

## Supporting Information

### **Ionic liquids vs. microporous solids as reusable reaction media for the catalytic C-H functionalization of indole with alcohols**

Francisco G. Cirujano\*, Maxime Stalpaert and Dirk E. De Vos\*

*Centre for Surface Chemistry and Catalysis, Department of Microbial and Molecular Systems (M2S), KU Leuven, Celestijnenlaan 200F, 3001 Leuven, Belgium*

\* corresponding authors: francisco.garcia@kuleuven.be; dirk.devos@kuleuven.be

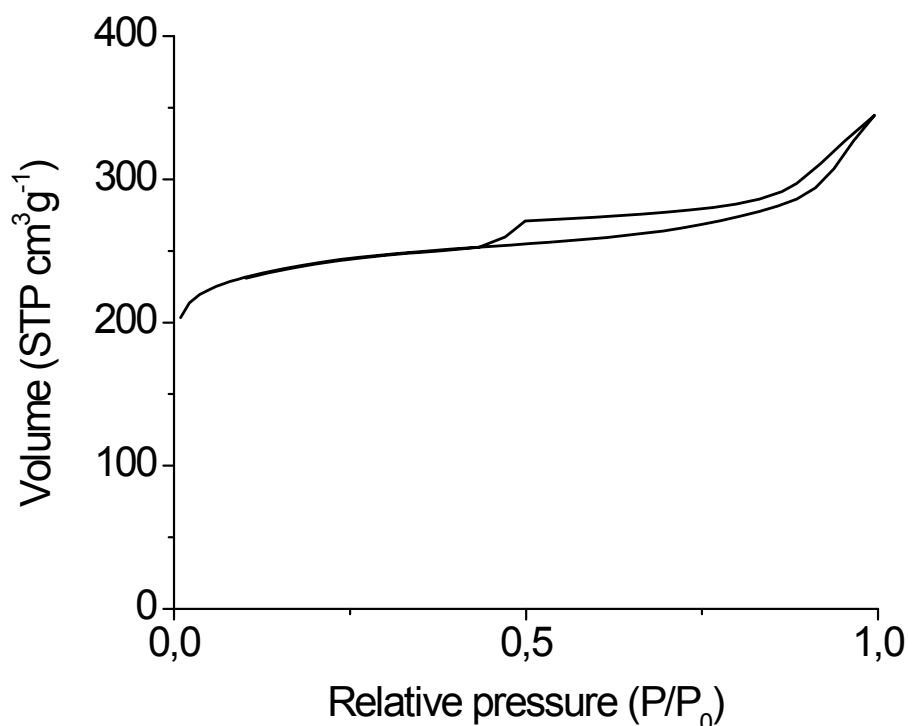
### **Table of Contents**

Chemicals.....	S3
Figure S1.....	S3
Synthesis of non-commercially available catalysts.....	S4
Figure S2.....	S4
Reaction conditions .....	S5
Figure S3.....	S5
Catalytic results for the synthesis of functionalized indoles.....	S6
Figure S4.....	S6
Table S1.....	S6
Figure S5.....	S7
Figure S6.....	S7
Figure S7.....	S8
Figure S8.....	S8
Figure S9.....	S9
Table S2.....	S10
Scheme S1.....	S10
Figure S10.....	S11

Figure S11.....	S11
Figure S12.....	S12
Figure S13.....	S12
Alcohol uptake in the ionic liquid or zeolite.....	S13
Table S3.....	S13
Figure S14.....	S13
Figure S15.....	S14
Spectral data of indole derivative products.....	S15
Figure S16.....	S15
Figure S17.....	S15
Figure S18.....	S16
Figure S19.....	S16
Figure S20.....	S17
Figure S21.....	S17
Figure S22.....	S18
Spectral data of intermediates and by-products.....	S19
Figure S23.....	S19
Figure S24.....	S19
Figure S25.....	S19
Figure S26.....	S20
Figure S27.....	S20
Scheme S2.....	S21
Figure S28.....	S21
Figure S29.....	S21
References.....	S22

## Chemicals

$\text{ZnCl}_2 \cdot x\text{H}_2\text{O}$ ,  $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ ,  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ ,  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ ,  $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ ,  $\text{Cr}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ ,  $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ , HBr (reagent grade 47%), *p*-toluenesulfonic acid monohydrate (*p*TSA), tetrabutylphosphonium bromide ( $\text{Bu}_4\text{PBr}$ ), mesitylene, indole, 4-methoxy- $\alpha$ -methylbenzyl alcohol, benzoin ( $\alpha$ -hydroxy- $\alpha$ -phenylacetophenone), (3,4-dimethoxy)benzyl alcohol, *N,N*-dimethylformamide (DMF), triethylamine (TEA), benzene-1,4-dicarboxylic acid (BDC), Al-BTC and Fe-BTC were used as received from Sigma-Aldrich without further purification. The H-Y Faujasite zeolites CBV400, 600, 720, 760, 901 were purchased from Zeolyst international. Tetraoctylphosphonium bromide, Tetrabutylphosphonium chloride and Tributyltetradecylphosphonium chloride were purchased from iolitec. Tributylmethylphosphonium bis(trifluoromethanesulfonyl)imide was purchased from TCI.



**Figure S1**  $\text{N}_2$  physisorption isotherm of the HY CBV720 commercial zeolite heterogeneous catalyst, performed at 77 K on a Micromeritics TriStar instrument. Before measurement, the sample was dried overnight at 573 K.

## Synthesis of non-commercially available catalysts

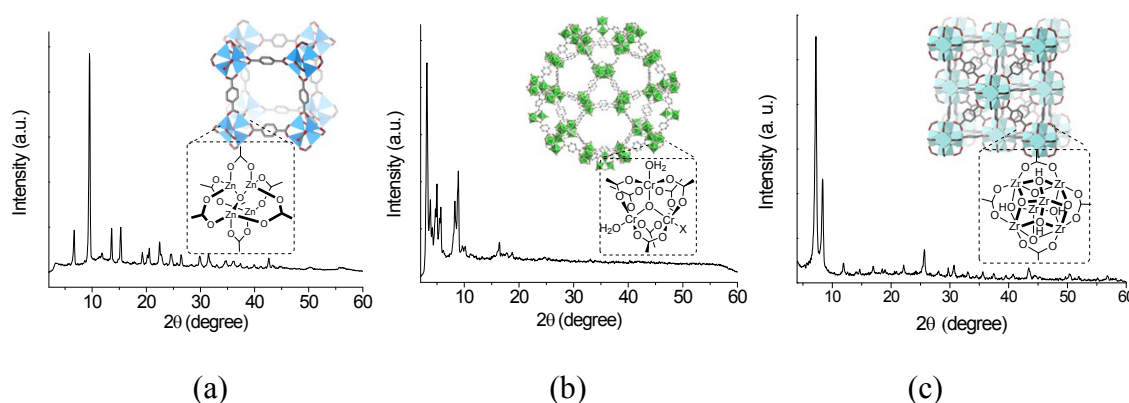
**HBr@Bu<sub>4</sub>PBr:** The synthesis of HBr@Bu<sub>4</sub>PBr was adapted from the method reported.<sup>1</sup> Briefly, 10  $\mu$ l HBr (48%) were added to 1 g of solid Bu<sub>4</sub>PBr. The partially melted HBr@Bu<sub>4</sub>PBr white solid was stirred at room temperature for 0.5 h and used as reaction media and catalyst. The same recipe was extended to other ionic liquids (see Table S2). The samples of ZnCl<sub>2</sub>@Bu<sub>4</sub>PBr, FeCl<sub>3</sub>@Bu<sub>4</sub>PBr, CrCl<sub>3</sub>@Bu<sub>4</sub>PBr, AlCl<sub>3</sub>@Bu<sub>4</sub>PBr and ZrCl<sub>4</sub>@Bu<sub>4</sub>PBr were prepared using the corresponding metal chlorides (1 wt.% respect to the amount of ionic liquid) instead of HBr and keeping the rest of the method the same.

The (Zn)BDC, (Cr)BDC and (Zr)UiO-66 metal-organic frameworks were prepared following reported methods,<sup>2-4</sup> in order to establish comparisons with the rest of the transition metal containing catalysts.

**MOF-5:** Zn(BDC) or MOF-5 was synthesized by adding 16 mmol of triethylamine to a DMF (40 ml) solution of benzene-1,4-dicarboxylic acid (2 mmol) and zinc nitrate hexahydrate (4 mmol). The addition takes place during 0.5-2 h under stirring conditions at room temperature. A white precipitate was formed, isolated by centrifugation, washed with DMF and dichloromethane and dried in an oven at 90 °C.<sup>2</sup>

**MIL-101:** Cr(BDC) or MIL-101 was prepared from a water (15 ml) solution of benzene-1,4-dicarboxylic acid (500 mg), Cr(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O (800 mg) and 40 $\mu$ L HF (40%), heated at 200 °C during 8 h in an oven. The blue-green solid was washed with hot DMF, water, ethanol and dried at 80 °C overnight.<sup>3</sup>

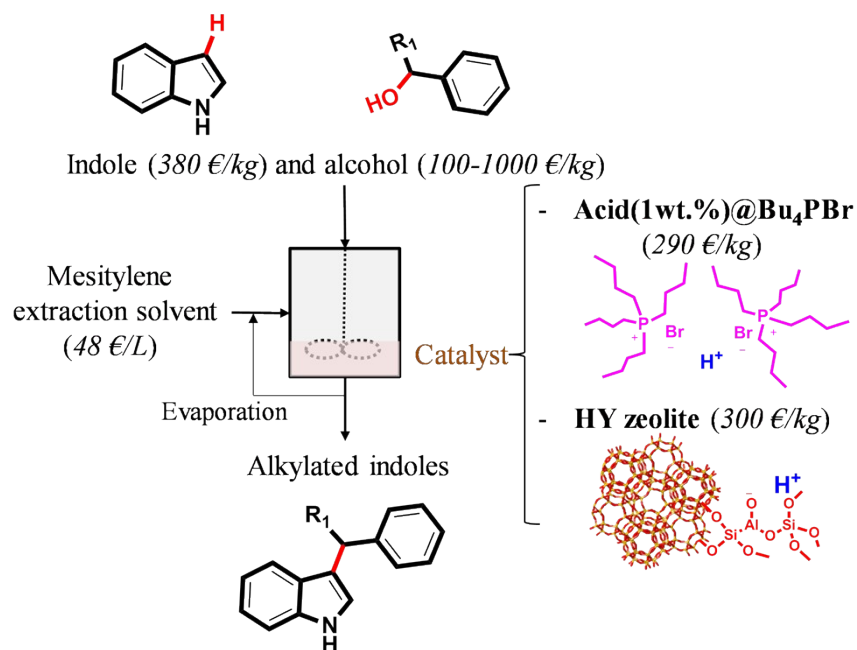
**UiO-66:** Zr(BDC) or UiO-66 was obtained from a DMF solution (90 ml) of ZrCl<sub>4</sub> (750 mg) and benzene-1,4-dicarboxylic acid (740 mg), heated at 80 °C for 12 h and at 100 °C for 24 h. The white powder obtained was recovered by filtration, washed with DMF and CH<sub>2</sub>Cl<sub>2</sub>, and dried under vacuum.<sup>4</sup>



**Figure S2.** XRD patterns of (a) Zn(BDC), (b) Cr(BDC) and (c) Zr(BDC) metal-organic frameworks. XRD patterns were recorded using a Panalytical Empyrean X-ray diffractometer with Cu K $\alpha$  radiation ( $\lambda=1.54778$  Å). The samples were prepared by filling the holder with the dry powder.

