Selective mono-chlorination of aromatic compounds

under mild conditions by *tert*-butyl hypochlorite in the presence of zeolites

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Summary

tert-Butyl hypochlorite/HNa faujasite X in acetonitrile represents an efficient and highly regioselective system for mono-chlorination of a wide range of mono- and di-substituted aromatic substrates in mild conditions. Partially protonated faujasite X is far superior to amorphous silicas and to other zeolites in terms of efficiency and regioselectivity. Advantages of *tert*-butyl hypochlorite over other chlorinating reagents have been demonstrated. The method is suitable for large scale work.

Introduction

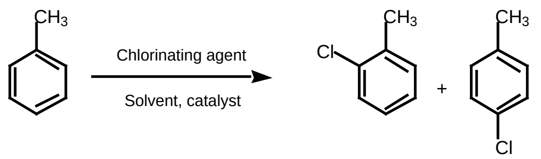
Owing to their numerous applications as fine chemicals for the synthesis of bio-active compounds such as pesticides and pharmaceuticals, isomerically pure chloroaromatics are very valuable materials. Unfortunately, the usual methods for chlorination of aromatics lead in many cases to mixtures of regioisomers that are difficult to separate. This leads to loss of material and waste of both time and energy. A further disadvantage is the use of a catalyst such as aluminium chloride, which is destroyed during work-up, produces a corrosive acid by-product, and presents a disposal problem. Therefore, there is a considerable need to devise reactions that avoid the use of such Lewis acid catalysts and provide greater regioselectivity in order to offer opportunities for much more environmentally benign processes.

Within recent decades, considerable efforts have been expended on the development of more efficient and selective aromatic chlorination processes,[1,2] but many problems remain, especially for simple compounds such as toluene. As part of our own studies on the use of solid supports in catalysing electrophilic aromatic substitution reactions,[3] we have investigated chlorination over heterogeneous catalysts[4] as an attractive approach to chloroaromatics. We now report details of a chlorination reaction that makes use of the shape selective properties of a reusable zeolite catalyst to provide remarkable *para*-selectivity, thereby overcoming two of the major disadvantages of the traditional approach.

Results and discussion

Chlorination over silicas

Our initial interest in the use of silica as a support arose from an experimental observation that purification on BDH silica of a crude reaction mixture containing dichloramine-T (DCT) led to the formation of some chlorinated side-products that were not present originally.[5] Toluene was used as a substrate [eqn. (1)] in



(1)

order to probe the factors that influence the reaction and various reagents were screened for their ability to perform electrophilic chlorinations.

The results, summarised in Table 1, clearly showed that, with silica as a catalyst, DCT, *N*,*N*-dichlorourethane, *tert*-butyl hypochlorite and SO_2Cl_2 were the reagents of most promise. In each case, the regioselectivity (65% *ortho* : 35% *para*) reflected the relative proportions of *ortho* to *para* positions in toluene (*i.e.* 2:1). Several acid chlorides (benzoyl chloride, oxalyl chloride, butyl chloroformate, tosyl chloride), metal chlorides (LiCl, BCl_3, $AlCl_3$, $HgCl_2$, $TiCl_4$) and other chlorine-containing compounds ($POCl_3$, $SOCl_2$, chloramine-T, Et_2NCl, chloroacetone, α-chloroacetamide) showed negligible reaction under these conditions even after a considerable period of time (*ca*. 2 days).

Green Context

Zeolites have found relatively little use in the liquid phase synthesis of organic compounds due to their small pore size and related diffusional limitations. However, in some cases, they offer unique advantages in terms of excellent selectivity towards mono substitution and positional isomerism. Exceptionally high selectivity is an essential requirement for the synthesis of precursors to many bioactive compounds. The combination of a bulky chlorinating agent and a zeolite has been shown to be an effective methodology in this respect. *DJM*

Table 1 Chlorination of toluene according to eqn. (1)[a]

Reagent	Time of reaction/h	Yield of chlorotoluenes (%)[b]
Dichloramine-T (DCT)	4	100
PCl_3	72	10
N,*N*-Dichlorourethane	2	100
N-Chlorosuccinimide	48	15
SO_2Cl_2	0.5	100[c]
HgO/Cl_2	2	'High'[d,e]
t-BuOCl	1	100
$H_2O/Ca(OCl)_2$	12	60[d]
$Cl_2NPO(OEt)_2$	4	'High'[d,f]
NaOCl	12	60[d]

[a] Toluene (2.5 mmol), chlorinating agent (2.5 mmol) in tetrachloromethane (10 ml) over silica (3 g) at 20°C. [b] By quantitative GC. [c] 3.5 mmol of chlorinating agent used. [d] A large excess of reagent was used. [e] Large amounts of polychlorinated compounds formed. [f] Initial preparation of the reagent proved hazardous (very exothermic).

