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Ionic liquids vs. microporous solids as reusable reaction media for the catalytic C–H functionalization of indoles with alcohols†

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High performance reusable catalysts and reaction media are evaluated for the green alkylation of indoles with alcohols under mild and solvent-free conditions. For a range of Brønsted and Lewis acid catalytic sites in different environments, such as inexpensive ionic liquids or microporous solids, we show a correlation between the acid strength and catalytic activity, achieving the highest turnovers reported for strong acid sites upon five reuses under mild conditions.

Homogeneous soluble acids are very active catalysts in the fine chemicals and pharmaceutical industries but suffer from complicated product purification, deactivation and moderate selectivities.¹ Reusable microporous solid acids (zeolites or metal-organic frameworks) have appeared as attractive alternative heterogeneous catalysts.² Despite their high porosity (Fig. S1†), the narrow pores of these microporous rigid frameworks can result in diffusion limitations for the synthesis of large organic molecules, especially if the channel system is of low dimensionality, or if the crystals are large (>100 nm).³ Furthermore, the use of porous solids typically requires organic solvents that most often have the largest contribution to the environmental footprint of any process.⁴ Alternative solvent-free reaction media and/or catalysts have been explored to obtain high yields of chemical and pharmaceutical compounds in a clean and efficient manner.⁵ We have shown that tetrabutylphosphonium bromide (Bu₄PBr) containing catalytic amounts of HBr is a very stable ionic liquid, both thermally and chemically; it can be reused multiple times for dehydrohalogenation and dehydration reactions.⁶ These ionic liquid systems bridge homogeneous and heterogeneous (microporous solid) catalysts for the high performance synthesis of relevant molecules. In this sense, indole scaffolds are of high interest in the treatment of neuropathic pain, drug addiction, eating disorders,

glaucoma, migraine headaches or Alzheimer's and Parkinson's diseases.⁷ A green approach to carry out the C–H functionalization of the indole heteroarene at C3 is to employ alcohols as alkylating agents (Fig. 1a), generating only water as waste, instead of 'traditional' haloalkanes or boronic acids.^{7d-f}

In this contribution, we investigate catalytic Brønsted (HBr) and Lewis (transition metal cations) acid sites embedded in reusable and inexpensive media: the ionic liquid Bu₄PBr (as a quasi-homogeneous catalyst) or microporous frameworks (as heterogeneous catalysts), illustrated in Fig. 1b. First, catalytic amounts of ZnCl₂·xH₂O, FeCl₃·6H₂O, Cr(NO₃)₃·9H₂O, AlCl₃·6H₂O, ZrCl₄·xH₂O (abbreviated as MX_n) and HBr are tested for the solvent-free alkylation of indole

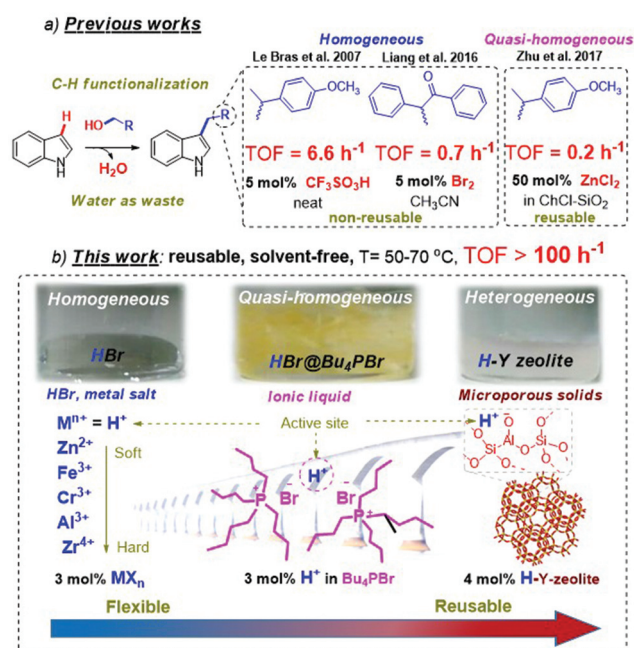


Fig. 1 C–H functionalization of indoles with alcohols catalyzed by acid catalysts (in mol% with respect to the indole). Bu₄PBr: tetrabutylphosphonium bromide; ChCl: choline chloride; X: Br or Cl.

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with 4-methoxy- α -methylbenzyl alcohol at 50 °C. The activity of such homogeneous catalysts (blue color in Fig. 1 and 2) is very high, with Turn-Over-Frequencies (TOFs or initial reaction rate per mole of acid site) of up to 600 h⁻¹ in the case of ZrCl₄. However, the recovery from the reaction mixture, and the regeneration and reuse of the homogeneous catalysts are difficult.