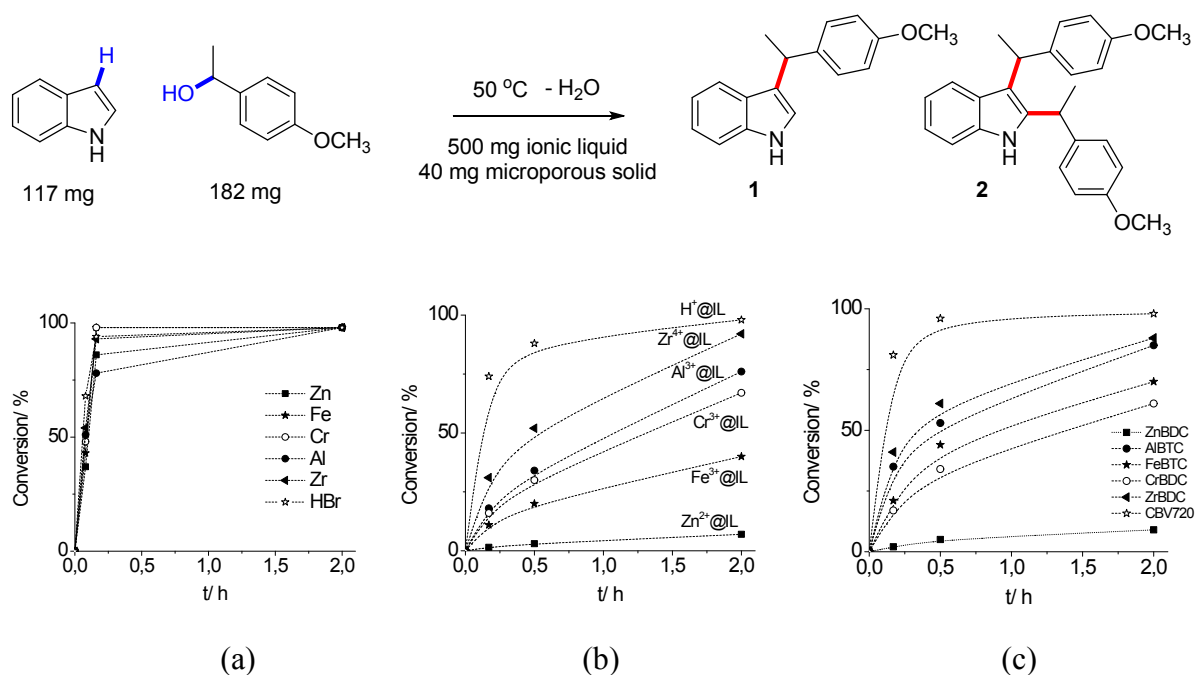
## Reaction conditions

The reactions were performed as follows: 1 mmol (117 mg) of indole, 1.2 mmol of alcohol (182 mg for 4-methoxy- $\alpha$ -methylbenzyl alcohol, 254 mg for benzoin, 168 mg for (3,4-dimethoxy)benzyl alcohol) and *n*-tetradecane (198 mg, 1 mmol) as the internal standard for the analysis with gas chromatography (GC) coupled with a flame ion detector (FID), were added to a glass vessel containing 500 mg of  $\text{MX}_n\text{@Bu}_4\text{PBr}$  (containing 1 %wt. of  $\text{MX}_n = \text{HBr}$ ,  $\text{ZnCl}_2$ ,  $\text{FeCl}_3$ ,  $\text{AlCl}_3$ ,  $\text{CrCl}_3$ ,  $\text{ZrCl}_4$ ) in the case of ionic liquids or 40 mg of porous solid. The vials were closed and transferred into an aluminum heating block preheated to 50 °C or 70 °C in order to obtain compounds **1**, **3** (50 °C) or **4** (70 °C). The mixture was stirred (400 rpm) at this temperature and sample aliquots were taken at different reaction times. In the case of the  $\text{MX}_n\text{@Bu}_4\text{PBr}$  ionic liquid (solid at room temperature), its viscosity decreases upon heating above room temperature, obtaining a homogeneous reaction mixture (see Figure S6a). The reaction products were recovered by extraction with mesitylene (1,3,5-trimethylbenzene) and analyzed by GC/MS using a GC Shimadzu 2014 GC instrument equipped with a FID detector and a CP-Sil 5 CB column. Mass Spectra were obtained with a GC/MS Agilent 6890 gas chromatograph, equipped with a HP-5MS column, coupled to a 5973 MSD mass spectrometer with electron impact ionization. The ionic liquid was reused after washing (50 °C, 5 min, 400 rpm) three times with mesitylene, separated by centrifugation and dried in a stream of nitrogen at room temperature. For the porous solids, the solvent-free suspension was stirred (300 rpm) at the desired temperature and sample aliquots were taken from the supernatant upon centrifugation (3000 rpm, 10 min) at different reaction times. The supernatant solution was analyzed with GC-FID. The solid was separated by centrifugation, washed with mesitylene, ethanol and subsequently dried in a stream of nitrogen at room temperature for a subsequent reuses.



**Figure S3.** Batch reaction between indole and alcohols using ionic liquid or microporous solid to obtain indole derivatives. To have an idea of the costs, the price values of the compounds were obtained from sigma-aldrich and zeolyst international.

## Catalytic results for the synthesis of functionalized indoles

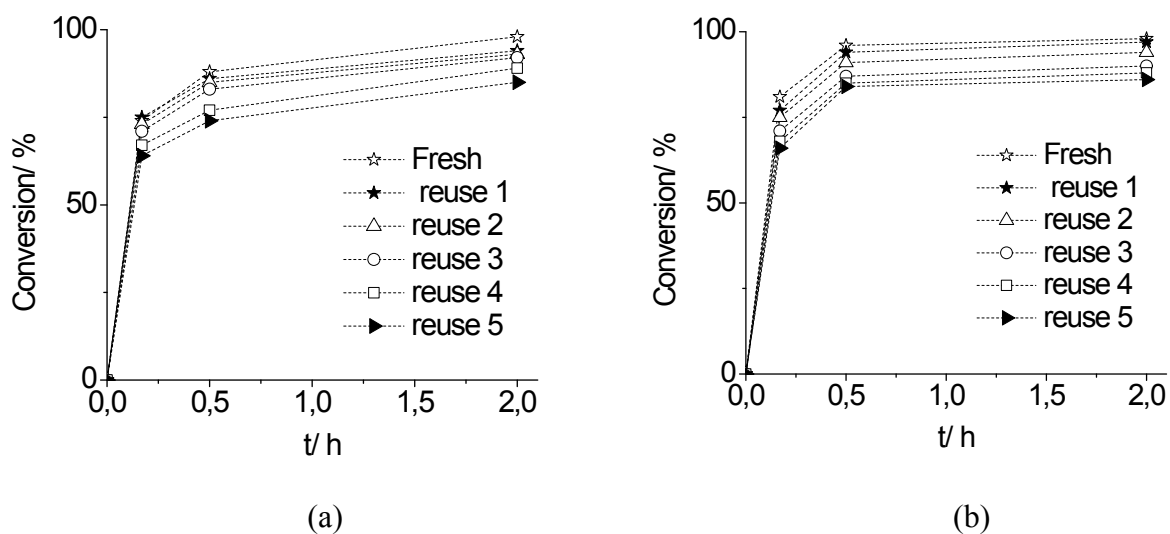


**Figure S4.** Conversion vs. time for the solvent-free alkylation of indole (1 mmol) with 4-methoxy- $\alpha$ -methylbenzyl alcohol (1.2 mmol) at 50 °C using homogeneous (a), *quasi*-homogeneous (b) and heterogeneous (c) catalysts.

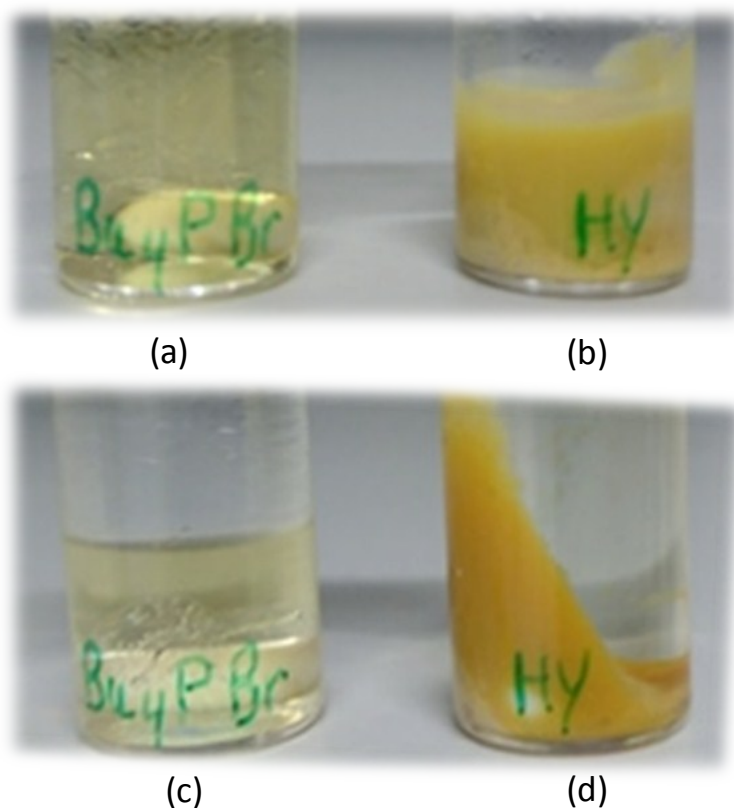
**Table S1.** Indole (1 mmol) alkylation with 4-methoxy- $\alpha$ -methylbenzyl alcohol (1.1 mmol) at 50 °C under solvent-free conditions, using different acid catalysts.