Of the two most reactive chlorinating agents (SO_2Cl_2 and *t*-BuOCl), only sulfuryl chloride had been used in conjunction with silica previously.[6] The two reagents were compared more critically and sulfuryl chloride proved to be much more sensitive to the physical form of the silica than *tert*-butyl hypochlorite. Table 2 depicts the results obtained in equimolar reactions between toluene and the two chlorinating agents in tetrachloromethane at room temperature. The results suggest that a small amount of water is needed to catalyse the reaction with the former reagent while too much water leads to its decomposition. In contrast, *tert*-butyl hypochlorite appears to be much more stable in the presence of water although the rate of the reaction is decreased in the presence of extra water. This factor, together with the undesirable evolution of HCl and SO_2 from SO_2Cl_2, made *tert*-butyl hypochlorite the more attractive chlorinating reagent and it was chosen for a more detailed study of the reaction.

Table 2 Comparison of SO_2Cl_2 and *t*-BuOCl using treated silica in reaction (1)[a]

Reagent	Pre-treatment of silica	Time of reaction/h	Yield of chlorotoluenes (%)[b]
SO_2Cl_2	None[c]	0.5	70
SO_2Cl_2	Extra 1% (w/w) of water	0.5	1
		48	30
SO_2Cl_2	Dried at 540 °C for 15 h	24	25
t-BuOCl	None[c]	0.5	60
		1	100
t-BuOCl	Extra 1% (w/w) of water	0.5	2
		48	95

[a] Toluene (2.5 mmol), chlorinating agent (2.5 mmol) in tetrachloromethane (10 ml) over silica (3 g) at 20°C. [b] By quantitative GC. [c] As supplied in a freshly opened bottle of chromatographic grade silica (BDH); contains a small amount of water.

Table 3 reports the influence of solvent on the outcome of the reaction. It appears that the *para* selectivity of the reaction is slightly increased in polar solvents, but relatively non-polar solvents give faster reactions and higher yields. The rate differences might be explained on grounds of more effective solvation of reactants and competitive adsorption of polar solvent molecules at catalytic sites. The particularly low yield in diethyl ether probably reflects a competitive reaction with the solvent. An experiment in tetrachloromethane, in which a small quantity of the powerful free radical scavenger galvinoxyl was added, gave the same result as without, and therefore suggested that free radicals are not involved in the reaction.

Table 3 Influence of solvent in reaction (1)[a]

Solvent	Time of reaction/h	Yield of chlorotoluenes (%)	*para*:*ortho*
CCl_4	1	100	35:65
CH_2Cl_2	1	100	35:65
Et_2O	24	5	35:65
$PhNO_2$	24	70	37:63
CH_3OH	2.5	100	43:57
CH_3CN	24	60	50:50

[a] Toluene (5 mmol), *t*-BuOCl (5 mmol), solvent (10 ml), silica (3.67 g) at 25 °C.

In order to gain insight into the role played by the silica, reactions were carried out with a range of silicas from different sources and after treatment of the silicas in various ways. The silicas were also characterised to some extent by measurement of the pH they generated in an aqueous slurry and by their mean pore diameters. The results are listed in Table 4.

From the results in Table 4, it can be seen that reaction occurred most readily with silicas that were quite acidic (pH of a 10% aqueous slurry <5). The successful silicas were also the ones with smaller mean pore diameters, so that it is possible that the presence of micropores (<20 Å) in such silicas might also enhance the reaction by bringing the reagents into closer proximity. Water had a major effect on the activity of the silica, as evidenced by the slower reaction of BDH silica to which water had been added. The deactivating effect of excess water was again brought into focus by the case of Mallinckrodt silicic acid. The untreated silica was from a very old bottle and had absorbed a significant quantity of water. It was totally unreactive in that state, but after drying became almost as active as the BDH silica.

