Chloroindate(III) ionic liquids as catalysts for alkylation of phenols and catechol with alkenes

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Chloroindate(III) ionic liquids are shown to be versatile catalysts for the alkylation of phenols with alkenes, giving high conversions to alkylated phenols with high selectivities.

Alkylated phenols and their derivatives are used in the production of resins,[1] durable surface coatings,[2] varnishes,[3] wire enamels,[4] printing inks,[5] surface active agents,[6] antioxidants,[7] flame retardants,[8] UV absorbers,[9] fungicide and insecticide formulations,[10,11] petroleum additives,[12] non-ionic surfactants and fragrances.[13] For example, the triphosphate derivative of 2,4-di-*tert*-butylphenol is employed as a stabiliser for poly(vinyl chloride) (PVC), whereas its benzotriazole derivative is used as a UV absorber in polyalkenes.[9] 4-*tert*-Butylcatechol is utilised as a polymerisation inhibitor for a number of monomers.[7] Thymol (2-isopropyl-3-methylphenol) and other isopropyl phenols have been used in the production of perfumes, and thymol (in particular) is a precursor of (−)-menthol.[13]

Many different catalysts have been used to facilitate alkylation processes of hydroxyarenes with alkenes, including Brønsted acids,[14] Lewis acids[15] and zeolites.[16] Also there are claims that the hexafluorophosphate ionic liquids[17] can catalyse this process, but this is almost certainly due to liberated HF by hydrolysis of the anion.[18]

Previously, we have reported on an indium-based ionic liquid catalyst system, which resembles the well established chloroaluminate ionic liquids, where their synthesis is simple and requires no 'glove box technology'. These chloroindate ionic liquids have been successfully employed to carry out acylation of electron-rich aromatic nuclei[19] using anhydrides as acylating agents. The advantage of using the methodology associated with indium(III) systems, compared with aluminium(III) catalyst systems, is their hydrolytic stability and reduced oxophilicity. By combining the indium(III) chloride with an organic halide salt, ionic liquids can be formed with good solvating ability and negligible vapour pressure, as well as the liquid being both inherently Lewis-acidic and water stable, in contrast to the analogous chloroaluminate systems.[20] Physico-chemical properties of an ionic liquid resulting from a 1 : 1 mixture of $[C_4mim]Cl$ (1-butyl-3-methylimidazolium chloride) and $InCl_3$ and its utility in an etherification reaction have been reported.[21] A similar type of chloroindate ionic liquid has been utilised for coupling CO_2 with epoxides to generate cyclic carbonates.[22]

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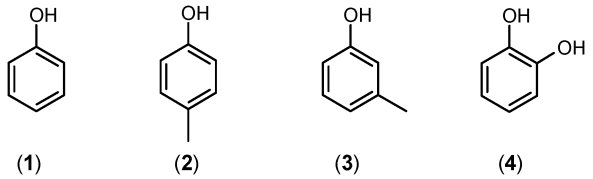


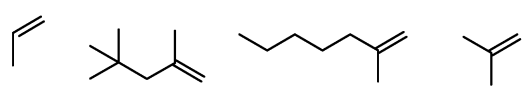
Scheme 1 Hydroxyarenes substrates.

To our knowledge, these chloroindate catalyst systems have not been utilised for alkylation of hydroxyarenes or any other active arenes (apart from our recent patent).[23] We report here that the same class of ionic liquids derived from 1,1-dialkyl-imidazolium chlorides and indium(III) chloride can be successfully utilised for alkylation of hydroxyarenes (see Scheme 1, **1**–**3**) to produce valuable products with excellent selectivity and conversions.

Although the exact speciation of the catalyst system is unknown, it contains a number of different chloroindate species.[24] In this study, mole fraction (χ) of $InCl_3$ in a $[cation]Cl : InCl_3$ catalyst system was maintained at 0.667. A series of different hydroxyarenes, including catechol (1,2-dihydroxybenzene, **4**: Scheme 1), has been examined with a selection of liquid and gaseous alkenes.

Examples of alkenes used in this study include propene, **5**, diisobutene, **6**, 2-methylhept-1-ene, **7**, and isobutene, **8** (Scheme 2). The results obtained with phenol **1** reacting with alkenes, **6** and **7**, catalysed by the $[C_4mim]Cl$–$InCl_3$ (χ = 0.667) system are shown in Table 1.