In order to turn the homogeneous MX_n system into an active, recoverable and reusable catalyst, the MX_n compounds were introduced (1 wt% loading) into the Bu₄PBr ionic liquid (Fig. 1b, middle). Of all the Mⁿ⁺ acids tested, both the HBr@Bu₄PBr and ZrCl₄@Bu₄PBr quasi-homogeneous systems show the best catalytic performance, generating the C3 monoalkylated indole **1** in more than 70% yield after 2 h, with TOFs of around 140 h⁻¹ (Fig. 2a). Moreover, the HBr@Bu₄PBr system maintains its good catalytic performance even after five additional reaction cycles: TOF = 130 h⁻¹, 70% yield of **1** (Fig. S5a[†]), allowing the separation of the reaction products by simple work-up with inexpensive hydrocarbons, *e.g.* mesitylene or hexane (Fig. S6[†]). The leaching of the protons from the ionic liquid is very low, since the pH of HBr@Bu₄PBr (200 mg) dissolved in water (10 ml) is only slightly higher after the alkylation reaction (pH = 2.7) *vs.* the fresh ionic liquid (pH = 2.6). This is due to: (i) the non-miscibility of both Bu₄PBr and HBr with mesitylene and (ii) the high solubility of HBr in Bu₄PBr, possibly due to the formation of bibromide BrHBr ions.⁸ The negligible conversion of indole (only 4% after 3 h), when catalytic amounts of HBr are added to mesitylene as a reaction solvent, is also indicative of

the poor solubility of HBr. In organic solvents with low dielectric constants, such as mesitylene, the aqueous acid is clustered in small poorly dispersed polar droplets (see Fig. 1b, left).⁹

In order to compare the performance of the ionic liquids with well-established microporous solids, indole alkylation with 4-methoxy- α -methylbenzyl alcohol is first carried out under the same reaction conditions (50 °C, neat), but using metal-organic frameworks (MOFs) as heterogeneous catalysts (burgundy color in Fig. 2a).¹⁰ The ionic liquid containing an acid cation (Zn²⁺, Fe³⁺, Cr³⁺, Al³⁺ and Zr⁴⁺) shows higher catalytic activity (from 4 to 8 times higher reaction rate per mole of metal) with respect to those immobilized in a solid microporous framework through an organic linker (BDC = benzene-1,4-dicarboxylate and BTC = benzene-1,3,5-tricarboxylate): Zn-BDC, Fe-BTC, Cr-BDC, Al-BTC and Zr-BDC (magenta *vs.* burgundy colors in Fig. 2a). This indicates that the acid sites are more available to interact with the reactants when they are in an ionic liquid than when immobilized in a more rigid porous framework. For both ionic liquid and metal-organic framework systems, highly charged and small cations are more active catalytic sites in this alkylation reaction (Fig. 2b). In fact, the reaction rate is about one order of magnitude higher for Zr⁴⁺ than for Fe³⁺, for which it is almost one order of magnitude higher than for Zn²⁺. As far as we know, a relationship between the catalytic activity and electronic properties of different transition metal cations in ionic liquids as active sites has not been tackled before. The dependence of the logarithm of the reaction rate on the nature of the acid cation (determined by its charge/size ratio) is higher for the quasi-homogeneous ($\alpha = 0.41$) and heterogeneous ($\alpha = 0.44$) systems than that for the pure homogeneous metal salts ($\alpha < 0.1$). An increase in the charge/size ratio of the acid cations employed as catalysts is indicative of their “hardness” or “polarizing power”.¹¹ Soft acids, *e.g.* Zn²⁺, show moderate activity and require a stoichiometric amount of metal,^{7d} while harder acids, *e.g.* Al³⁺ or Zr⁴⁺, show higher activity in this particular reaction.

The TOF values are higher for the ionic liquids when expressed per mole of active site but when the reaction rate is normalized to the mass of the reaction medium (500 mg of HBr@Bu₄PBr, and 40 mg of HY zeolite) the reaction rate/mass value is higher for the microporous solids (both HY zeolite and MOFs) than that for the ionic liquid (Fig. S7[†]). Of all the microporous solid catalysts tested, the commercial zeolite HY (CBV720) with an optimal acidity and hydrophobicity (Si/Al = 15) shows the highest performance under neat conditions (see H⁺ heterog. in Fig. 2). In fact, highly hydrophilic HY zeolites (low Si/Al) show a lower catalytic activity compared with the CBV720 zeolite. This is probably due to the adsorption of the water by-product, leading to the deactivation of the Al-O-H active sites and/or blocking the access of the alcohol. However, if the Si/Al is too high, the zeolite may lose its acidic properties (see Fig. S8a and S9a[†]).¹² The catalytic activity and selectivity of the H⁺ associated with framework aluminum in H-Y are also maintained after 5 reaction cycles (Fig. S5b[†]).

