

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

F.G. Cirujano*, Maxime Stalpaert, Dirk De Vos

Centre for Surface Chemistry and Catalysis, KU Leuven Celestijnenlaan 200F, 3001 Leuven, Belgium

*Corresponding author: francisco.garcia@kuleuven.be

Homogeneous soluble acids are very active catalysts in the fine chemicals and pharmaceutical industries but suffer from complicated product purification, deactivation and moderate selectivities. Reusable microporous solid acids have appeared as attractive alternative heterogeneous catalysts, but presents diffusion limitations for the synthesis of large organic molecules and typically requires organic solvents. 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. For instance, tetrabutylphosphonium bromide (Bu_4PBr) containing catalytic amounts of HBr is a very stable ionic liquid and it can be reused multiple times.

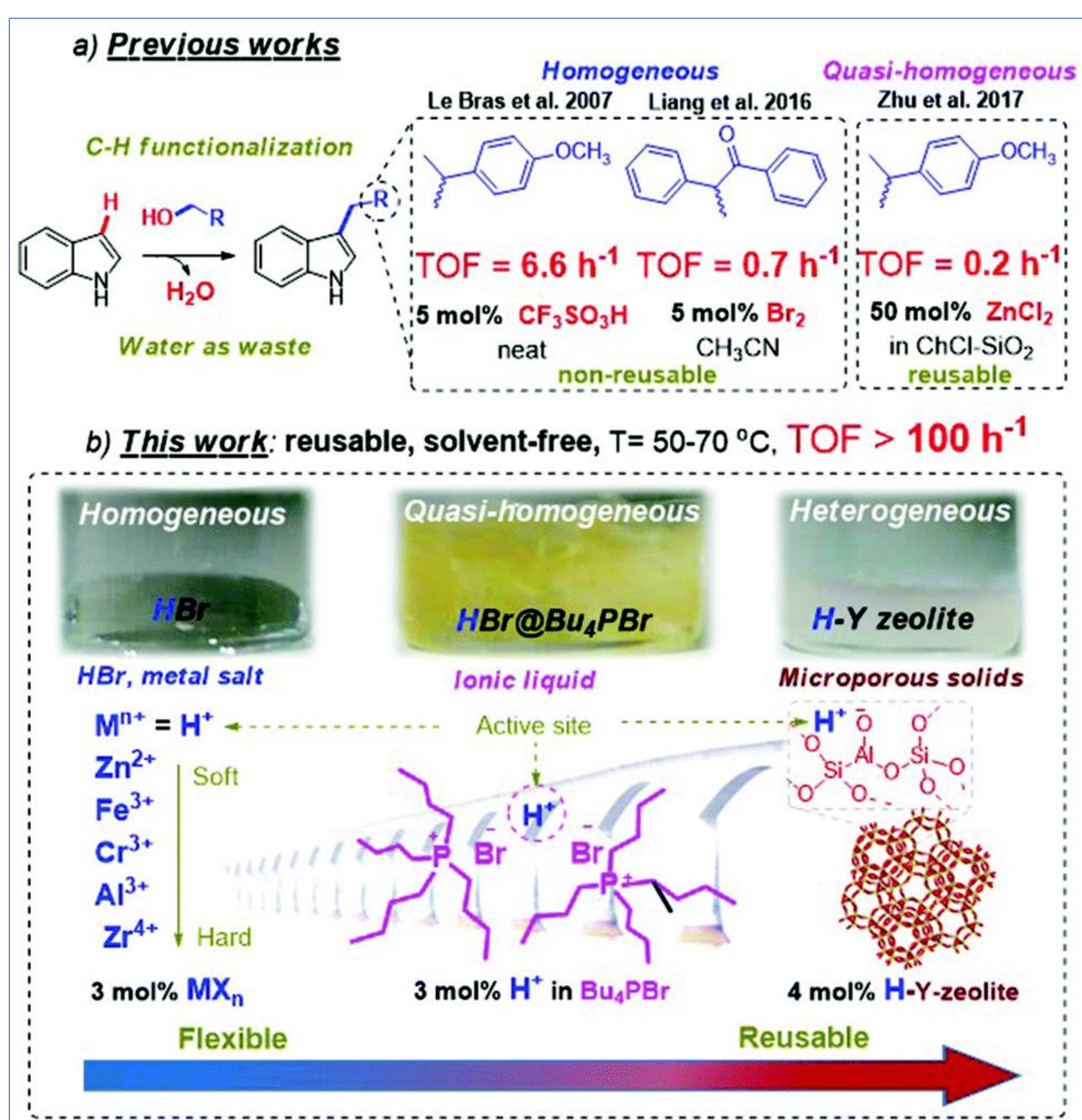


Figure 2. C–H functionalization of indoles with alcohols catalyzed by acid catalysts (in mol% with respect to the indole). Bu₄PBr: tetrabutylphosphonium bromide; ChCl: choline chloride; X: Br or Cl.