It is evident from the product distribution shown in Table 1, with both **6** and **7**, that the high yielding main product originates from mono-substitution at the 4-position of the benzene ring (entries A and B). However with isobutene **8**, which is more reactive than **6** and **7**, the main product originates from a di-substitution at the 2,4-positions of phenol. The observed yield of the mono-4-substituted *tert*-butylphenol is surprisingly very low (entry C). The higher reactivity of **8** could account for this lack of selectivity towards mono-substitution on the aromatic ring. Reducing the temperature of the reaction did not alter the product distribution significantly.

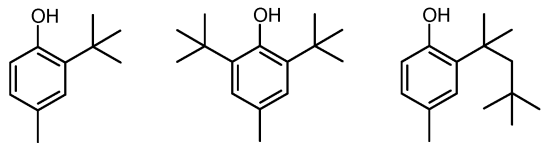


Scheme 2 Alkene reagents.

Table 1 The product distribution of phenol reacting[a] with alkenes (**6**), (**7**) and (**8**) using the $[C_4mim]Cl–InCl_3$ (χ = 0.667) catalyst system

Entry	Alkene	Products	% Yield
A	(**6**)	4-(*tert*-octyl)phenol	83
		2-(*tert*-octyl)phenol	0.5
		2,4-(di-*tert*-octyl)phenol	7.7
		2-(*tert*-butyl)-4-(*tert*-octyl)phenol	3.2
B	(**7**)	4-(2-methyl-l-heptyl)phenol	81
		2-(2-methyl-l-heptyl)phenol	5
		2,4-[(di-2-methyl)-l-heptyl]phenol	2
C	(**8**)	4-(*tert*-butyl)phenol	1.5
		2-(*tert*-butyl)phenol	0.05
		2,4-(di-*tert*-butyl)phenol	78
		2,4,6-(tri-*tert*-butyl)phenol	13
		Minor products with octyl-substituents on the ring	

[a] Phenol : indium mole ratio = 50 : 1; reaction temperature 100 °C.



Scheme 3 The product distribution of 4-methylphenol reacting with isobutene (**8**) using the $[C_4mim]Cl–InCl_3$ catalyst system. The yields and structure numbers of products are given in parenthesis below.

However, replacing phenol by 4-methylphenol (*p*-cresol) led to mono-substitution at the 2-position, 2-*tert*-butyl-4-methylphenol being the major product (Scheme 3). The reaction profile is given in Fig. 1. A significant fact is noticeable from both Fig. 1 and Scheme 3 when **8** is used as the alkene. A few minor products bearing octyl (C_8) substituents were observed, even though the starting alkene carries only four carbon atoms. This was shown to be due to the ability of the catalyst

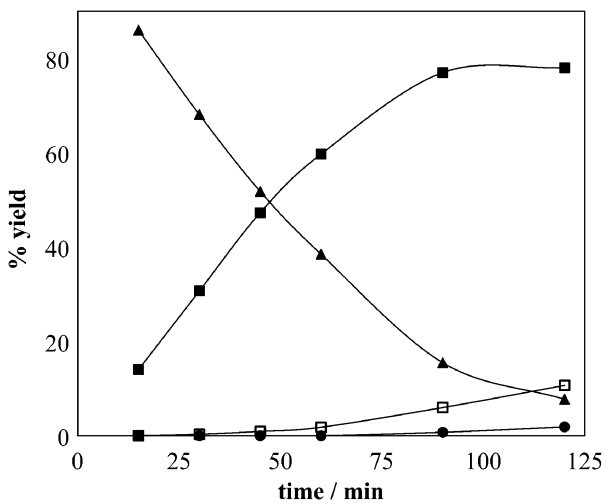
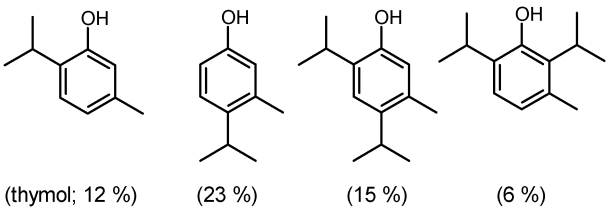


Fig. 1 The reaction profile for the 4-methylphenol (*p*-cresol) reacting with isobutene (**8**) using the $[C_4mim]Cl–InCl_3$ (χ = 0.667) catalyst system at 100 °C; the curves refer to the following: 4-cresol, ▲; (**9**), ■; (**10**), □; (**11**), ●.