	Zn <sup>2+</sup>	Al <sup>3+</sup>	Fe <sup>3+</sup>	Cr <sup>3+</sup>	Zr <sup>4+</sup>	H <sup>+</sup>
<b>Homogeneous</b>						
$r_0$ (mmol*h <sup>-1</sup> ) <sup>a</sup>	5.3	7.3	6.1	6.8	7.7	9,7
TOF (h <sup>-1</sup> ) <sup>b</sup>	257	350	330	363	580	315
<b>Quasi-homogeneous</b>						
$r_0$ (mmol*h <sup>-1</sup> )	0.1	1.0	0.6	0.9	1.8	4.3
TOF (h <sup>-1</sup> )	4	51	35	50	137	141
<b>Heterogeneous</b>						
$r_0$ (mmol*h <sup>-1</sup> )	0.1	2.0	1.2	1.0	2.4	4.8
TOF (h <sup>-1</sup> )	1	13	8	6	15	114

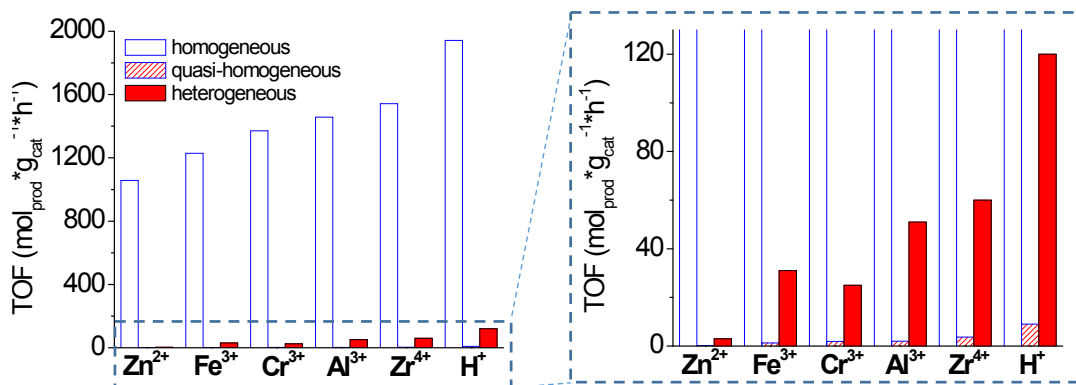
<sup>a</sup> Initial reaction rate ( $r_0$ ) expressed as moles of indole converted (for conversion lower than 50%) divided by time (in hours). <sup>b</sup> Turnover frequency (TOF) expressed as mol of indole converted per mol of active site and time in hours; in other words, initial reaction rate ( $r_0$ ) divided by mol of active site (Zn<sup>2+</sup>, Fe<sup>3+</sup>, Cr<sup>3+</sup>, Al<sup>3+</sup>, Zr<sup>4+</sup>, H<sup>+</sup>).



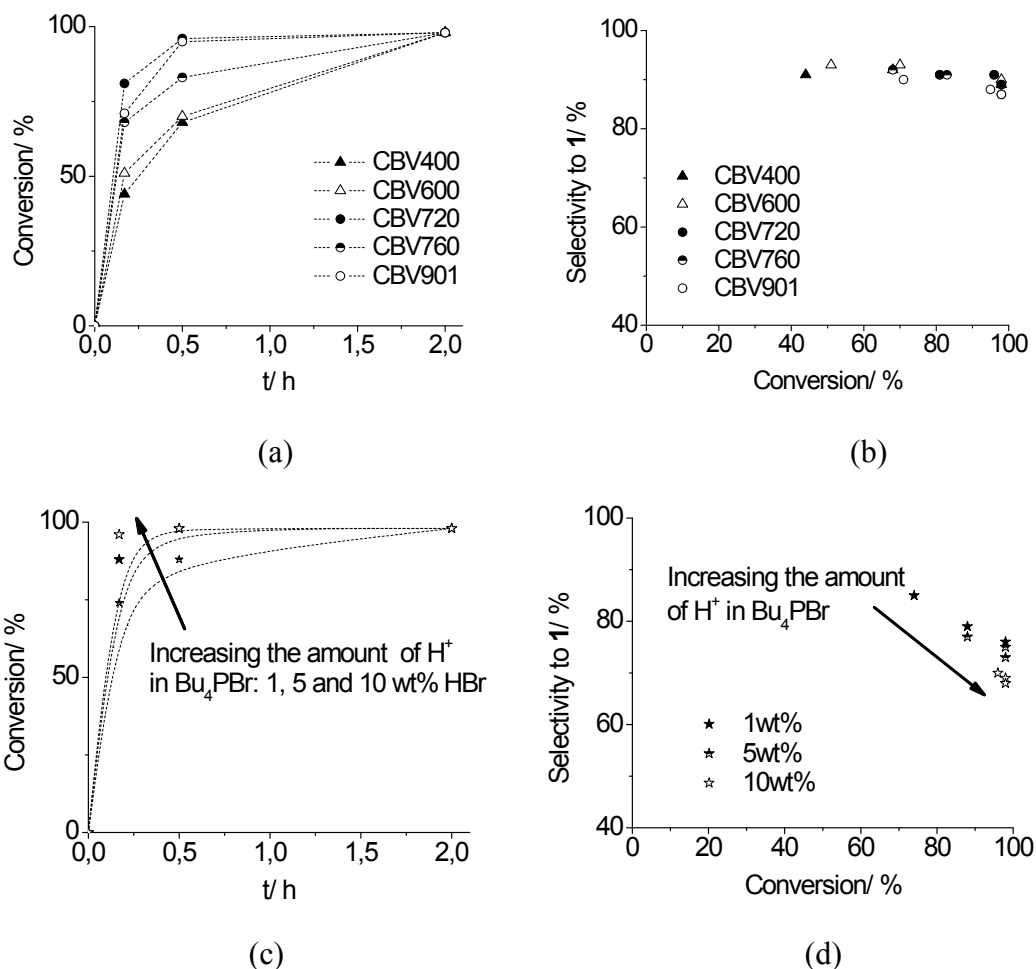
**Figure S5.** Reuses for the alkylation of indole (1 mmol) with 4-methoxy- $\alpha$ -methylbenzyl alcohol (1.2 mmol) at 50 °C using HBr@Bu<sub>4</sub>PBr ionic liquid (a) or HY CBV720 zeolite (b).



**Figure S6.** *Quasi*-homogeneous HBr@Bu<sub>4</sub>PBr (a), (c) and heterogeneous HY zeolite (b), (d) before (up) and after (down) the extraction of the products (**1** and **2**) with mesitylene.

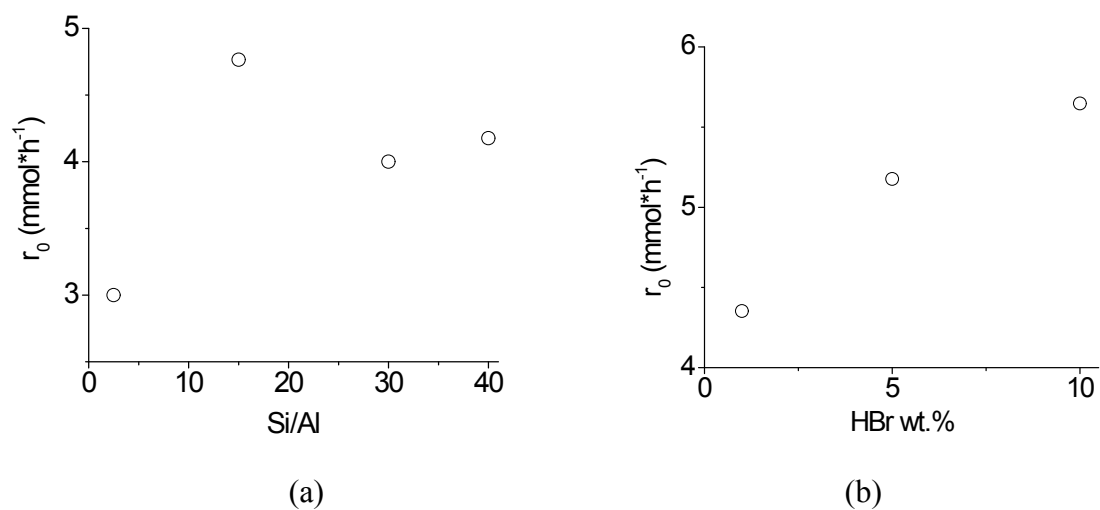


**Figure S7.** TOF (mols of products obtained per grams of acid catalyst and per hour) calculated at initial reaction times, when using different catalytic systems: (i) metal cations or HBr as acid catalysts (homogeneous), (ii) in the Bu<sub>4</sub>PBr ionic liquid (quasi-homogeneous) or (iii) in the structure of microporous MOFs and HY zeolite (heterogeneous).




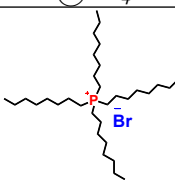

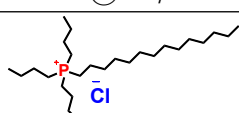
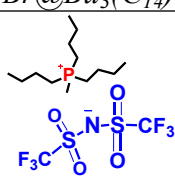
**Figure S8.** Conversion vs. time (a, c) and selectivity vs. time (b, d) for the alkylation of indole (1 mmol) with 4-methoxy- $\alpha$ -methylbenzyl alcohol (1.2 mmol) at 50 °C using different HY zeolite catalysts with different Si/Al= 2.5 (CBV600), 15 (CBV720), 30 (CBV760) and 40 (CBV901) (parts a, b) and HBr in the ionic Bu<sub>4</sub>PBr liquid (1, 5 and 10 wt%) (parts c and d).