Since the combination of BDH silica and *tert*-butyl hypochlorite in tetrachloromethane provided a reagent capable of quantitative chlorination of toluene within one hour at 20 °C, it was of interest to test the scope of this reagent system with different substrates. A range of simple aromatic compounds was therefore investigated [eqn. (2)]. The results are shown in Table 5.

$$\mathrm{Ar{-}H} \xrightarrow[\mathrm{CCl_4,\ Silica}]{t\text{-}\mathrm{BuOCl}} \mathrm{Ar{-}Cl} \qquad (2)$$

The reaction was very slow for substrates less active than benzene, but useful for those with an activity level between that of about benzene and that of about anisole, cleanly producing chlorinated aromatics in about the same proportions as in traditional aromatic chlorination reactions. With yet more reactive substrates, *tert*-butyl hypochlorite reacted readily even in the absence of silica, so that the silica had little effect on the outcome of the reactions. Aniline was so reactive that it produced only tarry products under comparable conditions.

Table 4 Influence of the nature of the silica in reaction (1)[a]

Silica	Treatment[b]	pH[c]	Mean pore diameter/Å[d]	Time of reaction/h	Yield of chlorotoluenes (%)[e]	*para*:*ortho*
Shell	None	7.4	200	24	Trace	—
	A	n.d.	n.d.	24	Trace	—
Davison 57	None	7.1	146	24	Trace	—
	B	6.9	n.d.	24	10	35:65
Kieselgel 60	None	6.9	58	24	5	—
	A	n.d.	n.d.	24	0	—
	B	6.2	n.d.	2	80	40:60
Kieselgel 60G	None	5.8	58	20	80	44:56
Mallinckrodt	None	5.3	34	72	0	—
	B	4.5	n.d.	2	100	35:65
BDH	None	4.7	18	1	100	35:65
	C	n.d.	n.d.	48	95	35:65

[a] Toluene (5mmol), *t*-BuOCl (5 mmol), silica (3.67 g), in tetrachloromethane (10 ml) at 20 °C. [b] The following methods of treatment were used: A, reflux in a 1 M solution of NH_4Cl for one hour; calcination in a 520 °C furnace for 15 hours; B, drying in a 150 °C oven for 48 hours; C, 1% (w/w) water added. [c] pH meter reading of a 10% w/w slurry in deionized water; n.d. means not determined. [d] Determined by nitrogen BET adsorption isotherm; n.d. means not determined. [e] By quantitative GC.

Table 5 Chlorination of aromatic substrates with *t*-BuOCl in CCl_4 according to eqn. (2)[a]

Substrate	Temperature/°C	Time of reaction/h	Conversion of substrate (%)[b]	Product distribution (%)[b,c]
PhH	50	72	80	mono:dichloro = 81:19
PhMe	25	1	100	*para*:*ortho* = 35:65
PhEt	25	144	86	*para*:*ortho* = 43:57
Ph*i*-Pr	25	192	75[d]	*para*:*ortho* = 56:44
Ph*i*-Pr	40	4	97	*para*:*ortho* = 53:47
Ph*t*-Bu	25	120	70[d]	*para*:*ortho* = 85:15
PhPh	25	96	70[d]	*para*:*ortho* = 44:56
Naphthalene	40	3	93	α:β = >99:<1
p-Xylene	25	1	78	mono:dichloro = 67:33
PhOMe	25	0.7	100	*para*:*ortho* = 70:30
PhOH	25	0.1	100	n.d.
PhNHAc	25	0.1	100	n.d.
PhCl	50	96	low	n.d.
PhBr	60	24	15	n.d.
$PhNO_2$	40	120	0	—

[a] Substrate (5 mmol), *t*-BuOCl (5 mmol), BDH silica (3.67 g), tetrachloromethane (10 ml) under the stated conditions. [b] By quantitative GC. [c] n.d. means not determined. [d] The reaction could be brought to completion within 2 to 4 more days by further addition of *tert*-butyl hypochlorite.

Although an acidic silica had proved to be capable of catalysing the reaction of *tert*-butyl hypochlorite with aromatic substrates of moderate activity, it provided little benefit in terms of regioselectivity of the reactions. Zeolites are capable of both stronger surface acidity and enhancing regioselectivity through exerting shape-selectivity within their pores. Therefore it was of interest to investigate the use of zeolites as catalysts in the new chlorination reaction.

Chlorination over zeolites

Zeolites are well-defined, crystalline microporous aluminosilicates with active sites embedded within pores or cavities of molecular dimensions.[7] They are capable of acting as powerful acid catalysts and also providing selectivity for *para*-isomer production in aromatic substitution reactions. Recent papers have reported liquid-phase chlorination of aromatic substrates over zeolites using either chlorine[8] or sulfuryl chloride[9] as the electrophilic chlorine source, but selectivity in the reactions of simple substrates like toluene remains a problem. The chlorination of toluene by *tert*-butyl hypochlorite over various zeolites was therefore investigated and the results are presented in Table 6.

