Catalytic dehydrative etherification and chlorination of benzyl alcohols in ionic liquids†

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Dibenzyl ethers and benzyl chloride can be obtained in moderate to excellent yields through Pd-catalysed reactions in hydrophobic ionic liquids using microwave or conventional heating.

Dehydrative reactions can be used for a wide variety of transformations including etherifications, esterifications and thioetherifications.[1] Generally, this route is more environmentally friendly than classical methods (Williamson and Ullmann) as the only byproduct is water, whereas the use of strongly basic alkoxides or phenoxides with alkyl or aryl halides in the Williamson method produces considerable amounts of salt byproducts. In etherification reactions, a wide variety of catalysts have been employed including alumina,[2] phase transfer catalysts,[3] Lewis acids,[4] and several transition metal complexes.[5] Among these catalysts, Pd(II) compounds have a special position,[6] which has led to a recent review in this area.[7] It should be noted that dehydrative etherification of benzylic alcohols has been investigated to a lesser extent than phenols, however, such catalytic reactions could be useful in synthetic chemistry, *e.g.* for protecting alcohols.[4c]

In the area of catalytic dehydration reactions, we thought that the use of hydrophobic ionic liquids (ILs) as reaction media could provide an added benefit to homogeneous catalytic systems by aiding in water abstraction from the reaction mixture. Furthermore, we have employed microwave heating to reduce reaction times and energy consumption. In general, room temperature ILs have attracted great attention during the last decade, since they are non-volatile, non-flammable, potentially recyclable and benign solvents with the ability to dissolve a wide variety of compounds.[8] In terms of ether synthesis, Ullmann and Williamson methods have been performed using ILs as the reaction media,[5a,9] as well as the promoter.[10] As far as we are aware, catalytic dehydrative etherification reactions have not been performed in ILs previously.

In our preliminary studies, benzyl alcohol was selected as it is the simplest benzylic alcohol, Table 1. Conventional heating as well as microwave irradiation was used as the energy source. Scheme 1 presents the general reaction conditions and the benzyl alcohol derivatives used in further studies, Table 2. Two hydrophilic and three hydrophobic ILs were used along with several transition metal sources (Table 1, entries 1–15).

1-Butyl-3-methyl imidazolium hexafluorophosphate ([BMIm]PF$_6$) gave the highest yields under microwave irradiation in combination with Pd(CH$_3$CN)$_2$Cl$_2$ (Table 1, entry 1). It should be noted that other environmentally-friendly solvent systems—solvent-free (Table 1, entry 5) and aqueous (Table 1, entry 6)—were not suitable for this reaction. Additionally, reactions in conventional polar, aprotic organic solvents (Table 1, entries 7 and 8) only gave low yields of the desired product. The increased yields obtained in ILs may be due to the unique highly ionic environments afforded by these media that can support ionic intermediates that have been proposed for similar Pd-catalysed reactions in conventional reaction media.[6a]