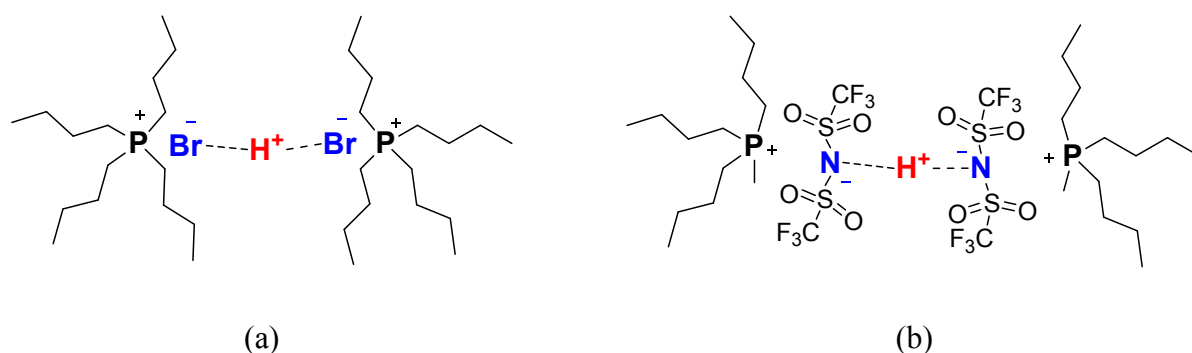


**Figure S9.** Reaction rate ( $r_0$ ) for the synthesis of **1** from indole and 4-methoxy- $\alpha$ -methylbenzyl alcohol with (a) HY zeolites with increased Si/Al ratio (increased Lewis acid strength & hydrophobicity) and (b)  $\text{Bu}_4\text{PBr}$  containing increased amounts of HBr.

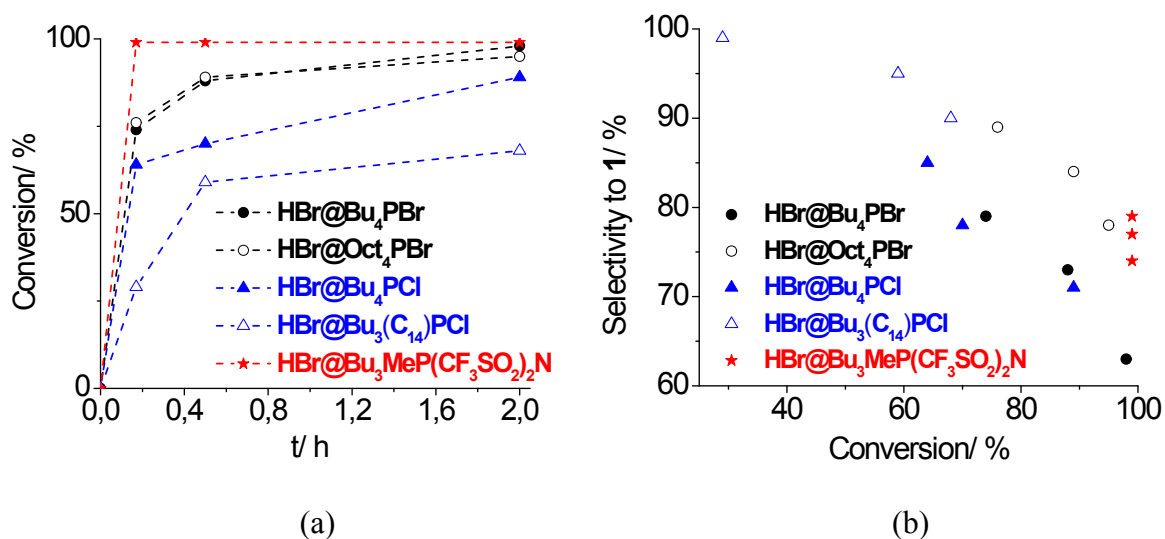
**Table S2.** Conversion of indole and selectivity to **1** in different HBr @ Ionic liquids (1%wt. HBr).<sup>a</sup>

Ionic liquid	Reaction rate (mmol·h <sup>-1</sup> )	Selectivity to <b>1</b> (%) <sup>b</sup>
 <i>HBr@Bu<sub>4</sub>PBr</i>	4.4	79
 <i>HBr@Oct<sub>4</sub>PBr</i>	4.4	89
 <i>HBr@Bu<sub>4</sub>PCl</i>	3.8	85
 <i>HBr@Bu<sub>3</sub>(C<sub>14</sub>)Cl</i>	1.8	90
 <i>HBr@Bu<sub>3</sub>MeP(CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>N</i>	5.8	79

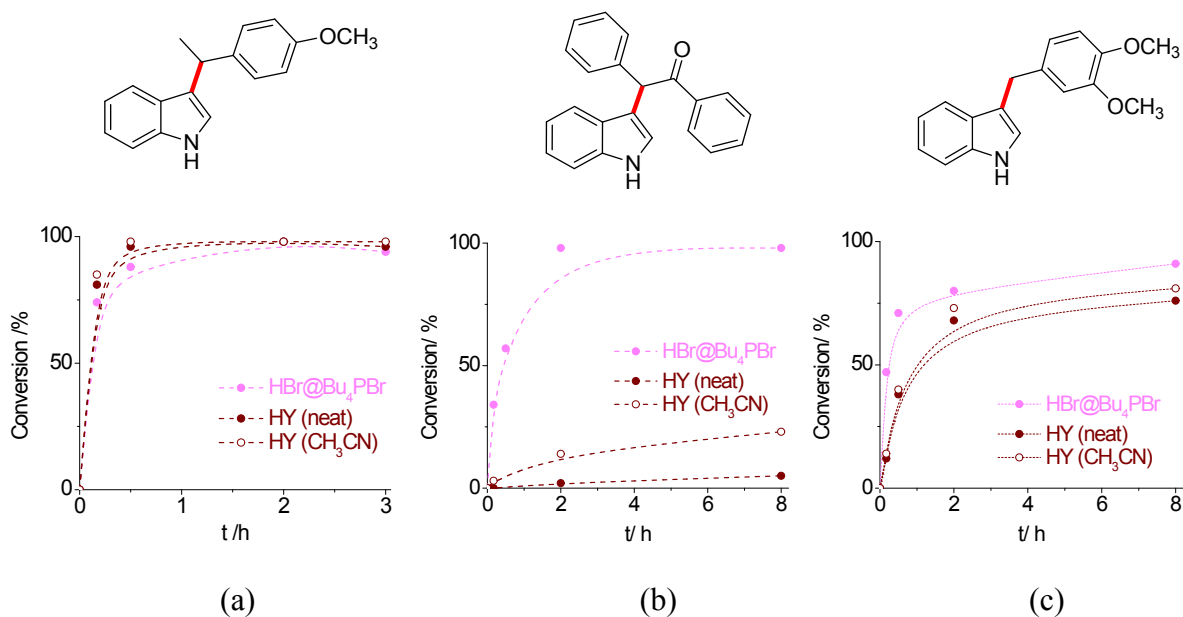
<sup>a</sup> Reaction conditions: indole (1 mmol), 4-methoxy- $\alpha$ -methylbenzyl alcohol (1.2 mmol) at 50 °C. <sup>b</sup> For 70-80% indole conversion.



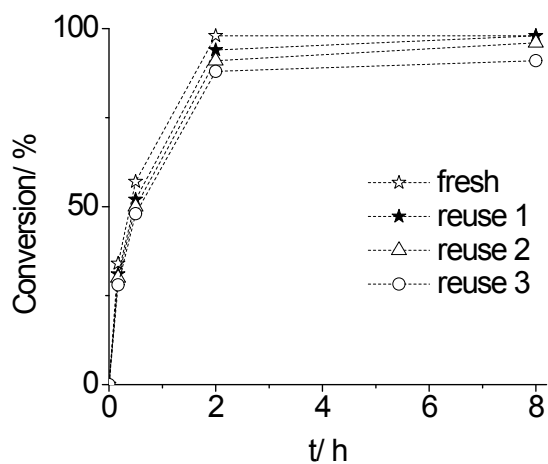
**Scheme S1.** Proposed clustered structures of anionic dimers in *HBr@Bu<sub>4</sub>PBr* (a) or *HBr@Bu<sub>3</sub>MeP(CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>N* (b) ionic liquids, which favors the proton conduction.



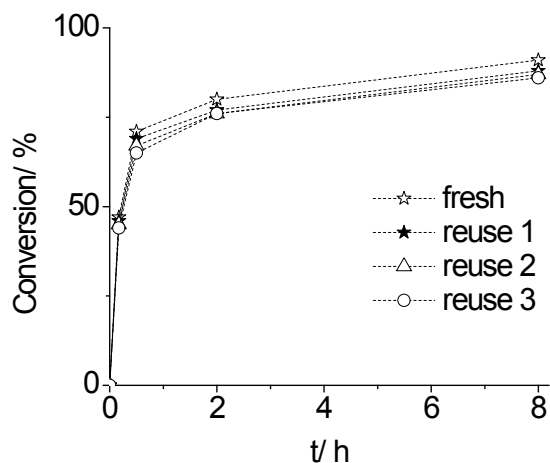
**Figure S10.** Conversion vs. time (a) and selectivity to **1** vs. conversion (b) for the alkylation of indole (1 mmol) with 4-methoxy- $\alpha$ -methylbenzyl alcohol (1.2 mmol) at 50 °C using 500 mg of HBr containing ionic liquids (3 mol% H<sup>+</sup> respect to the indole) with different anions: Br, Cl or (CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>N; or hydrocarbon chain length: Butyl (Bu), Octyl (Oct) or tetradecyl (C<sub>14</sub>).



**Figure S11.** Conversion vs. time profile of the alkylation of 1 mmol of indole with 1.2 mmol of 4-methoxy- $\alpha$ -methylbenzyl alcohol at 50 °C (a),  $\alpha$ -hydroxy- $\alpha$ -phenylacetophenone at 50 °C (b) or (3,4-dimethoxy)benzyl alcohol at 70 °C (c) using 500 mg of the HBr@Bu<sub>4</sub>PBr ionic liquid (3 mol% H<sup>+</sup> respect to the indole) or 40 mg of HY zeolite (4 mol% H<sup>+</sup> respect to the indole) in 1 ml of acetonitrile (CH<sub>3</sub>CN) or solvent-free (neat).