Silicalite, which does not have acidic sites, generated no ring-chlorinated products, although a substantial amount of benzyl chloride was formed after a long reaction period. The small pore A-type zeolite and those other zeolites which were not proton-exchanged (*i.e.* NaZSM-5, KL and NaX) provided little or no catalysis of the reaction so that the yields of chlorinated products were low even after several days. The proton-exchanged forms of ZSM-5, L and mordenite zeolites were somewhat better catalysts, but reactions were still slow and the *para*-selectivity, though somewhat greater than with silica as catalyst, was not remarkable, suggesting that most of the reaction was catalysed by sites

Table 6 Chlorination of toluene according to eqn. (1) at 25 °C in tetrachloromethane using *tert*-butyl hypochlorite over zeolite catalysts[a]

Zeolite	Pore size/Å	Time of reaction/h	Conversion of toluene (%)[b]	Products and distribution[b]
HCaA	4.5	24	0	—
NaZSM-5	5.2–5.4	120	7	52% *p*-Chlorotoluene 48% Dichlorotoluenes
HNaZSM-5	5.4–5.6	36	20	47% *p*-Chlorotoluene 53% *o*-Chlorotoluene
Silicalite-1	5.5	96	30	100% Benzyl chloride
HNaMordenite	6.7–7.0	72	15	40% *p*-Chlorotoluene 60% *o*-Chlorotoluene
KL	7.0	48	0	—
HKL	7.1	48	25	56% *p*-Chlorotoluene 44% *o*-Chlorotoluene
NaX	7.4	72	11	65% *p*-Chlorotoluene 35% *o*-Chlorotoluene
HNaX	7.5	1	90	65% *p*-Chlorotoluene 35% *o*-Chlorotoluene

[a] Toluene (2.5 mmol), *t*-BuOCl (2.5 mmol), zeolite (1.5 g), tetrachloromethane (10 ml) at 25°C. [b] By quantitative GC.

on the external surfaces of the solids rather than within the pores. Only partially proton-exchanged faujasite X (HNaX) proved to be an efficient catalyst, producing almost quantitative ring chlorination within one hour at 25°C. This result is consistent with the fact that faujasite has the largest pore diameter of all the zeolites tried (the more restricted profile of toluene, in a planar view, measures roughly 5.8 Å) and also has a three dimensional lattice structure with many interconnecting cavities of even greater dimensions, so that diffusion of substrate and reagents through the pores is relatively easy. The selectivity obtained was moreover a complete contrast to that achieved over silica gel in the same conditions and thus indicated that a change of support has a remarkable effect upon the regioselectivity of the reaction, again consistent with the idea that reaction takes place within the inner cavities of the zeolite.

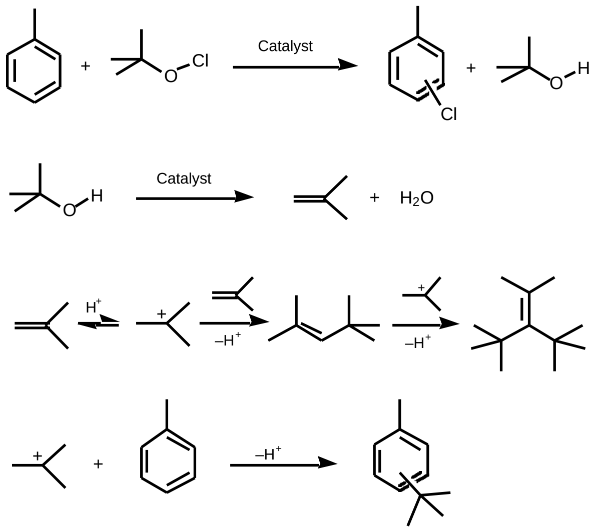
Since the faujasite zeolite had proved to be such an active catalyst, it was investigated in more detail to see if manipulation of its structural parameters could further influence the reaction in a positive manner. Thus, a series of experiments was performed with catalysts for which the Si : Al ratio of the material varied over the range 1.23 to 2.40:1 (Table 7).