- The activity of MX_n homogeneous catalysts (blue color in Fig. 1 and 2) is very high, with TOFs of up to 600 h⁻¹. However, the recovery from the reaction mixture, and the regeneration and reuse of the homogeneous catalysts are difficult.
- The MX_n compounds were introduced into the Bu₄PBr ionic liquid (Fig. 1b, middle). The HBr@Bu₄PBr and ZrCl₄@Bu₄PBr quasi-homogeneous systems show the best catalytic performance and maintains its good catalytic performance even after five additional reaction cycles, allowing the separation of the reaction products by simple work-up.
- 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).
- 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, specially with the quasi-homogeneous catalysts compared to the heterogeneous acid catalysts.

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. 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. 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.

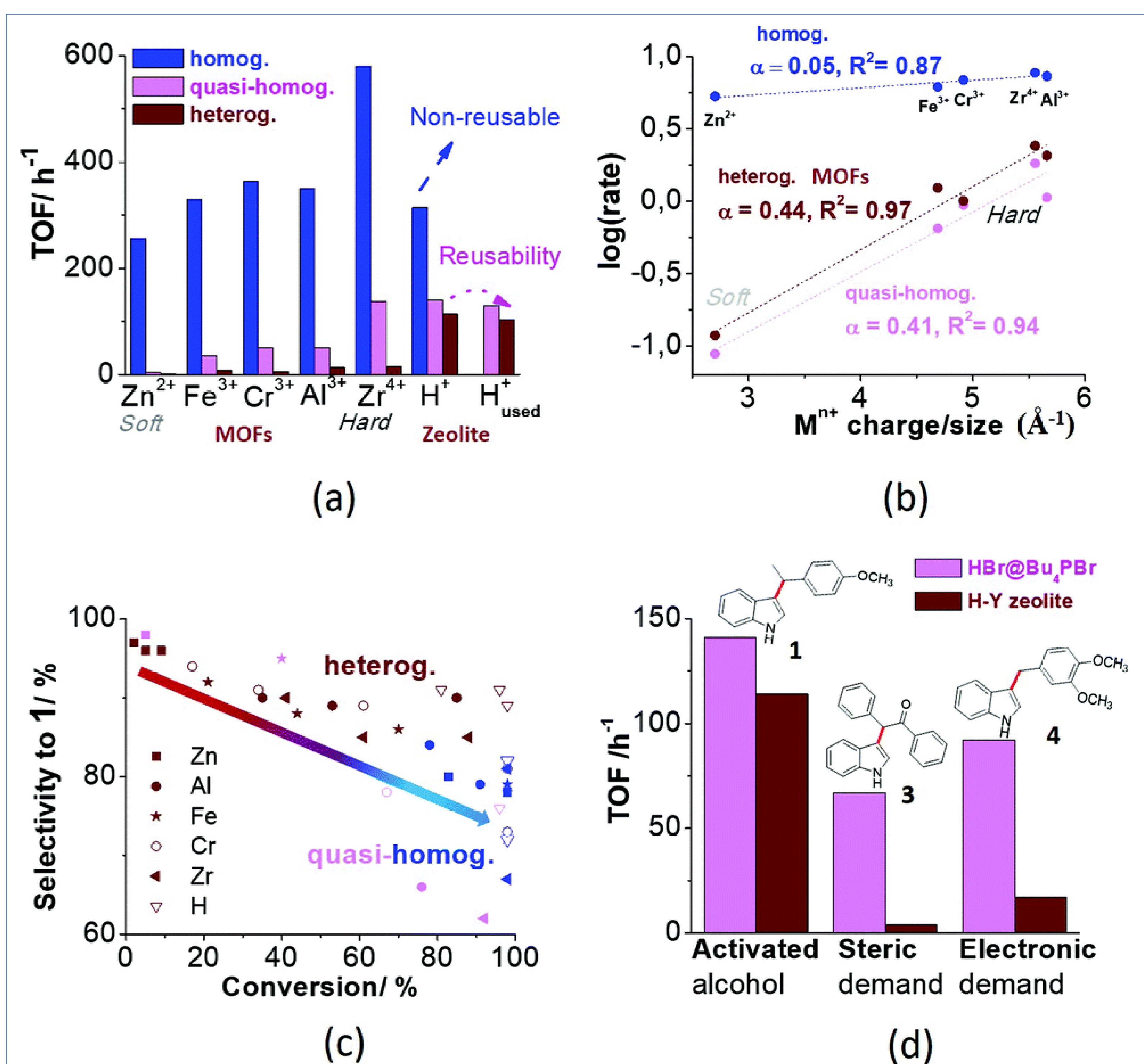


Figure 2. (a) TOFs in ionic liquids (quasi-homogeneous) or microporous metal–organic frameworks “MOFs” (Zn²⁺, Fe³⁺, Cr³⁺, Al³⁺ and Zr⁴⁺) or zeolite (H⁺) solids (heterogeneous). (b) Initial reaction rate vs. charge/size of the Mⁿ⁺ active site. (c) Selectivity to 1 vs. indole conversion. (d) TOFs in the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