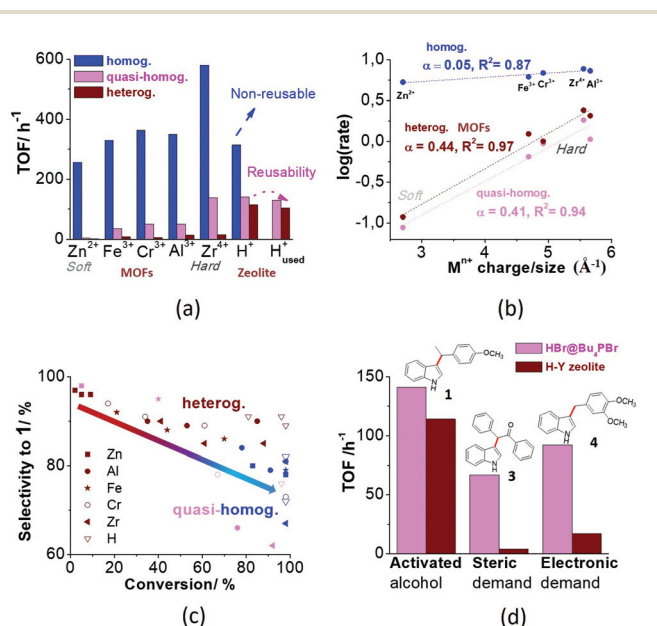


Fig. 2 (a) TOFs in ionic liquids (quasi-homogeneous) or microporous metal-organic frameworks “MOFs” (Zn²⁺, Fe³⁺, Cr³⁺, Al³⁺ and Zr⁴⁺) or zeolite (H⁺) solids (heterogeneous). (b) Initial reaction rate vs. charge/size of the Mⁿ⁺ active site. (c) Selectivity to **1** vs. indole conversion. (d) TOFs in the ionic liquid or HY zeolite to obtain **1**, **3** (at 50 °C) or **4** (70 °C).

Fig. 2c indicates that there is a decrease in the selectivity to **1** with the indole conversion, due to the subsequent alkylation of **1** at C2 to produce product **2**. While the quasi-homogeneous catalysts are generally more active when compared per mole of active site, the heterogeneous acid catalysts are more selective, even at high conversion levels (Fig. 2c and S8[†]). All the heterogeneous systems show a selectivity higher than 90% to product **1**, which is attributed to transition state shape selectivity (Fig. 3a).¹³ In contrast, the HBr@Bu₄PBr system converts the indole completely after just 15 minutes at an expense of moderate selectivity to **1** (76%). This is due to the easy accessibility of the mono-alkylated indole **1** and the alcohol to the acid sites incorporated into the flexible Bu₄PBr system, forming the bulky product **2** in about 20% yield. This by-product **2** is minimized when the hydrocarbon chain of the R₄PBr ionic liquid is increased from 4 (R = Bu) to 8 (R = Oct) carbon atoms. When the alkylation is performed in tetraoctylphosphonium bromide (HBr@Oct₄PBr), the selectivity to **1** at 100% indole conversion is slightly higher (87%) than for the HBr@Bu₄PBr system (76%) at the same indole conversion (see Table S2 and Fig. S10[†]). However, when the ionic liquid reaction media contains a very large hydrocarbon chain, *i.e.* tributyltetradecylphosphonium chloride, its catalytic activity significantly decreases with respect to tetrabutylphosphonium chloride (3.8 *vs.* 1.8 mmol h⁻¹). This may be due to a better diffusion of the reactants and products in the less bulky HBr@Bu₄PBr ionic liquid. Moreover, the formation of bridged proton structures with the anion (*i.e.* Cl, Br or (CF₃SO₂)₂N) in the HBr@butylphosphonium type ionic liquid favors the proton-conduction (through a Grotthuss-like mechanism), enhancing its acidic properties (Scheme S1[†]).¹⁴