Scheme 4 The product distribution of 3-methylphenol (*m*-cresol) reacting with propene using the $[C_4mim]Cl–InCl_3$ (χ = 0.667) catalyst system; 3-methylphenol : indium mole ratio 50 : 1; reaction temperature 110–130 °C. The remainder is unreacted (**3**).

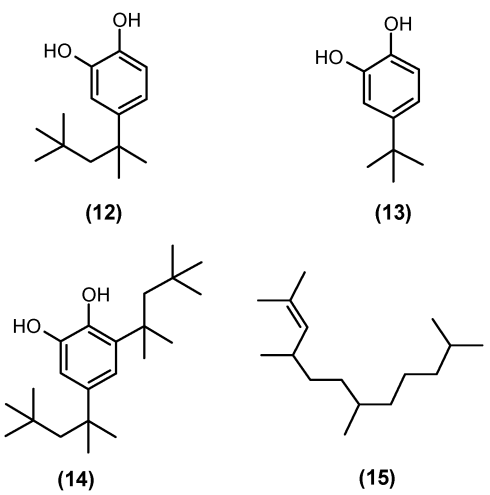
system to dimerise isobutene to a C_8-alkene,[25] and then subsequently adding on to phenol substrates.

Thymol is a mono-iso-propylated product from 3-methylphenol (*m*-cresol) which finds uses as an antifungal and antibacterial agent, anæsthetic and antiseptic in mouth washes. For these reasons, isopropylation of 3-methylphenol was examined with our catalyst system. The results are summarised in Scheme 4.

The reaction to the isopropylated products had low selectivity. The main product was the other isomer of thymol where the alkylation has occurred at the position *para* to the hydroxy group. Thymol was obtained in 12% yield. In a recent publication, it was claimed[26] that 52% yield of thymol was obtained by a catalytic process in supercritical CO_2. It appears that a highly selective process for the production of thymol is still an elusive goal.

Finally, reactions of alkenes with more reactive 1,2-dihydroxybenzene (catechol) were explored with our catalyst system (Scheme 5). Both isobutene, **8**, and diisobutene, **6**, produced highly selective and high yield reactions with catechol under the prescribed reaction conditions. The results are included in Table 2.

Our catalyst system provides a selective alkylation process for reactive aromatic compounds. The origin of the by-product 4-(*tert*-octyl)catechol (entry D; Table 2) comes from dissociation of diisobutene to form isobutene under the reaction conditions. Similarly, the by-product 4-(*tert*-octyl)catechol



Scheme 5 Structures of products, as shown in Fig. 2, from the reaction of catechol with alkene (**6**).

Table 2 The product distribution of catechol reacting[a] with diisobutene (**6**) and isobutene (**8**) using the $[C_4mim]Cl–InCl_3$ catalyst system ($\chi = 0.667$)

Entry	Alkene	Products	% Yield
D	(**6**)	4-(*tert*-octyl)catechol	88
		4-(*tert*-butyl)catechol	3.2
		3,5-(di-*tert*-octyl)catechol	2.4
		2-(*tert*-butyl)-4-(*t*-octyl)catechol	3.2
		Miscellaneous minor products	
E	(**8**)	4-(*tert*-butyl) catechol	85
		3,5-(di-*tert*-butyl) catechol	7
		4-(*tert*-octyl) catechol	2
		Miscellaneous minor products	

[a] Catechol : indium ratio = 50 : 1; reaction temperature 110 °C

(entry E; Table 2) originates from the dimer formed from isobutene under the same reaction conditions. Hence the alkene dimerisation–dissociation appears to be reversible under the influence of the catalyst system. Fig. 2 shows the reaction profile of catechol reacting with diisobutene with $[C_4mim]Cl–InCl_3$ catalysis.

The reaction profile for catechol alkylation with (**6**), using $[C_4mim]Cl–InCl_3$, clearly indicates the best possible reaction conditions (slow addition of the alkene ~0.8–0.85 molar equivalents with respect to catechol) that are desirable to run this reaction, industrially and efficiently to obtain cleaner, greener products with high yields and selectivity.