As many ether syntheses are pH dependent, the reactions were examined in the presence of several additives. Under basic conditions (Table 1, entries 16 and 17), no conversion was seen. Conducting the reaction in the presence of acetic acid led to the formation of benzyl acetate, **3** (Table 1, entry 18), while benzyl chloride, **2**, was obtained in excellent yield (84%) in the presence of NH$_4$Cl (Table 1, entry 19). NH$_4$Cl is less hazardous to human health and the environment than other common chlorinating agents including thionyl chloride and concentrated hydrochloric acid. Further studies are ongoing to determine the applicability of this environmentally benign halogenation process. Control reactions have also been performed. In the absence of a transition metal, with and without additives, no conversion of the benzyl alcohol was seen. This indicates that although the hexafluorophosphate anion has a tendency to degrade and can potentially form HF in the reaction mixtures, the reactions are not acid catalysed and the metal, ideally palladium, is an essential component of the catalytic system. The degradation of [BMIm]PF$_6$ was evident through the formation of a precipitate in many of the reactions especially upon prolonged heating. The precipitate contained significant amounts of Na and Si which could only have originated from the glass reaction vessels due to their sodium borosilicate content. Furthermore, mild etching of the vessels was seen after some reactions, presumably through *in situ* action of HF from PF$_6^-$ degradation.‡
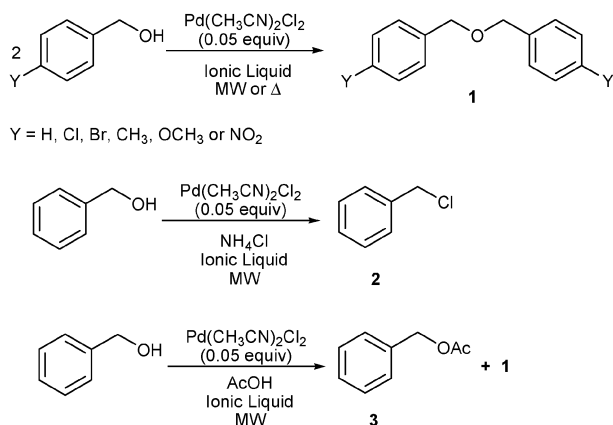
Based on our initial studies, reactions using other benzyl alcohol derivatives (Table 2) and ionic liquids were performed under similar conditions. When 4-methoxy benzyl alcohol was used as the substrate (Table 2, entry 4), the highest yield was obtained. We propose that this is due to the higher stability of the benzylic carbocation formed from this reagent. All other alcohols, with the exception of 4-nitro benzyl alcohol, were successfully coupled and yields of 50–60% obtained. Furthermore, it should be noted that no precipitate formed during the transformation of 4-methoxy benzyl alcohol. Whereas for

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Table 1 Reactions of benzyl alcohol under different reaction conditions[a]

Entry	Solvent	Metal source[b]	Additive	Yield[c] (%)	Time (min)/Temp (°C)[d]	
					Microwave	Conventional
1	[BMIm]PF$_6$	Pd(CH$_3$CN)$_2$Cl$_2$	—	55 (**1**)	7/140	—
2	[BMIm]PF$_6$	Pd(CH$_3$CN)$_2$Cl$_2$	—	23 (**1**)	—	24 h/80
3	[BMMIm]PF$_6$	Pd(CH$_3$CN)$_2$Cl$_2$	—	50 (**1**)	6/140	—
4	[BMIm]BF$_4$	Pd(CH$_3$CN)$_2$Cl$_2$	—	0	10/135	—
5	No solvent	Pd(CH$_3$CN)$_2$Cl$_2$	—	0	7/90	24 h/90
6	H$_2$O	Pd(CH$_3$CN)$_2$Cl$_2$	—	Trace (**1**)	7/90	24 h/90
7	DMSO	Pd(CH$_3$CN)$_2$Cl$_2$	—	5 (**1**)[g]	9/130	—
8	DMF	Pd(CH$_3$CN)$_2$Cl$_2$	—	12 (**1**)[g]	9/130	—
9	[BMIm]PF$_6$	Pt(COD)Cl$_2$	—	0	7/125	—
10	[BMIm]PF$_6$	RuCl$_3$·xH$_2$O	—	12 (**1**)	7/145	—
11	[BMIm]PF$_6$	RuCl$_3$·xH$_2$O	—	23 (**1**)	—	24 h/80
12	[BMIm]BF$_4$	RuCl$_3$·xH$_2$O	—	0	—	24 h/80
13	[BMIm]Cl	RuCl$_3$·xH$_2$O	—	Trace (**1**)	—	18 h/80
14	[BMIm]PF$_6$	FeCl$_3$·6H$_2$O	—	24 (**1**)	9/130	—
15	[BMIm]PF$_6$	FeCl$_3$·6H$_2$O	—	14 (**1**)	—	4 h/100
16	[BMIm]PF$_6$	Pd(CH$_3$CN)$_2$Cl$_2$	KOH[e]	0	15/158	—
17	[BMIm]PF$_6$	Pd(CH$_3$CN)$_2$Cl$_2$	K$_2$CO$_3$[e]	0	15/150	—
18	[BMIm]PF$_6$	Pd(CH$_3$CN)$_2$Cl$_2$	CH$_3$COOH[f]	36 (**1**) and 14 (**3**)	10/135	—
19	[BMIm]PF$_6$	Pd(CH$_3$CN)$_2$Cl$_2$	NH$_4$Cl[f]	84 (**2**) and trace (**1**)	10/135	—
20	[BMIm]PF$_6$	No catalyst	NH$_4$Cl[f]	0	10/95	—