Table 7 Effect of the variation of the Si : Al ratio of faujasite catalysts on the chlorination of toluene by *tert*-butyl hypochlorite according to eqn. (1)[a]

Si:Al	Time of reaction/h	Conversion of toluene (%)[b]	*para*:*ortho*	By-products present
1.23	0.25	90	73:27	No
1.53	0.25	80	72:28	No
1.82	0.25	50	62:38	Yes
2.11	4	42	54:46	Yes
2.40	6	40	42:58	Yes

[a] Toluene (2.5 mmol), *t*-BuOCl (2.5 mmol), faujasite zeolite (1.5 g), tetrachloromethane (10 ml) at 25 °C. [b] By quantitative GC.

Faujasite zeolites are referred to as zeolite X when the Si : Al ratio is ⩽1.5 and zeolite Y when the ratio is >1.5. The results showed that as the Si : Al ratio increased, the amount of chloroaromatics formed and the *para*-regioselectivity dropped off. Instead, the *tert*-butyl hypochlorite was consumed in side-reactions leading to *tert*-butyltoluene and isobutene oligomers (Scheme 1).



Scheme 1 Side-reactions in the chlorination of toluene by *tert*-butyl hypochlorite over HNaY.

The alkylation side-reaction is analogous to the one occurring on benzene in the presence of $AlCl_3$[10] and reflects the fact that HY is more strongly acidic than HX. Whatever the precise reasons for the change, it was clear that zeolite HX was the optimum catalyst and it was studied further. The effect of different solvents was next investigated and the results are given in Table 8.

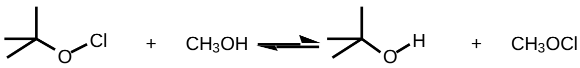
The results clearly showed that there was no simple correlation with solvent polarity.[11] Good yields of monochlorotoluenes were obtained in a non-polar solvent such as pentane and in a very polar solvent like acetonitrile. Solvents having a strongly coordinating functionality (amines and DMF) tended to deactivate the acid sites of the zeolite and so to inhibit the reaction completely. The slow reaction rate and the low selectivity observed in methanol may reflect the fact that methanol is also capable of

Table 8 Effect of solvent on the chlorination of toluene over partially protonated X zeolite by *tert*-butyl hypochlorite at room temperature[a]

Solvent	Time of reaction/h	Conversion of toluene (%)[b]	*para*:*ortho*[b]
n-Pentane	1	78	63:37
Toluene	28	—	71:29
CH_2Cl_2	1	95	74:26
CCl_4	1	95	74:26
Et_2O	0.5	63	92:8
CH_2Cl_2: Et_2O (3:1)	1	95	91:9
1,4-Dioxane	1	0	—
THF	1	0	—
1,2-Dimethoxyethane	1	0	—
DMF	24	5	50:50
CH_3CN	0.5	100	82:18
CH_3OH	20	46	40:60
TMEDA	24	0	—
Piperidine	24	0	—
Pyridine	24	0	—

[a] Toluene (2.5 mmol), *t*-BuOCl (2.5 mmol), HX (1.5 g), solvent (10 ml) at 25 °C. [b] By quantitative GC.

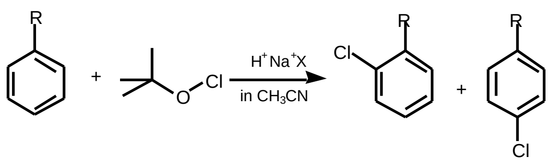
forming strong hydrogen bonds with the acid sites of the faujasite pores, diminishing their activity and also inhibiting diffusion of reactants in and out of the lattice. However, chlorine exchange to give the less hindered methyl hypochlorite [eqn. (3)] might also play a role.



(3)

It appeared quite remarkable that from the selection of ethers tried, only diethyl ether produced any chlorotoluenes, but with outstanding *para*-selectivity. However, the modest yield (63%) was accounted for by a side reaction of the chlorinating reagent system with the ether. Presumably, therefore, the more reactive ethers completely consumed all of the *tert*-butyl hypochlorite in a similar way. The high regioselectivity (92% *para*) obtained in diethyl ether probably depends on a delicate interplay of factors, such as the geometrical flexibility and electron density distribution in diethyl ether, which may render it capable within the pores of stabilising the *tert*-butyl hypochlorite oxonium cation that is likely to be involved in the reaction mechanism.[12] The benefits of high regioselectivity in diethyl ether and high yield in dichloromethane could be combined by use of a mixture of the two solvents (CH_2Cl_2:Et_2O = 3:1), which gave a 95% yield of monochlorotoluenes as a 91:9 mixture of *para* and *ortho* isomers. However, even this mixture caused some decomposition of the hypochlorite and its use with any substrate less active than toluene would not be practical.