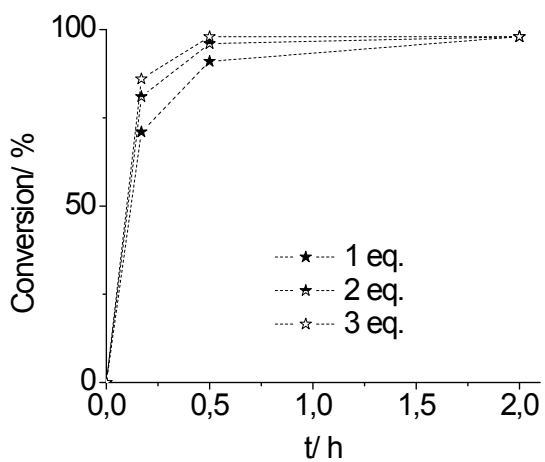


(a)

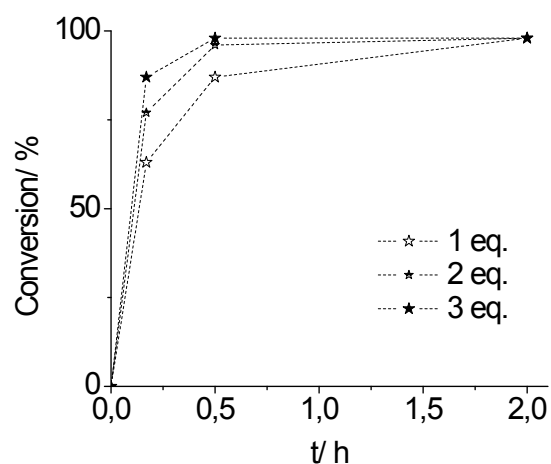


(b)

**Figure S12.** Reuses for the alkylation of indole (1 mmol) with (a)  $\alpha$ -hydroxy- $\alpha$ -phenylacetophenone (1.2 mmol) at 50 °C and (b) (3,4-dimethoxy)benzyl alcohol at 70 °C using the HBr@Bu<sub>4</sub>PBr ionic liquid (3 mol% H<sup>+</sup> respect to the indole).



(a)



(b)

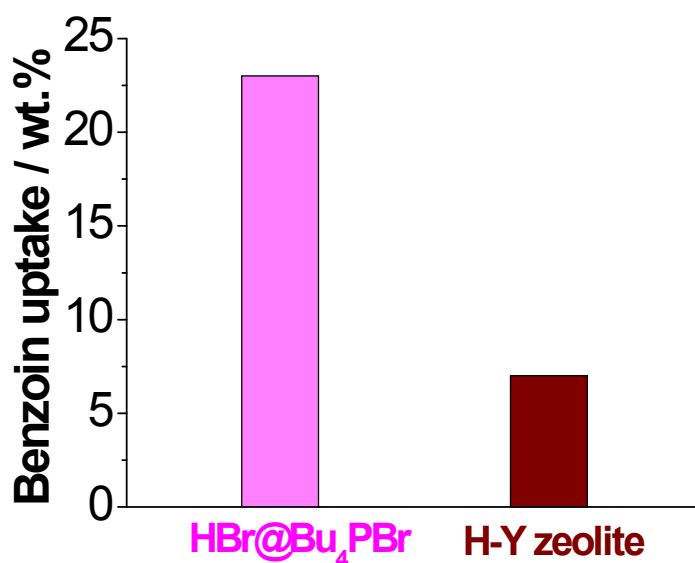
**Figure S13.** Conversion vs. time for the alkylation of indole (1 mmol) with an increasing amount of 4-methoxy- $\alpha$ -methylbenzyl alcohol (1 mmol, 2 mmol, 3 mmol) using HBr@Bu<sub>4</sub>PBr ionic liquid (a) or HY zeolite (b).

## Alcohol uptake in the ionic liquid or zeolite

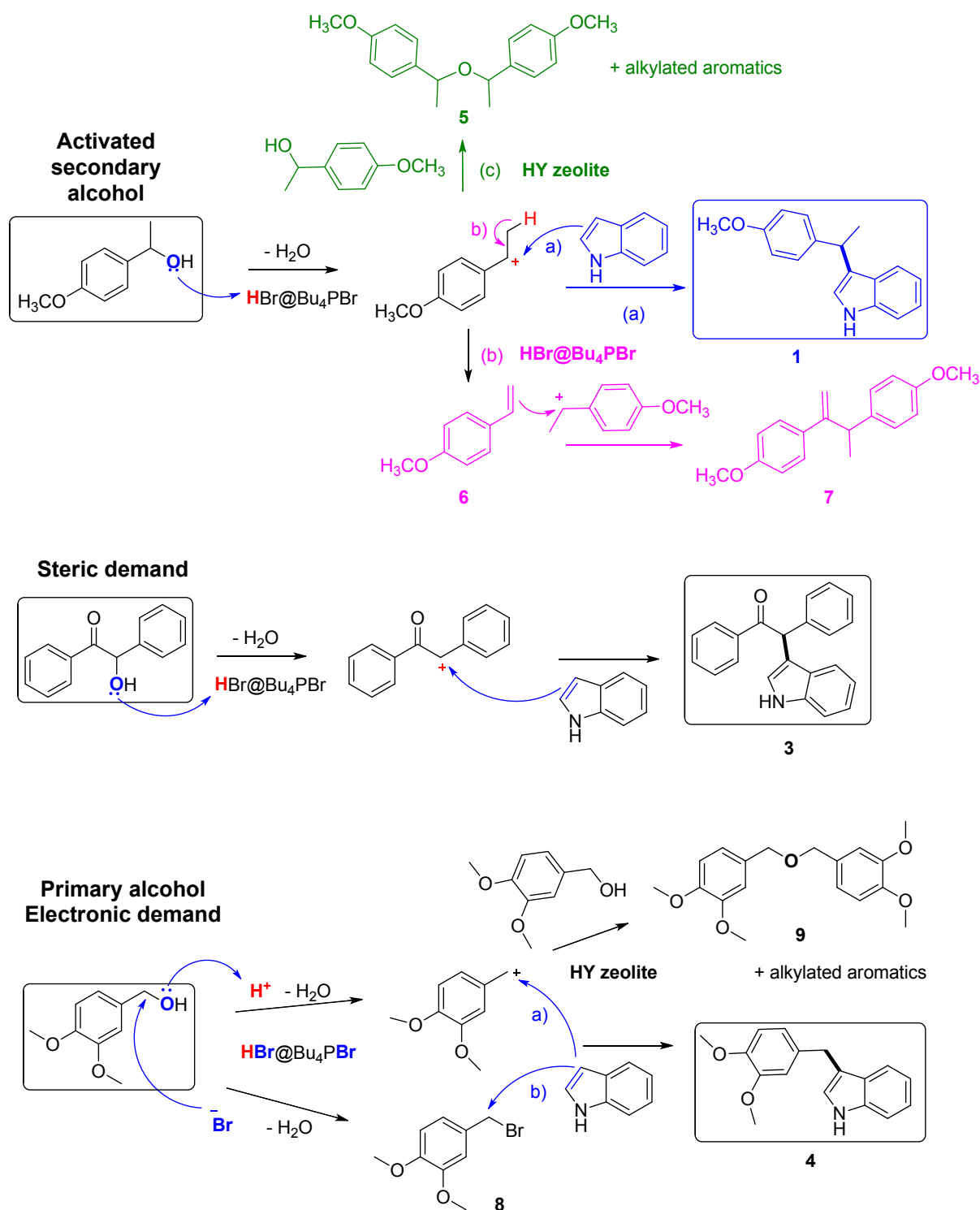
**Table S3.**  $\alpha$ -hydroxy- $\alpha$ -phenylacetophenone (benzoin or simply abbreviated as “OH”) uptake from a mesitylene solution (10 mg OH /ml) into the HBr@Bu<sub>4</sub>PBr or HY CBV720 zeolite, determined by GC-FID after 15 min at 50 °C and using C<sub>14</sub> as internal standard:

$$\% \text{ benzoin uptake} = \frac{(\text{benzoin: C14})_0 - (\text{benzoin: C14})_{15\text{min}}}{(\text{benzoin: C14})_0} \cdot 100$$

<i>GC Areas in the mesitylene solution</i>	<i>HBr@Bu<sub>4</sub>PBr</i>	<i>HY zeolite</i>
$(A_{\text{OH}}/A_{\text{C14}})_{t=0}$	0.92	0.68
$(A_{\text{OH}}/A_{\text{C14}})_{t=15\text{min}}$	0.71	0.63
$\% \text{ benzoin uptake} = \frac{\Delta(A_{\text{OH}}/A_{\text{C14}})}{(A_{\text{OH}}/A_{\text{C14}})_{t=0}}$	23%	7%

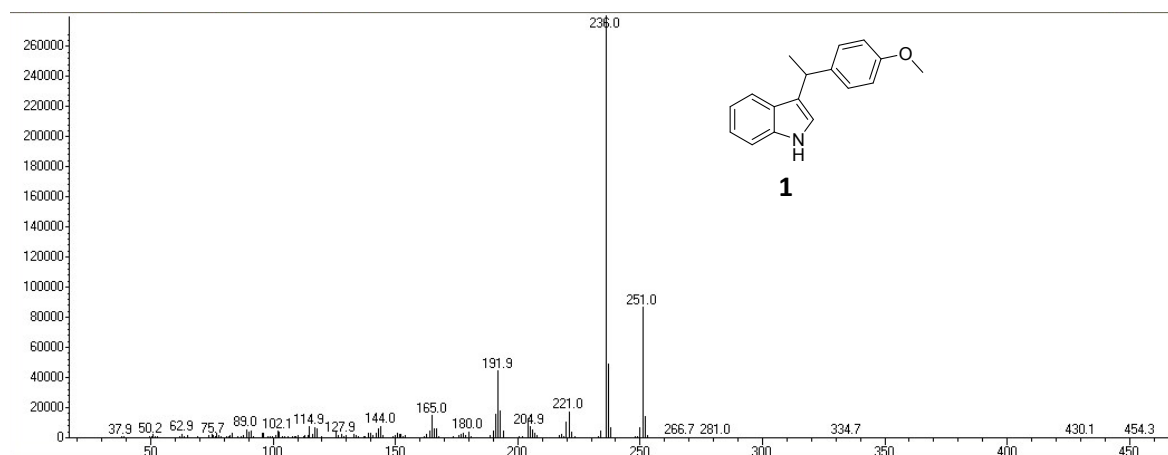


**Figure S14.** (a) Benzoin uptake (wt.%) from mesitylene to the reusable *quasi*-homogeneous (magenta color) and heterogeneous (burgundy color) catalyst and reaction media.