[a] Typical reaction conditions (for entry 1): IL 0.5408 g, benzyl alcohol 0.0610 g, Pd(CH$_3$CN)$_2$Cl$_2$ 0.0080 g. The homogeneous reaction mixture was sealed with a PTFE cap under a nitrogen blanket. Microwave powers of 150–200 W were used. BMMIm = 1-butyl-2,3-dimethylimidazolium. [b] 0.05 equiv. of Pd with respect to benzylic alcohol. [c] Yields were calculated relative to benzyl alcohol using ¹H-NMR spectroscopy with acetophenone as the internal standard (for more information see ESI†). [d] Time is in minutes unless otherwise mentioned. [e] 0.5 equiv. with respect to benzyl alcohol. [f] 1 equiv. with respect to benzyl alcohol. [g] Y = OMe.

Scheme 1 Pd-catalysed transformations of benzyl alcohols investigated in this study.

other substrates, especially upon prolonged reaction times either thermally or in a microwave, quantities of a catalytically inactive solid were formed (*vide supra*). Initial recycling studies (Table 2, entries 5 and 6) using the ionic liquid (catalyst phase) from the transformation of 4-methoxy benzyl alcohol (Table 2, entry 4) are promising; yields were maintained or improved when the catalyst/ionic liquid was reused.

Many Pd(II)-catalysed reactions require or are enhanced by the presence of a copper co-catalyst.[11] Surprisingly, when CuCl$_2$ was used with the Pd for these reactions, the yield dropped from 57% to 8% (Table 2, entries 3 and 10). This information may be useful in determining the nature of the catalytic cycle. Also, [BMMIm]PF$_6$ (BMMIm = 1-butyl-2,3-dimethylimidazolium) was used to assess whether an *N*-hetero-cyclic carbene complex of Pd was the active species in this reaction. In [BMMIm]PF$_6$, the generation of the carbene

intermediate is impossible. Results using this solvent were similar to [BMIm]PF$_6$ (Table 2, entries 1 and 13). Analysis of the reaction mixture by TEM analysis showed no evidence of colloidal Pd. Therefore, we propose that the catalyst is a homogeneous form of Pd.
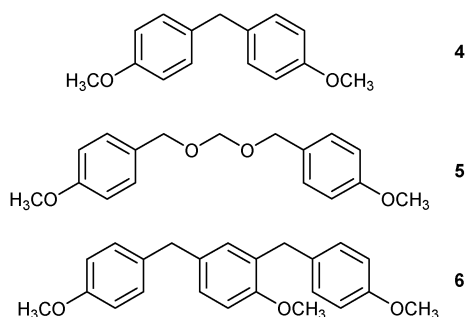
Since hydrophobic [BMIm]PF$_6$ afforded higher yields than hydrophilic ILs ([BMIm]BF$_4$ and [BMIm]Cl) and PF$_6^-$ was underdoing degradation, an alternative hydrophobic ionic liquid was used. Trihexyl(tetradecyl)phosphonium dodecylbenzene sulfonate ([P$_{66614}$]DBS) was employed but did not show a reasonable absorptivity for MW irradiation due to the large size of its cations and anions (Table 2, entry 11); however, under conventional heating, 56% yield was obtained (Table 2, entry 9). This is comparable with results obtained using [BMIm]PF$_6$. Potentially, by doping the [P$_{66614}$]DBS phase with a strong microwave absorber, the reaction could still be performed using microwave heating.

In attempts to further increase the yield of these reactions, the effects of increased reaction time and temperature were studied for the transformation of 4-methoxy benzyl alcohol in [BMIm]PF$_6$. When the reaction mixture (Table 2, entry 4) was heated for twenty minutes instead of nine, very little starting material but no ether was seen in the NMR spectrum. However, 4,4′-dimethoxydiphenyl methane (**4**) was detected as the main product *via* GC-MS analysis (Fig. S4 and S5, ESI†).§ When the reaction was performed at a higher temperature (7 minutes at 125 °C), bis-(4-methoxybenzyl) acetal (**5**) was detected *via* GC-MS. As **4** and **5** (Fig. 1) are only seen after prolonged reaction times or at higher temperatures, one can assume that **1** is an intermediate in their formation. These products have been observed by other researchers in photo-chemical and acid-catalysed reactions.[12] Dehydration products more complex than **1** were also observed when we performed