In view of the problems with the possible use of diethyl ether for many substrates, acetonitrile appeared to be the best solvent for development of a general procedure. It was thus used with a series of monosubstituted aromatic compounds [eqn. (4)] and the results are shown in Table 9.



(4)

Table 9 Chlorination of substituted benzenes with *tert*-butyl hypochlorite over HNaX in acetonitrile according to eqn. (4)[a]

R	Temp./°C	Time of reaction/h	Yield of product (%)[b]	Isomer distribution (*p*:*o*)[b]
OMe[d]	25	3	100	82:18
Me	25	1	100	82:18
H	40	3.5	92[c]	—
Et	40	3.5	100	90:10
i-Pr[e]	40	96	90	80:20
t-Bu[e]	40	96	99	98:2[f]
Ph[e]	45	72	86	86:14
Cl	40	120	95	97:3
Br	40	96	75	97:3

[a] Substrate (2.5 mmol), *t*-BuOCl (2.5 mmol), CH_3CN (10 ml), HX (1.5 g) under the stated conditions. [b] By quantitative GC. [c] Product was 92% chlorobenzene and 4% dichlorobenzene. [d] Anisole could be chlorinated by *tert*-butyl hypochlorite without zeolite within 4 hours with the same regioselectivity. [e] *tert*-Butyl hypochlorite was added in two portions, half at the beginning and half mid-way through the reaction period. [f] The *ortho* and *meta* isomers could not be separated so the figure for *ortho* may include a trace of *meta* isomer.

As shown in Table 9 the reaction was successful with a range of aromatic substrates of moderate activity, ranging from about anisole at the most active end to halogenobenzenes at the less active limit. Yields and *para*-selectivities were excellent although the reactions with the less active substrates were rather slow. Furthermore, the reaction was shown to be suitable for larger scale work by the preparations of *para*-chlorotoluene and *para*-dichlorobenzene on 0.1 mole scale without any detrimental effects on either the yield or the selectivity. Benzonitrile, nitrobenzene, benzoic acid and methyl benzoate were also tested, but gave no significant reaction over a period of 3 days at 40 °C.

In view of the lack of success in chlorination of toluene over zeolites other than HX, even other large pore zeolites, it was likely that the transition state for the reaction was taking up most of the space within the cavity of the HX zeolite. Indeed, it was likely that the geometrical constraints imposed as a result were in large part responsible for the impressive regioselectivity. Therefore, it was by no means certain that disubstituted benzenes would react at all readily with *tert*-butyl hypochlorite over zeolite HX. Nevertheless, following the success with monosubstituted benzenes, the new reaction system comprising *tert*-butyl hypochlorite and HX zeolite in acetonitrile was applied to a range of disubstituted aromatics. The results are shown in Table 10.

As the results in Table 10 show, none of the disubstituted substrates reacted readily with *tert*-butyl hypochlorite over zeolite HX. The low rates of reaction were particularly remarkable for the xylenes, which are quite highly activated substrates, and for the two *para*-substituted compounds (*para*-xylene and *para*-chlorotoluene), where there would be negligible inhibition to diffusion of the substrates. In the case of *para*-chlorotoluene the conversion was only 11% after 10 days at 40 °C even though the *tert*-butyl hypochlorite level was regularly replenished. These results are very strongly suggestive of transition state selectivity at the acidic catalytic sites of the zeolite. In the case of disubstituted benzenes with such slow reactions, it must be expected that

Table 10 Chlorination of disubstituted aromatic compounds by *tert*-butyl hypochlorite in acetonitrile in the presence of HNaX[a]