The HBr@Bu₄PBr quasi-homogeneous system shows good performance for the alkylation of indoles with bulky alcohols,

such as benzoin (α -hydroxy- α -phenylacetophenone), generating the bulky indole derivative **3** in much higher yields (96%) than the microporous acid HY zeolite (4%) after 2 h under neat conditions (Fig. 2d, 3b and S11b[†]). This is probably due to the size restrictions of the 7.4 Å faujasite pore windows that impede either the diffusion of the bulky benzoin alcohol into the inner H⁺ active sites of the crystalline framework and/or the formation of product **3** inside the zeolite, as occurs during the formation of **2**. In fact, the adsorption of benzoin from mesitylene to the ionic liquid is much higher (23%) than that in the case of the zeolite (7%), as indicated in Fig. S14.[†] To the best of our knowledge, HBr@Bu₄PBr is the only reusable system (up to 4 times with no apparent loss in activity) currently reported to obtain this large indole derivative **3** in high yields (Fig. S12a[†]).

Lignin model compounds such as (3,4-dimethoxy)benzyl alcohol can also be used as an alkylating agent for the selective C–H functionalization of indoles at C3 at 70 °C under solvent-free conditions (see Fig. 2d and S11c[†]). When the alkylation is carried out in the HBr@Bu₄PBr quasi-homogeneous system, this results in 91% yield of **4** after 8 h (TOF = 92 h⁻¹). However, only 76% yield of **4** after 8 h is obtained when employing the H–Y zeolite (TOF = 17 h⁻¹). The lower stability of primary carbocations compared to those formed from secondary alcohols can explain the lower reaction rate of the formation of **3** with respect to **1**. Since the reaction rate increases with the amount of alcohol, the alcohol seems to participate in the rate limiting step (Fig. S13[†]). We propose a proton transfer from ionic liquid reaction media to the secondary or primary alcohols generating carbocation or brominated intermediates,^{5d,6b} respectively, which will react with the electron rich C3 of the indole to form the C–C bond in the functionalized indole (Fig. S15[†]).

Conclusions

Given the importance of recoverable and reusable catalytic systems that still maintain the high activity and selectivity of their homogeneous counterparts, here we have described how the number of turnovers of catalytic sites can be improved by increasing the flexibility of their environment; from rigid microporous frameworks to flexible ionic liquids (here named quasi-homogeneous catalyst). This ionic liquid system combines the high activity of homogeneous catalysts with the reusability of heterogeneous catalysts. The use of highly active HBr@Bu₄PBr as the reaction medium and catalytic system allows the easy separation of the indole derivatives by extraction with hydrocarbon solvents and reuse in subsequent reaction cycles. While the quasi-homogeneous catalysts are generally more active when compared per mole of active site, the heterogeneous acid catalysts (MOFs and zeolites) are more selective towards relatively small mono-alkylated products, even at high conversion levels. A critical comparison of various microporous solids suggests that the HY zeolite is the most attractive option, in terms of catalytic performance and price,

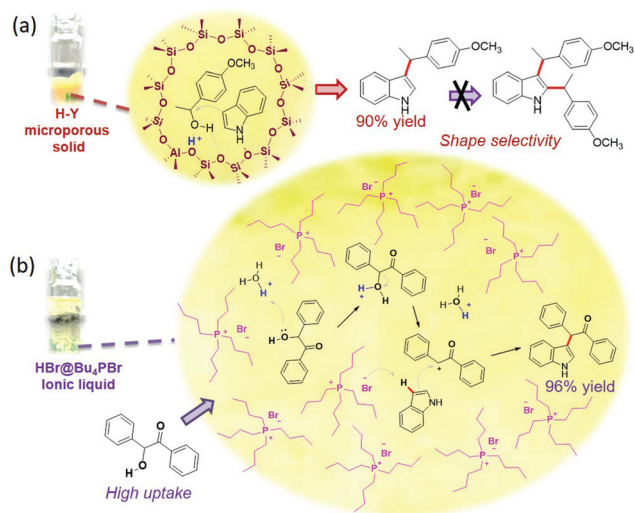


Fig. 3 (a) Selective synthesis of **1** in the 12-membered ring HY large pore zeolite. (b) Reaction mechanism proposed for the alkylation of indole with benzoin to produce **3** in HBr@Bu₄PBr.

of all the microporous frameworks tested. The high activity of the HBr@Bu₄PBr quasi-homogeneous system for the alkylation of indoles with sterically and electronically demanding alcohols encourages further research into ionic liquids as alternative catalysts and reaction media to (porous) solid catalysts. Only by understanding the advantages and limitations of the catalytic systems available, the final goal of an eco-friendly synthesis of fine chemicals and pharmaceutical intermediates will be established in the near future.

Conflicts of interest

There are no conflicts to declare.

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