Table 2 Etherification reactions of *para*-substituted benzyl alcohol derivatives[a]

Entry	Catalyst	Y	IL	Yield (%) (1)[b]	Time (min)/Temp (°C)
1	Pd(CH$_3$CN)$_2$Cl$_2$	H	[BMIm]PF$_6$	55	7/140
2	Pd(CH$_3$CN)$_2$Cl$_2$	Cl	[BMIm]PF$_6$	55	10/145
3	Pd(CH$_3$CN)$_2$Cl$_2$	CH$_3$	[BMIm]PF$_6$	57	12/114
4	Pd(CH$_3$CN)$_2$Cl$_2$	OCH$_3$	[BMIm]PF$_6$	71	9/113
5	Recycle 1 (reuse entry 4)	OCH$_3$	[BMIm]PF$_6$	96	2 × 15/106
6	Recycle 2 (reuse entry 5)	OCH$_3$	[BMIm]PF$_6$	78	8/116
7	Pd(CH$_3$CN)$_2$Cl$_2$	NO$_2$	[BMIm]PF$_6$	0	10/115
8	Pd(CH$_3$CN)$_2$Cl$_2$	Br	[BMIm]PF$_6$	6	12/170
9	Pd cat. precipitate	Cl	[BMIm]PF$_6$	8	11/131
10	Pd(CH$_3$CN)$_2$Cl$_2$/CuCl$_2$·2H$_2$O	CH$_3$	[BMIm]PF$_6$	8	10/115
11	Pd(CH$_3$CN)$_2$Cl$_2$	OCH$_3$	[P$_{66614}$]DBS	0	10/58[c]
12	Pd(CH$_3$CN)$_2$Cl$_2$	OCH$_3$	[P$_{66614}$]DBS	56	24 h/90[d]
13	Pd(CH$_3$CN)$_2$Cl$_2$	H	[BMMIm]PF$_6$	50	6/140

[a] For reaction conditions, see Table 1 footnote a. [b] Yields were calculated using ^{1}H-NMR spectroscopy (for more information see ESI†). [c] Using same MW power settings as other reactions. At the highest power setting, 9 minutes were needed to achieve 108 °C and this temperature could only be held safely for 2 minutes. Yield of (1) and conversion of BnOH was 0. [d] Reaction mixture was heated in an oil bath due to lower dielectric heating using [P$_{66614}$]DBS.

Fig. 1 Byproducts formed upon prolonged heating of reaction mixtures.

reactions using PdCl$_2$ rather than Pd(CH$_3$CN)$_2$Cl$_2$. **4** and **6** were observed as the main products (Fig. S6, S7 and S8, ESI†).§ This demonstrates that acetonitrile is required and probably coordinated to the Pd in order to give control to the etherification reactions.

In summary, we have shown that Pd(CH$_3$CN)$_2$Cl$_2$ in a hydrophobic ionic liquid affords a simple catalytic system for the direct condensation of substituted benzyl alcohols to afford their corresponding ethers. In the presence of NH$_4$Cl, benzyl chloride can be obtained in excellent yield. Although some clues about the mechanism for both reactions have been obtained, *e.g.* the absence of colloids and *N*-heterocyclic carbene species, the role of the ionic liquid, metal and ligands and the reaction pathway are still under investigation.

Notes and references

‡ EDX (energy dispersive X-ray) analysis of the precipitate showed the presence of Pd, F, Si, P and Na (Fig. S1, ESI†). Solid-state ^{19}F and ^{31}P-NMR experiments also confirmed the presence of F and P (Fig. S2 and S3, ESI†). Attempts to use the precipitate as a catalyst (as it contained Pd) were made. It was separated, dried and used (Table 2, entry 9), but the yield was low.

§ **4**, **5** and **6** (and their analogues) were not observed by GC-MS upon extracting samples from other reaction mixtures (Tables 1 and 2) and analysing under the same conditions. Furthermore, GC calibration samples of alcohols and ethereal products did not show **4**, **5** and **6**. Therefore, it is highly unlikely that **4**, **5** and **6** were formed within the GC-MS instrument and indeed did form during the microwave-assisted catalytic reactions.

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