Substrate	Temp./°C	Time of reaction/days	Conversion of substrate (%)[b]	Chlorinated products [Yields (%)][b]
o-Chlorotoluene	20	15[c]	100	2,5-Dichlorotoluene [61]
				2,4-Dichlorotoluene [22]
				2,6-Dichlorotoluene [1]
o-Chlorotoluene	40	10[c]	100	2,5-Dichlorotoluene [59]
				2,4-Dichlorotoluene [21]
				2,6-Dichlorotoluene [10]
o-Chlorotoluene[c]	40	4	100	2,5-Dichlorotoluene [50]
				2,4-Dichlorotoluene [26]
				2,6-Dichlorotoluene [6]
m-Chlorotoluene	20	18[c]	100	2,5-Dichlorotoluene [66]
				3,4-Dichlorotoluene [24]
m-Chlorotoluene	40	10[c]	100	2,5-Dichlorotoluene [61]
				3,4-Dichlorotoluene [22]
p-Chlorotoluene	40	10[c]	11	2,4-Dichlorotoluene [9]
o-Xylene	20	4	100	4-Chloro-*o*-xylene [70]
				3-Chloro-*o*-xylene [9]
o-Xylene	40	1	94	4-Chloro-*o*-xylene [60]
				3-Chloro-*o*-xylene [11]
				Polychloro-*o*-xylenes [6]
m-Xylene	20	4	100	4-Chloro-*m*-xylene [82]
				2-Chloro-*m*-xylene [8]
m-Xylene	40	1	97	4-Chloro-*m*-xylene [67]
				2-Chloro-*m*-xylene [7]
				Polychloro-*m*-xylenes [3]
p-Xylene	40	1	90	2-Chloro-*p*-xylene [73]
				Polychloro-*p*-xylenes [10]
Naphthalene	20	8	25	1-Chloronaphthalene [16]
				2-Chloronaphthalene [2]
Naphthalene	40	5	64	1-Chloronaphthalene [44]
				2-Chloronaphthalene [9]
				Polychloronaphthalene [1]
o-Chloroanisole	20	10[c]	100	2,4-Dichloroanisole [82]
o-Chloroanisole	40	7[c]	100	2,4-Dichloroanisole [88]

[a] Substrate (2.5 mmol), *t*-BuOCl (2.5 mmol), CH_3CN (10 ml), HX (1.5 g) under the stated conditions. [b] Yields and product distributions were determined by 400 MHz NMR, GC, and GC-MS. [c] *tert*-Butyl hypochlorite was added during the course of the reaction as it decomposes with time. [d] The reaction was carried out with three molar equivalents of *tert*-butyl hypochlorite.

a significant part of the reaction that does actually occur takes place on the external surface rather than within the pores.

Notwithstanding the above, most disubstituted aromatics tried could eventually be chlorinated in high yield with moderate to excellent selectivities. Slightly deactivated *ortho*- and *meta*-chlorotoluenes gave predominantly chlorination *para* to one of the substituents with a substantial preference for substitution *para* to chlorine. *para*-Chlorotoluene was very selectively chlorinated *ortho* to the methyl group but the very low rate of the reaction makes it impractical for synthetic purposes. More activated *ortho* and *meta*-xylenes gave good *para*-selectivity (*ca.* 90% at 20 °C), but heating the reaction mixture to 40°C led to the emergence of unwanted polychlorinated compounds. *para*-Xylene afforded 2-chloro-*p*-xylene together with polychlorinated aromatics at 40°C. Finally, naphthalene was chlorinated only to the extent of 65% after 5 days at 40 °C. Although the selectivity obtained was higher for the 2-chloro isomer than that achieved on silica, it was not sufficient for synthetic purposes. *ortho*-Chloroanisole was very selectively (*ca.* 100%) chlorinated *para* to the methoxy moiety and the zeolite provided a genuine catalytic effect on the reaction as a control reaction performed without the zeolite showed a ten times lower rate.

In view of the slowness of the reactions of disubstituted benzenes with *tert*-butyl hypochlorite over zeolite HX, attention was turned again to sulfuryl chloride which had proved to be a more reactive if more troublesome reagent over silica as catalyst (see above). Former work carried out on chlorination over zeolites by sulfuryl chloride had made use of basic forms of the solids and led to side-chain chlorination.[9] In the present study partially proton-exchanged zeolites were used. Toluene was again chosen as the test substrate and a survey of several zeolites for its chlorination by excess sulfuryl chloride was conducted. The results are shown in Table 11.

A significant yield of chlorination products was encountered at room temperature within one hour only for the faujasite zeolites X and Y and those reactions gave the same products whether in dark conditions or not. HNaX was once more the zeolite of most interest. There was only a trace of *meta*-product and no observable amount of side-chain chlorinated products, in sharp contrast to the results observed with its sodium form.[9] Furthermore, the reaction showed some regioselectivity. It was thereafter observed that good conversions could be obtained with just three molar equivalents of the chlorinating reagent in either dry petroleum spirit (30–40 °C) or dry dichloromethane. Therefore, a study of different solvents was carried out (Table 12).