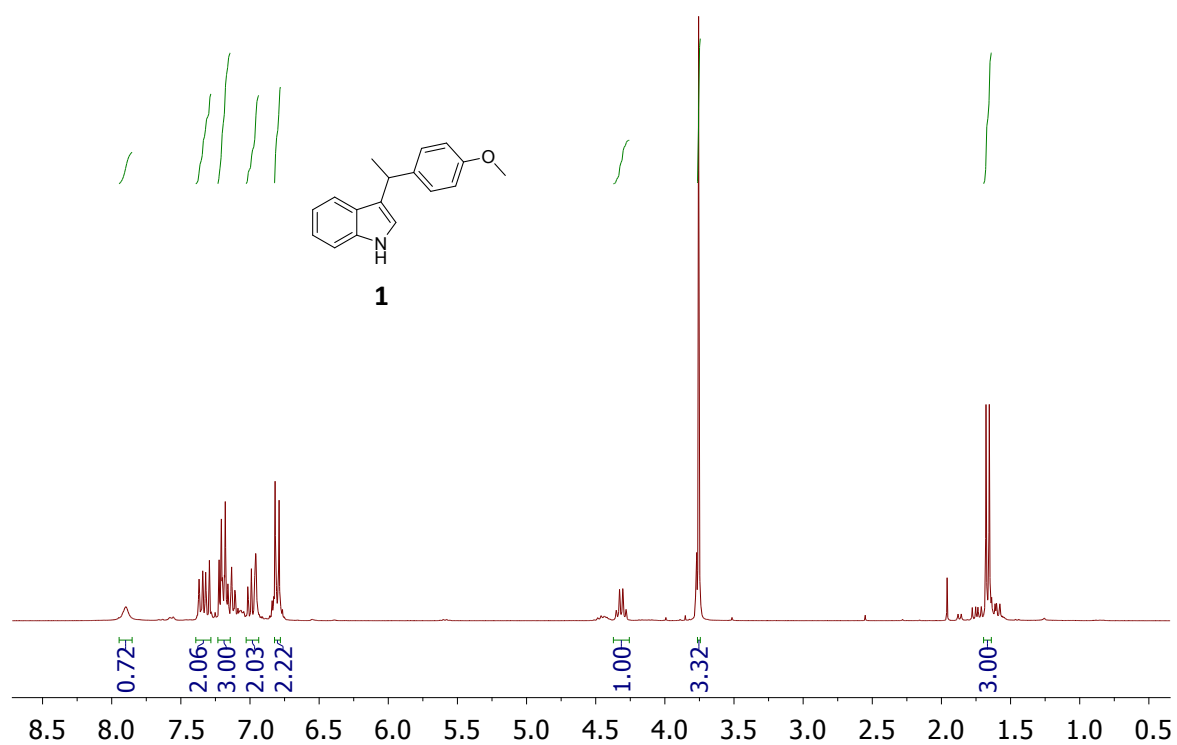


**Figure S15.** Intermediates and by-products detected by GC-MS in the presence of an excess of 4-methoxy- $\alpha$ -methylbenzyl alcohol, benzoin and (3,4-dimethoxy)benzyl alcohol.

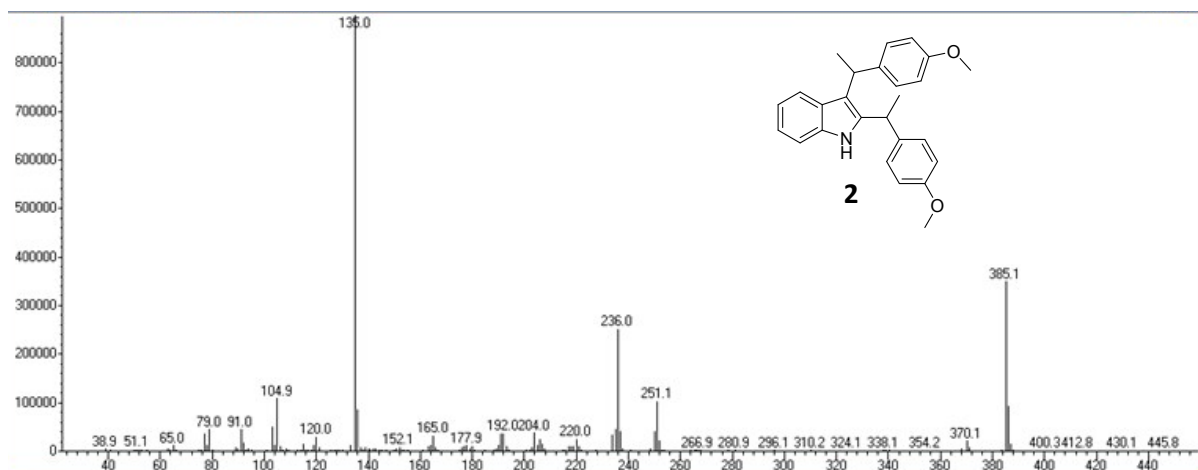
## Spectral data of indole derivative products



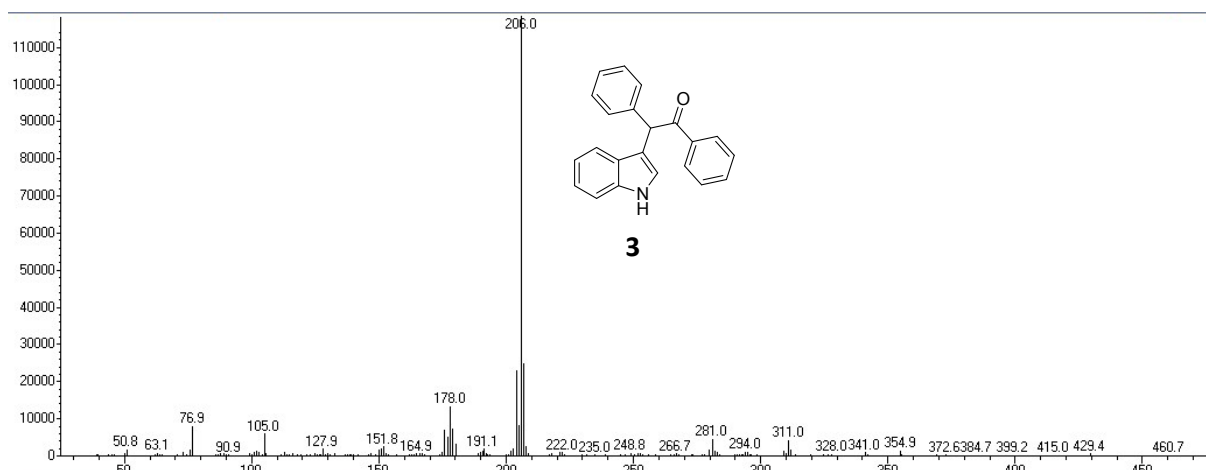
**Figure S16.**  $m/z$  calculated for  $C_{17}H_{17}NO^+$  [ $M^+$ ] = 251



**Figure S17.**  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.90 (br s, 1H,  $NH$ ), 7.32 (dt,  $J$  = 11.3 Hz, 2H,  $Ar$ ), 7.23-7.15 (m, 3H,  $Ar$ ), 7.02-6.94 (m, 2H,  $Ar$ ), 6.82-6.78 (m, 2H), 4.32 (q,  $J$  = 7.1 Hz, 1H,  $-CH-$ CH<sub>3</sub>), 3.76 (s, 3H,  $-OCH_3$ ), 1.67 (d,  $J$  = 7.1 Hz, 3H,  $-CH_3$ ).