The study was extended to explore the effect of the cationic component in the ionic liquid on the % yield of products of the reaction between catechol and diisobutene (**6**). As can be seen in Fig. 3, the cation does not have significant influence on the yield of **12**.

Marginally higher yields are obtained when smaller hydrophilic cations were coupled with chloroindate(III) catalyst system.

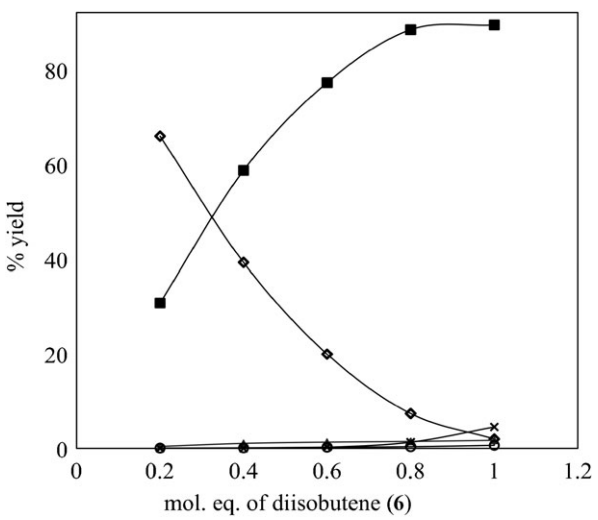


Fig. 2 The reaction profile of catechol reacting with diisobutene (**6**), at 100 °C, using the $[C_4mim]Cl–InCl_3$ catalyst system ($\chi = 0.667$), with the addition of varying molar equivalents of the alkene. The curves refer to the following: (**12**), ■; catechol, ◇; (**14**), ×; (**13**), ▲; (**15**), ○.

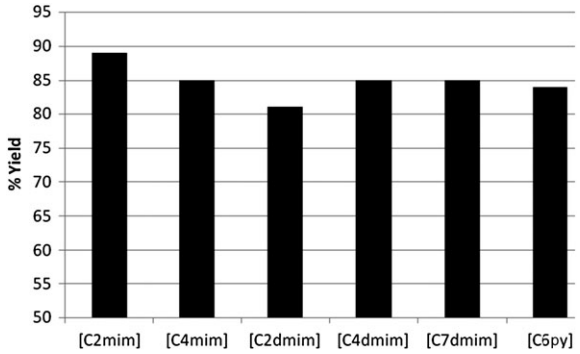


Fig. 3 The effect of the nature of the cation on the yield of the main product (**12**) distribution for the catechol (**4**)-diisobutene (**6**) reaction using a [cation]$Cl–InCl_3$ catalyst system ($\chi = 0.667$); $[C_2mim]^+$ and $[C_4mim]^+$ = 1-ethyl-3-methylimidazolium and 1-butyl-3-methylimidazolium; $[C_2dmim]^+$, $[C_4dmim]^+$ and $[C_7dmim]^+$ = 1-ethyl, butyl and heptyl-2,3-dimethylimidazolium; $[C_6py]^+$ = 1-hexylpyridinium.

Experimental

All experiments were carried out without the use of an additional solvent, as described in the table headings and footnotes. All reactions were monitored and analysed by ^1H NMR spectroscopy, GC and GC-MS. Product identification was performed by the aid of authentic samples and their GC and GC-MS analysis. The yields of all products were deduced from GC analysis.

Conclusions

We have demonstrated here, the versatility of the [cation]-$Cl–InCl_3$ catalyst system for alkylation of hydroxyarenes with alkenes to form industrially relevant high value alkylated phenols. Most reactions were highly selective, associated with high yields. All processes were energy efficient at moderate temperatures. Indeed, the reaction between catechol, **4**, and diisobutene, **6**, was performed at the kilogram scale with excellent yields and selectivity to **12**. The protocols that are described here are shown to be clearly superior to others that have been reported in the literature.

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Notes and references

1 D. Juhue and J.-M. Sage, *US Pat*. 7488784, 2009.
2 G. R. John, *US Pat*. 4613384, 1986.
3 C. H. Thomas, *US Pat*. 4500689, 1985.
4 M. R. Loftin and K. B. Sanborn, *US Pat*. 5804633, 1998.
5 M. L. Daví and F. Gnudi, *Water Res*., 1999, **33**, 3213–3219.

