.*, 1998, **37**, 2046; (*b*) A. R. Muci and S. L. Buchwald, *Top. Curr. Chem.*, 2002, **219**, 131; (*c*) B. Schlummer and U. Scholz, *Adv. Synth. Catal.*, 2004, **346**, 1599; (*d*) J. F. Hartwig, *Nature*, 2008, **455**,

314; (*e*) S. Enthaler and A. Company, *Chem. Soc. Rev.*, 2011, **40**, 4912.

4 (*a*) F. Theil, *Angew. Chem., Int. Ed.*, 1999, **38**, 2345; (*b*) J. S. Sawyer, *Tetrahedron*, 2000, **56**, 5045; (*c*) R. Frlan and D. Kikelj, *Synthesis*, 2006, 2271; (*d*) E. N. Pitsinos, V. P. Vidali and E. A. Couladouros, *Eur. J. Org. Chem.*, 2011, 1207; (*e*) J. Zhu, *Synlett*, 1997, 133; (*f*) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 273.

5 (*a*) A. Williamson, *Justus Liebigs Ann. Chem.*, 1851, **77**, 37; (*b*) A. W. Williamson, *J. Chem. Soc.*, 1852, **4**, 229.

6 Selected examples: (*a*) C. S. Sevov and J. F. Hartwig, *J. Am. Chem. Soc.*, 2013, **135**, 9303; (*b*) H. Shigehisa, T. Aoki, S. Yamaguchi, N. Shimizu and K. Hiroya, *J. Am. Chem. Soc.*, 2013, **135**, 10306; (*c*) M. C. Haibach, C. Guan, D. Y. Wang, B. Li, N. Lease, A. M. Steffens, K. Krogh-Jespersen and A. S. Goldman, *J. Am. Chem. Soc.*, 2013, **135**, 15062; (*d*) Y. Miller, L. Miao, A. S. Hosseini and S. R. Chemler, *J. Am. Chem. Soc.*, 2012, **134**, 12149; (*e*) M. Kondo, T. Kochi and F. Kakiuchi, *J. Am. Chem. Soc.*, 2011, **133**, 32; (*f*) Z. J. Wang, C. J. Brown, R. G. Bergman, K. N. Raymond and F. D. Toste, *J. Am. Chem. Soc.*, 2011, **133**, 7358; (*g*) K. M. Gligorich, M. J. Schultz and M. S. Sigman, *J. Am. Chem. Soc.*, 2006, **128**, 2794; (*h*) C.-G. Yang and C. He, *J. Am. Chem. Soc.*, 2005, **127**, 6966; (*i*) H. Qian, X. Han and R. A. Widenhoefer, *J. Am. Chem. Soc.*, 2004, **126**, 9536; (*j*) M. Beller, J. Seayad, A. Tillack and H. Jiao, *Angew. Chem., Int. Ed.*, 2004, **43**, 3368.

7 Selected examples: (*a*) J. Kim, D.-H. Lee, N. Kalutharage and C. S. Yi, *ACS Catal.*, 2014, **4**, 3881; (*b*) M. Roggen and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2011, **50**, 5568; (*c*) A. Corma and M. Renz, *Angew. Chem., Int. Ed.*, 2007, **46**, 298; (*d*) M. Georgy, V. Boucard and J.-M. Campagne, *J. Am. Chem. Soc.*, 2005, **127**, 14180; (*e*) H. Saburi, S. Tanaka and M. Kitamura, *Angew. Chem., Int. Ed.*, 2005, **44**, 1730; (*f*) B. D. Sherry, A. T. Radosevich and F. D. Toste, *J. Am. Chem. Soc.*, 2003, **125**, 6076; (*g*) Y. Nishibayashi, I. Wakiji and M. Hidai, *J. Am. Chem. Soc.*, 2000, **122**, 11019.

8 Selected examples: (*a*) S. Bhadra, C. Matheis, D. Katayev and L. J. Gooβen, *Angew. Chem., Int. Ed.*, 2013, **52**, 9279; (*b*) G. Shan, X. Yang, Y. Zong and Y. Rao, *Angew. Chem., Int. Ed.*, 2013, **52**, 13606; (*c*) F.-J. Chen, S. Zhao, F. Hu, K. Chen, Q. Zhang, S.-Q. Zhang and B.-F. Shi, *Chem. Sci.*, 2013, **4**, 4187; (*d*) B. Xiao, T.-J. Gong, Z.-J. Liu, J.-H. Liu, D.-F. Luo, J. Xu and L. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 9250; (*e*) R. M. Trend, Y. K. Ramtohul and B. M. Stoltz, *J. Am. Chem. Soc.*, 2005, **127**, 17778; (*f*) X. Wang, Y. Lu, H.-X. Dai and J.-Q. Yu, *J. Am. Chem. Soc.*, 2004, **126**, 7359; (*g*) T. Shintou and T. Mukaiyama, *J. Am. Chem. Soc.*, 2004, **126**, 7359.