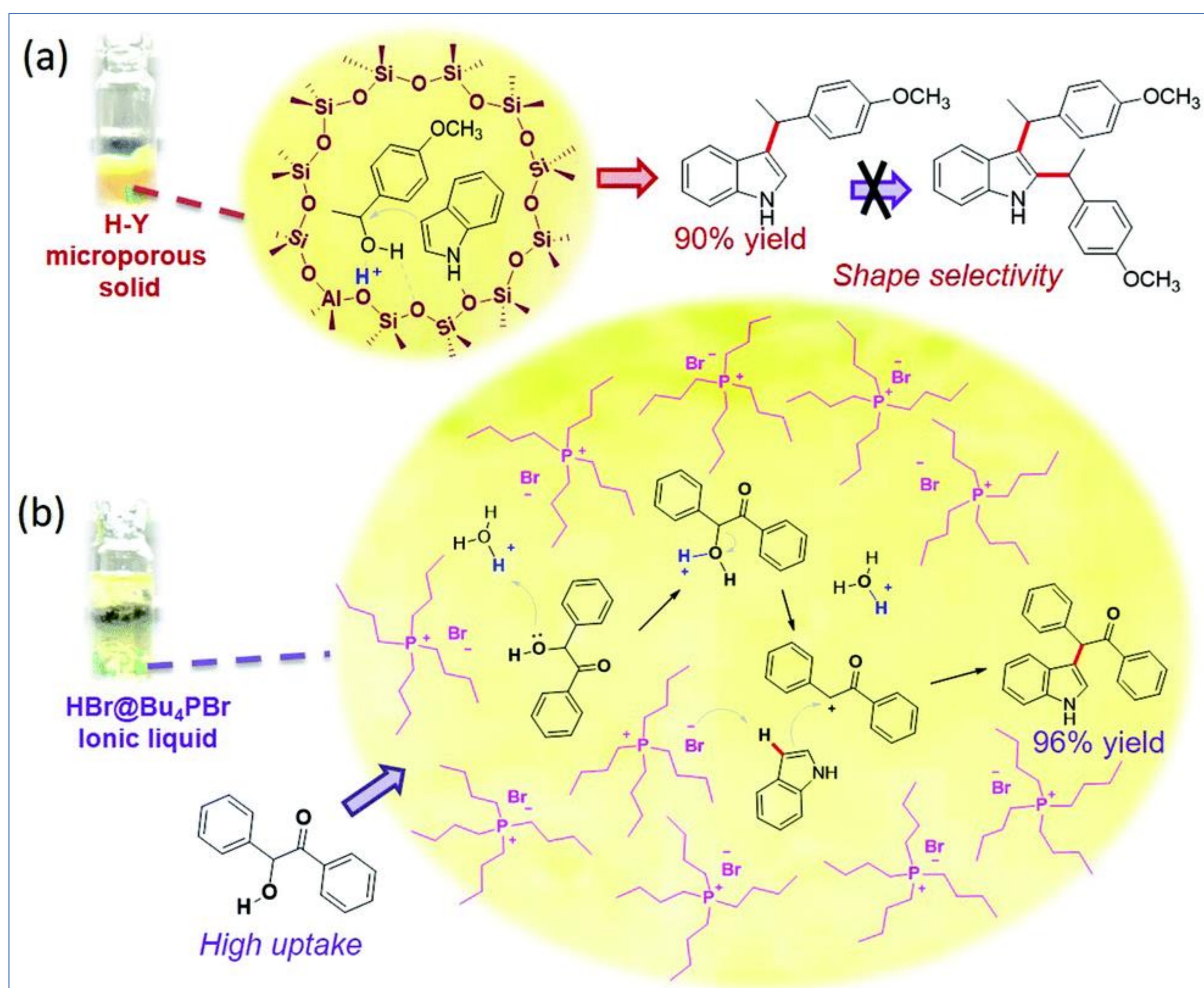


Figure 3. (a) Selective synthesis of 1 in the 12-membered ring HY zeolite. (b) Reaction mechanism proposed for the alkylation of indole with benzoin in HBr@Bu₄PBr.

- The HBr@Bu₄PBr quasi-homogeneous system generates the bulky indole derivative 3 in much higher yields (96%) than the microporous acid HY zeolite (4%) after 2 h due to size restrictions of the zeolite pore size (Fig. 2d)
- Lignin model compounds can also be used as an alkylating agent for the selective C–H functionalization of indoles in the HBr@Bu₄PBr quasi-homogeneous system, resulting in 91% yield of 4 (TOF = 92 h⁻¹), vs. only 76% yield of 4 obtained when employing the H–Y zeolite (TOF = 17 h⁻¹).

Conclusions

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). 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, 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.

ACKNOWLEDGMENTS

F.G.C. acknowledges the European Commission-Horizon 2020 for funding through Marie Skłodowska Curie Individual Fellowship under the grant agreement number: 750391 (SINMOF)