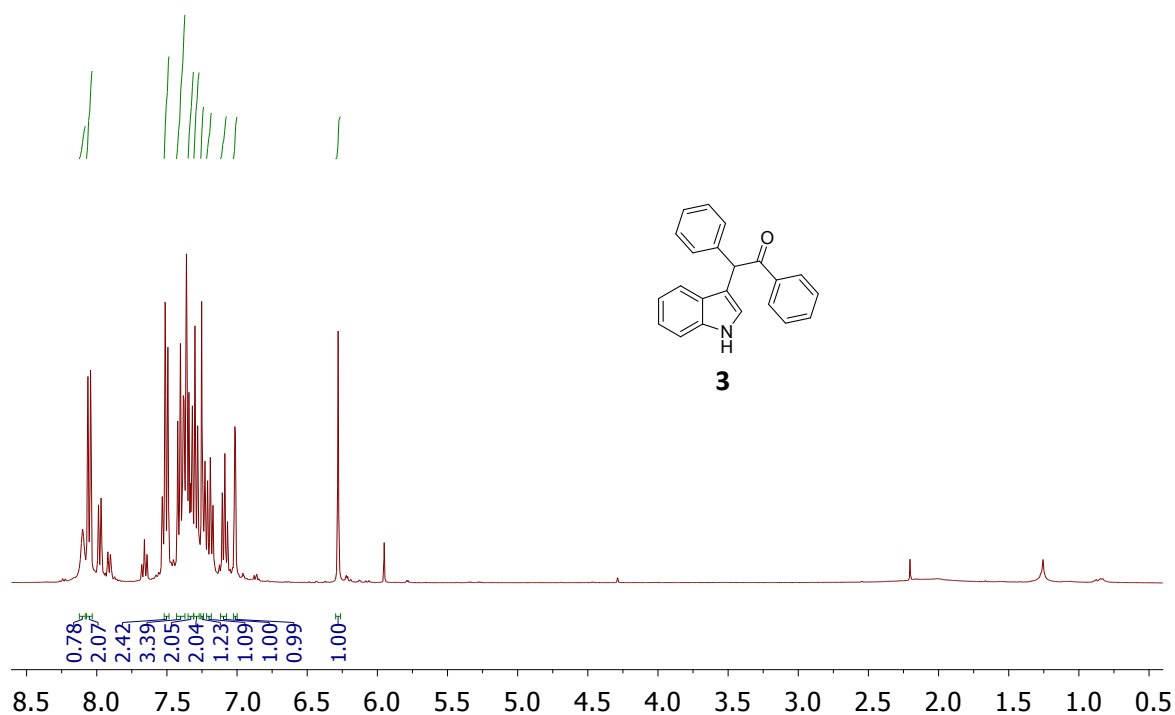


**Figure S18.**  $m/z$  calculated for  $C_{26}H_{27}NO_2^{++}$  [ $M^{++}$ ] = 385

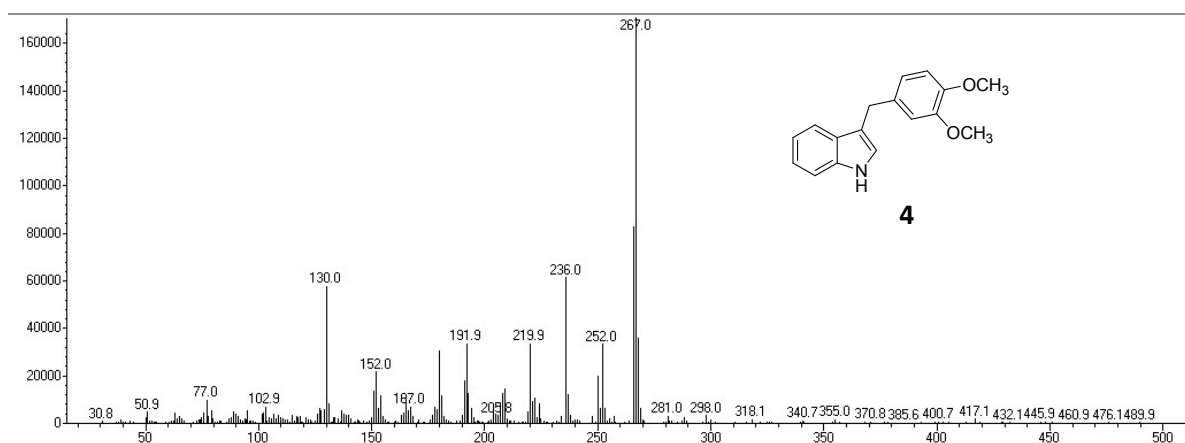


**Figure S19.**  $m/z$  calculated for  $C_{22}H_{17}NO^+$  [ $M^{++}$ ]: 311

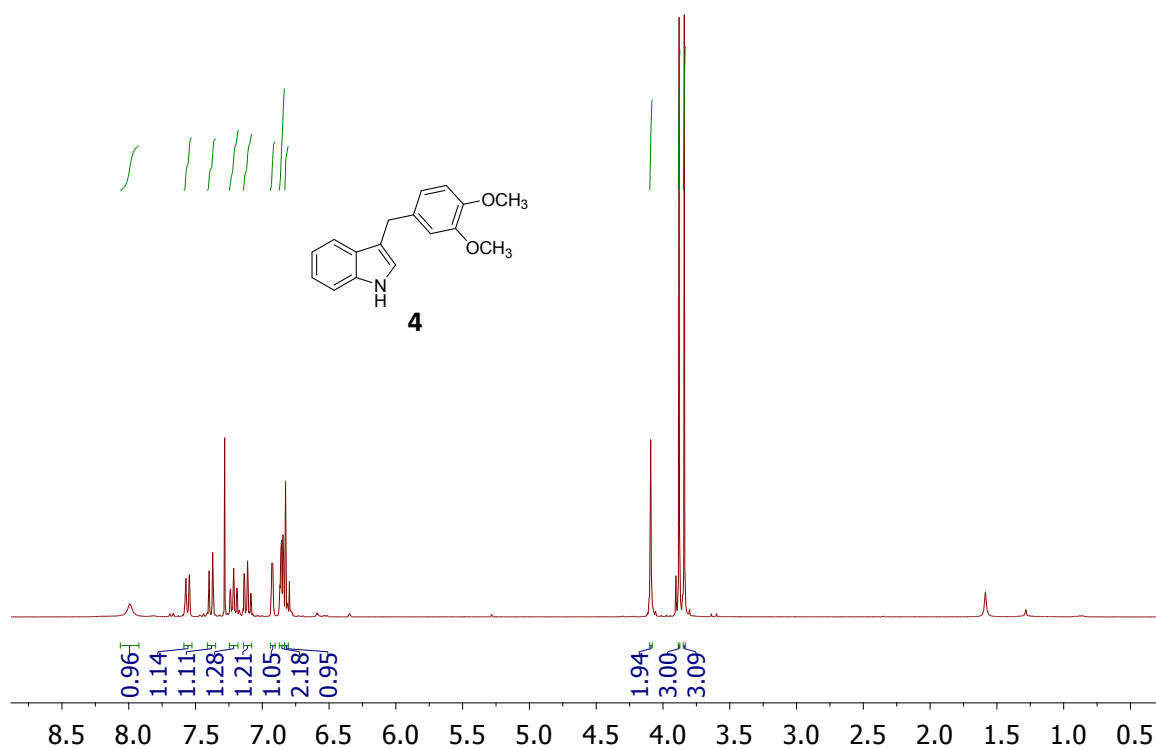




**Figure S20:**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.10 (br s, 1H,  $\text{NH}$ ), 8.05 (d,  $J = 7.4$  Hz, 2H, *Ar*), 7.50 (d,  $J = 7.5$  Hz, 2H), 7.40 (dd,  $J = 13.1$  Hz, 4.7 Hz, 3H) 7.34 - 7.32 (m, 2H, *Ar*), 7.29 (d,  $J = 7.7$  Hz, 2H, *Ar*), 7.25 (d,  $J = 2.3$  Hz, 1H, *Ar*), 7.20 (d,  $J = 7.8$  Hz, 1H, *Ar*), 7.10 (d,  $J = 7.3$  Hz, 1H, *Ar*), 7.01 (d,  $J = 1.1$  Hz, 1H, *Ar*), 6.28 (s, 1H,  $\text{C-CH-C}$ ).



**Figure S21.**  $m/z$  calculated for  $\text{C}_{17}\text{H}_{17}\text{NO}_2^{+\bullet}$  [ $\text{M}^{+\bullet}$ ]: 267



**Figure S22.** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.99 (br s, 1H, NH), 7.56 (dd,  $J = 7.9$  Hz, 0.5 Hz 1H, ArH), 7.41-7.36 (m, 1H, ArH), 7.25-7.18 (m, 1H, ArH), 7.15-7.07 (m, 1H, ArH), 6.94-6.91 (m, 1H, ArH), 6.87-6.83 (m, 1H, ArH), 6.82 (d,  $J = 3.0$  Hz, 1H, ArH), 4.09 (s, 2H, C-CH<sub>2</sub>-C), 3.88 (s, 3H, -OCH<sub>3</sub>), 3.84 (s, 3H, -OCH<sub>3</sub>).