6 M. Bernabei, G. Bocchinfuso, P. Carrozzo and C. De Angelis, *J. Chromatogr., A*, 2000, **871**, 235–241.
7 A. Takahashi, T. Toyoda, C. Kondo, A. Tamura, S. Yamaguchi and S. Asai, *Japan Pat*. 07098885, 1978.
8 B. J. Stucker, *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, Chapter on Flame Retardants; published online (2000), DOI: 10.1002/14356007.a11_123.
9 D. H. Lorenz and B. A. Gruber, *US Pat*. 4260768, 1981; R. Liebler, S. Besecke and M. Munzer, *US Pat*. 4576870, 1986.
10 J. R. Roberts, G. C. Volgas and P. T. Delashmit, *US Pat. Appl*. 0262061A1, 2008.
11 W. Wolff, R. Faber and K. Ruclack, *US Pat*. 3849556, 1974.
12 L. A. Potolovskii, V. N. Vasileva, N. M. Kukui, M. V. Nazarova and T. I. Kirsanova, *Chem. Technol. Fuels Oils*, 1972, **8**, 920–922; K. J. L. Paciorek, R. H. Kratzer, J. Kaufman, T. I. Ito and J. H. Nakahara, *US Pat*. 4192757, 1980.
13 K.-G. Fahlbusch, F.-J. Hammerschmidt, J. Panten, W. Pickenhagen, D. Schatkowski, K. Bauer, D. Garbe and H. Surburg, *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, Flavours and fragrances, 2003, vol. 14, pp. 73–200, DOI: 10.1002/14356007.a11_141.
14 H. Fiege, H.-W. Voges, T. Hamamoto, S. Umemura, T. Iwata, H. Miki, Y. Fujita, H.-J. Buysch, D. Garbe and W. Paulus, *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, phenol derivatives; published online 2000, DOI: 10.1002/14356007.a19_313.
15 A. Lange and H. P. Rath, *US Pat*. 20030187171A1, 2003; *Thompson-Hayward Chemical Company*, *GB Pat*. 1142233, 1969.
16 A. Vinu, B. M. Devassy, S. B. Halligudi, W. Bohlmann and M. Hartmann, *Appl. Catal., A*, 2005, **281**, 207–219.
17 H.-Y. Shen, Z. M. A. Judeh, C. B. Ching and Q.-H. Xia, *J. Mol. Catal. A: Chem*., 2004, **212**, 301–308.
18 M. G. Freire, C. M. S. S. Neves, I. M. Marucho, J. A. P. Countunho and A. M. Fernandes, *J. Phys. Chem. A*, 2010, **114**, 3744–3749; C. Villagrán, M. Deetlefs, W. R. Pitner and C. Hardacre, *Anal. Chem*., 2004, **76**, 2118–2123.
19 K. R. Seddon, C. Hardacre and B. Mcauley, *World Pat*. 03028883, 2003; M. J. Earle, U. Hakala, C. Hardacre, J. Karkkainen, B. J. McAuley, D. W. Rooney, K. R. Seddon, J. M. Thompson and K. Wahala, *Chem. Commun*., 2005, 903–905.
20 A. K. Abdul-Sada, A. M. Greenway, K. R. Seddon and T. Welton, *Org. Mass Spectrom*., 1993, **28**, 759–765.
21 B. A. S. Neto, G. E. Reinaldo, S. Gonçalves, F. C. Gozzo, M. N. Eberlin and J. Dupont, *Synthesis*, 2004, 1155–1158.
22 Y. J. Kim and R. S. Varma, *J. Org. Chem*., 2005, **70**, 7882–7891.
23 H. Q. N. Gunaratne, T. J. Lotz and K. R. Seddon, *World Pat*. 074401 A1, 2006.
24 C. Hardacre, K. R. Seddon, G. Srinivasan and M. Swadźba-Kwaśny, *Aust. J. Chem*., 2010, **64**, 1–4.
25 M. J. Earle, J. Karkkainen, N. V. Plechkova, A. Tomaszowska and K. R. Seddon, *US Pat. Appl*. 0306319 A1, 2008.
26 R. Amandi, J. R. Hyde, S. K. Ross, T. J. Lotz and M. Poliakoff, *Green Chem*., 2005, **7**, 288–293.