9 (*a*) Q. Xu and Q. Li, *Chin. J. Org. Chem.*, 2013, **33**, 18; (*b*) D.-H. Lee, K.-H. Kwon and C. S. Yi, *Science*, 2011, **333**, 1613; (*c*) S.-Y. Zhang, F.-M. Zhang and Y.-Q. Tu, *Chem. Soc. Rev.*, 2011, **40**, 1937; (*d*) E. Emer, R. Sinisi, M. G. Capdevila, D. Petruzziello, F. De Vincentiis and P. G. Cozzi, *Eur. J. Org. Chem.*, 2011, 647; (*e*) A. J. A. Watson and J. M. J. Williams, *Science*, 2010, **329**, 635; (*f*) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 681; (*g*) G. Guillena, D. J. Ramón and M. Yus, *Chem. Rev.*, 2010, **110**, 1611; (*h*) E. Skucas, M.-Y. Ngai, V. Komanduri and M. J. Krische, *Acc. Chem. Res.*, 2007, **40**, 1394; (*i*) K.-I. Fujita and R. Yamaguchi, *Synlett*, 2005, 560.

10 (*a*) S. L. Feng, C. Z. Liu, Q. Li, X. C. Yu and Q. Xu, *Chin. Chem. Lett.*, 2011, **22**, 1021; (*b*) C. Liu, S. Liao, Q. Li, S. Feng, Q. Sun, X. Yu and Q. Xu, *J. Org. Chem.*, 2011, **76**, 5759; (*c*) X. Yu, C. Liu, L. Jiang and Q. Xu, *Org. Lett.*, 2011, **13**, 6184; (*d*) Q. Li, S. Fan, Q. Sun, H. Tian, X. Yu and Q. Xu, *Org. Biomol. Chem.*, 2012, **10**, 2966; (*e*) S. Liao, K. Yu, Q. Li, H. Tian, Z. Zhang, X. Yu and Q. Xu, *Org. Biomol. Chem.*, 2012, **10**, 2973; (*f*) X. Yu, L. Jiang, Q. Li, Y. Xie and Q. Xu, *Chin. J. Chem.*, 2012, **30**, 2322.

11 (*a*) Q. Xu, Q. Li, X. Zhu and J. Chen, *Adv. Synth. Catal.*, 2013, **355**, 73; (*b*) Q. Xu, J. Chen and Q. Liu, *Adv. Synth. Catal.*, 2013, **355**, 697.

12 (*a*) Q. Xu, J. Chen, H. Tian, X. Yuan, S. Li, C. Zhou and J. Liu, *Angew. Chem., Int. Ed.*, 2014, **53**, 225; (*b*) For a closely related ketone-initiated dehydrative alkylation of indole and pyrrole: X. Han and J. Wu, *Angew. Chem., Int. Ed.*, 2013, **52**, 4637.

13 (*a*) L. Jiang, L. Jin, H. Tian, X. Yuan, X. Yu and Q. Xu, *Chem. Commun.*, 2011, **47**, 10833; (*b*) H. Tian, X. Yu, Q. Li, J. Wang and Q. Xu, *Adv. Synth. Catal.*, 2012, **354**, 2671; (*c*) B. Huang, H. Tian, S. Lin, M. Xie, X. Yu and Q. Xu, *Tetrahedron Lett.*, 2013, **54**, 2861; (*d*) E. Zhang, H. Tian, S. Xu, X. Yu and Q. Xu, *Org. Lett.*, 2013, **15**, 2704.

14 (*a*) X. Jia, L. Yu, J. Liu, Q. Xu, M. Sickert, L. Chen and M. Lautens, *Green Chem.*, 2014, **16**, 3444; (*b*) P. Chen, S. Lu, X. Hu and Q. Xu, *Chin. J. Org. Chem.*, 2014, **34**, 112; (*c*) Q. Liu, Z. Lu, W. Ren, K. Shen, Y. Wang and Q. Xu, *Chin. J. Chem.*, 2013, **31**, 764; (*d*) C. Liu, X. Zang, B. Yu, X. Yu and Q. Xu, *Synlett*, 2011, 1143.

15 In contrast, no **2a** was detected in Ph_2CHBr- or Ph_2CHCl-catalyzed reactions (Scheme 2, entries 1 and 2) (see ESI†), suggesting that Ph_2CHBr or Ph_2CHCl directly reacted with **1a** to give **3a** and was then regenerated specifically without formation of $PhCH_2Br$ or $PhCH_2Cl$.

16 R. Felstead, S. E. Gibson, A. Rooney and E. S. Y. Tse, *Eur. J. Org. Chem.*, 2008, 4963.

17 Loss of X due to distillation of low b.p. HX can result in ineffective regeneration of RX and ineffective catalysis of the etherification reaction, which is clearly not the case in the present reactions.