## Spectral data of intermediates and by-products

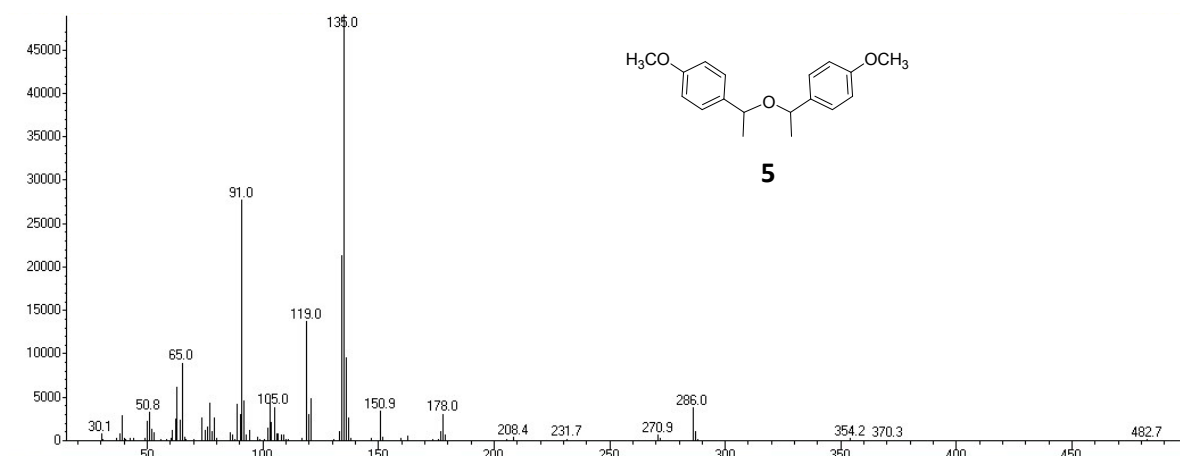


Figure S23.  $m/z$  calculated for  $C_{18}H_{22}O_3^{+}$  [ $M^{+}$ ] = 286

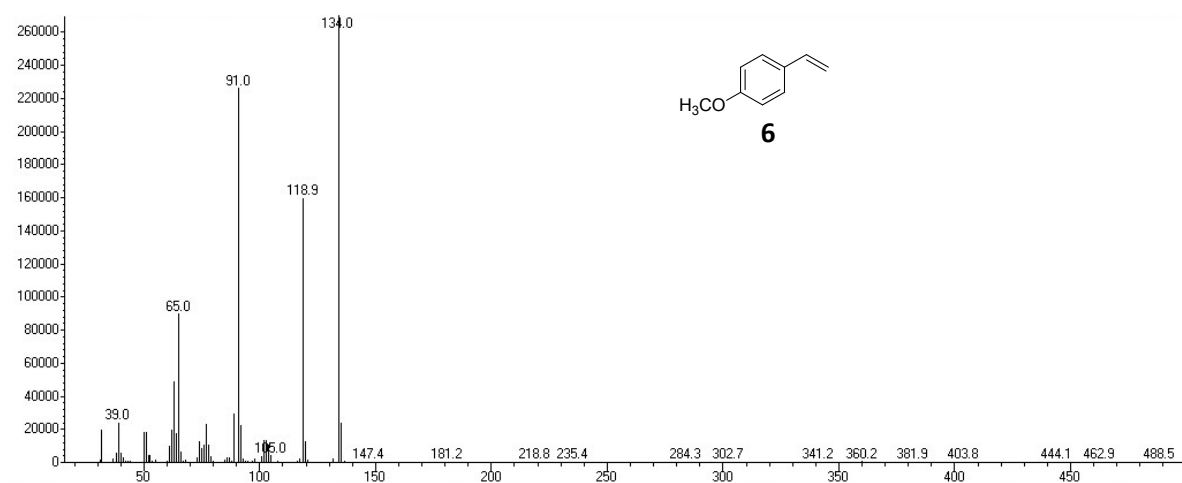


Figure S24.  $m/z$  calculated for  $C_9H_{10}O^{+}$  [ $M^{+}$ ] = 134

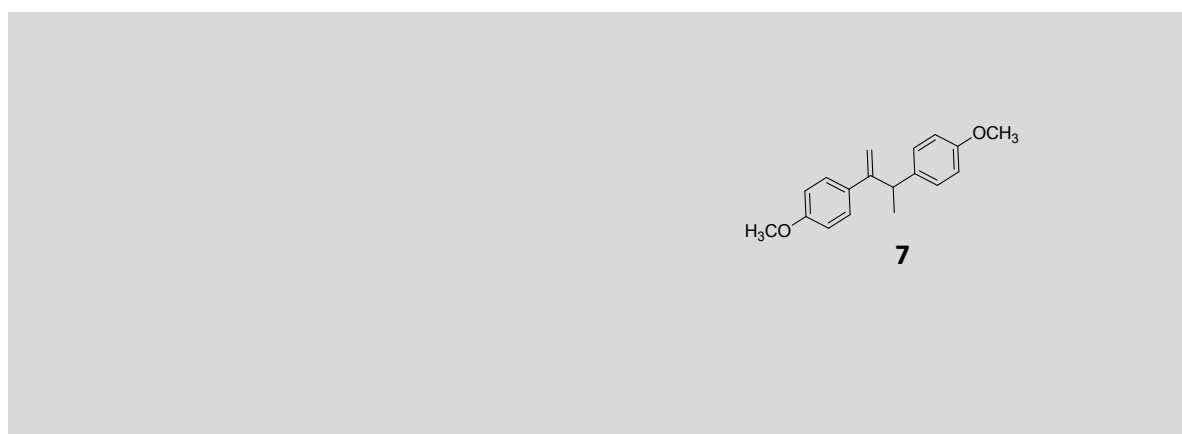
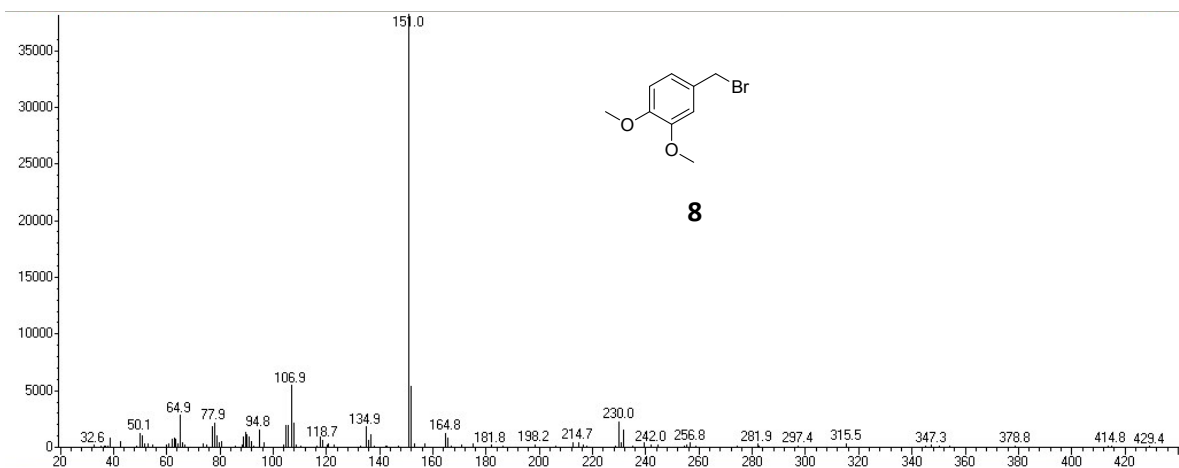
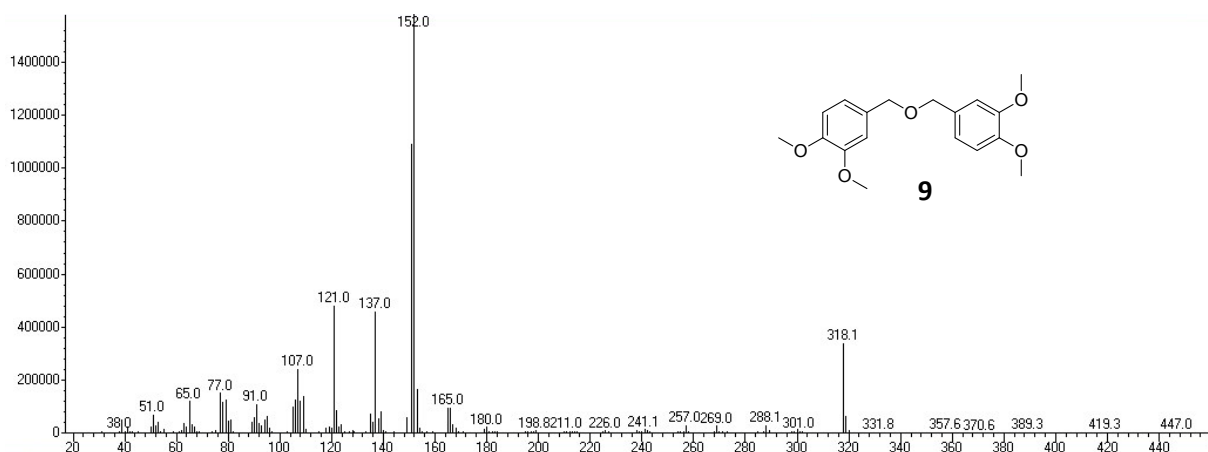


Figure S25.  $m/z$  calculated for  $C_{18}H_{20}O_2^{+}$  [ $M^{+}$ ] = 268

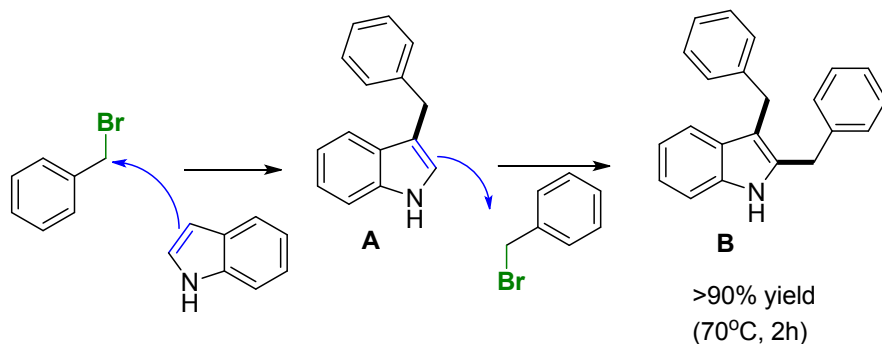


**Figure S26.**  $m/z$  calculated for  $C_9H_{11}BrO_2^{+}$  [ $M^{+}$ ] = 231

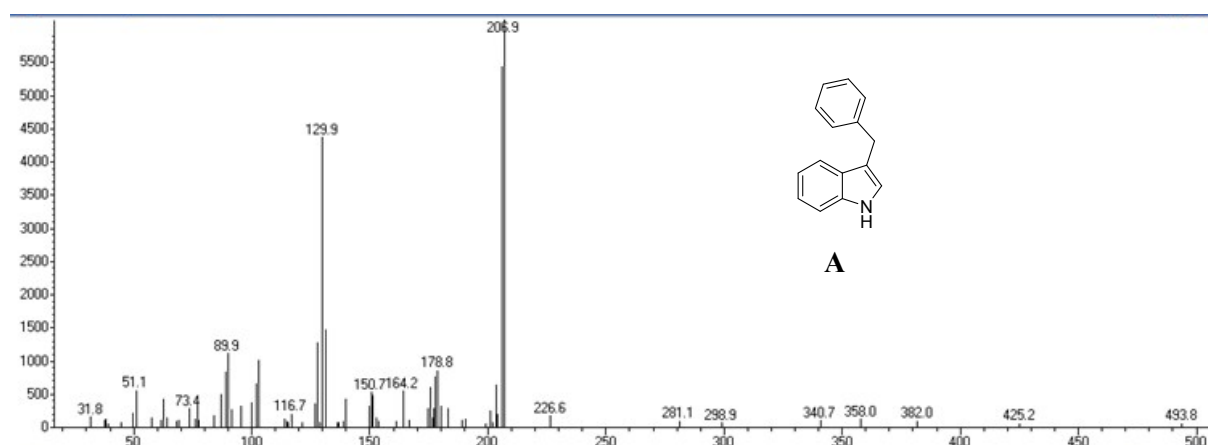


**Figure S27.**  $m/z$  calculated for  $C_{18}H_{22}O_5^{+}$  [ $M^{+}$ ] = 318

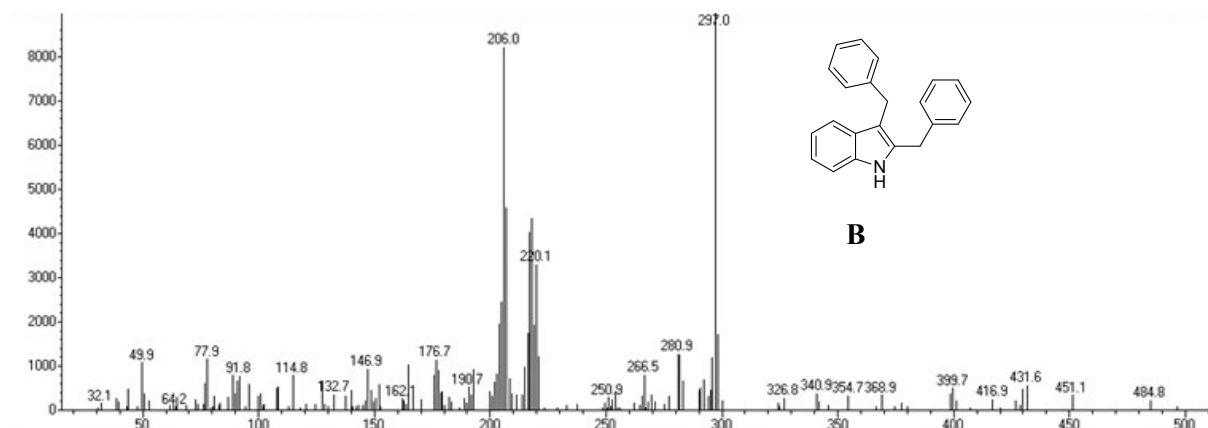
The almost instantaneous reaction of benzyl bromide with indole respect to the slower reaction of indole with benzyl alcohol to form de mono and di-benzylic indole (see Scheme S2 and Fig. S28-S29) suggest the formation (by nucleophilic substitution) of the reactive bromide intermediate **8** in the HBr@Bu<sub>4</sub>PBr media (see Fig. S15).



**Scheme S2.** Reaction of benzyl bromide electrophile intermediate with the indole nucleophile results in the formation of mono- and di-alkylated indole **A** and **B** products.



**Figure S28.**  $m/z$  calculated for C<sub>15</sub>H<sub>13</sub>N<sup>++</sup> [M<sup>++</sup>] = 207



**Figure S29.**  $m/z$  calculated for C<sub>22</sub>H<sub>19</sub>N<sup>++</sup> [M<sup>++</sup>] = 297

## References

1. M. Stalpaert, F. G. Cirujano, D. E. De Vos, *ACS Catal.*, 2017, **7**, 5802-5809.
2. L. Huang, H. Wang, J. Chen, Z. Wang, J. Sun, D. Zhao, Y. Yan, *Microporous Mesoporous Mater.*, 2003, **58**, 105-114.
3. G. Ferey, G. Mellot-Draznieks, C. Serre, F. Millange, J. Dutour, S. Surble, I. Margiolaki, *Science*, 2005, **309**, 2040-2042.
4. M. Kandiah, M. H. Nilsen, S. Usseglio, S. Jakobsen, U. Olsbye, M. Tilset, C. Larabi, E. A. Quadrelli, F. Bonino, K. P. Lillerud, *Chem. Mater.*, 2010, **22**, 6632-6640.