Table 11 Chlorination of toluene over partially proton-exchanged zeolites by sulfuryl chloride according to eqn. (1)[a]

Zeolite	Conversion of toluene (%)[b]	Yield of *o*-chloro-toluene (%)[b]	Yield of *p*-chlorotoluene (%)[b]
HNaβ	<5	2.0	1.2
HNaZSM-5	0	0	0
HNaMord	<5	1.5	0.8
HNaY 760[c]	<5	1.8	0.8
HNaY 500[c]	24	11	6
HNaY 712[c]	76	48	21
HNaX	100[d]	34	48

[a] Toluene (2.5 mmol), SO_2Cl_2 (12.5 mmol), zeolite (1.5 g), CH_2Cl_2 (10 ml), 20°C, 1 h. [b] By quantitative GC. [c] Refs. to Si:Al ratios of 60.3, 10.5 and 5.5 for HNaY 760, HNaY 712 and HNaY 500 respectively. [d] 10% Polychlorinated compounds also observed.

Table 12 Effect of the solvent on the chlorination of toluene over HNaX by sulfuryl chloride according to eqn. (1).[a]

Solvent	Conversion of toluene (%)[b]	Yield of chloro-toluenes (%)[b]	*p*:*o*[b]
CH_2Cl_2	100	84[c]	58:42
CH_3CN	69	59	65:35
CH_3NO_2	70	68	57:43
Et_2O	5	3	89:11
THF	0	0	—
Pet.Sp.[d] (30–40 °C)	100	82[e]	60:40
CH_2Cl_2:CH_3CN (1:1)	28	20	69:31
DME	5	1	63:37
Pet.Sp. (80–100 °C)	27	18	60:40
CH_2Cl_2:Et_2O (1:1)	19	12	86:14
CH_2Cl_2:Et_2O (4:1)	51	32	85:15
CH_2Cl_2:Et_2O (9:1)	63	42	83:17
CH_2Cl_2:Et_2O (49:1)	71	53	65:35
Pet.Sp. (30–40 °C):Et_2O (1:1)	27	13	87:13

[a] Toluene (2.5 mmol), SO_2Cl_2 (7.5 mmol), HX (1.5 g), solvent (10 ml), 20 °C, 1 h. [b] By quantitative GC. [c] 5% of polychlorinated products also formed. [d] Pet. Sp. = petroleum spirit. [e] 8% of polychlorinated products also formed.

The results in Table 12 show that the reaction is quite efficient in dichloromethane, light petroleum, acetonitrile and nitromethane, but selectivities are lower than with *tert*-butyl hypochlorite and excess reagent is needed. Tremendous regioselectivity could be achieved in anhydrous diethyl ether, but the conversion of toluene was very poor as the formation of a volatile by-product from the solvent and the chlorinating reagent consumed the reagent and may have poisoned the catalyst. Conversion of toluene increased if either petroleum spirit or dichloromethane was mixed with diethyl ether, but to the detriment of the *para*-selectivity. Overall, therefore, sulfuryl chloride proved inferior to *tert*-butyl hypochlorite again and was not studied further for reactions of disubstituted substrates.

Conclusion

The present work shows that monochlorination of a wide range of aromatic substrates is feasible in mild conditions with good to excellent regioselectivity in the presence of zeolites. The best general system involves HNaX/*tert*-butyl hypochlorite in acetonitrile.

Experimental

GC measurements were carried out on a Hewlett Packard 5890 Series II apparatus fitted with a 30 m long RTX-1 column (ID 0.32; DF 0.8) with microprocessor control (oven temperature programming, injector temperature 250 °C, FID detector temperature 300 °C). The head pressure of N_2 carrier gas was 8.5 psi. All quantifications of reaction constituents were achieved using a known quantity of dry decane as reference standard. This was added together with the reactants in all reactions. Oven temperature rampings were chosen in order to obtain 'base line' separation of all components in a mixture.

Sulfuryl chloride was distilled prior to use and the colourless fraction, bp 68–70°C, was collected. *tert*-Butyl hypochlorite was prepared using a standard procedure,[12] diluted in the dry solvent used for the reaction and estimated before use by iodometric titration. *N,N*-Dichloramine-T was obtained following an established method[13] and recrystallized before use. *N,N*-Dichlorodiethylphosphoramidate was prepared using a modification of a known procedure (sodium hypochlorite was used instead of chlorine gas).[14] *N*-Chlorodiethylamine was synthesised by a literature method.[15] Other chlorinating agents were commercial samples and required no further purification.

Solvents were purified and dried by standard techniques[16] before use. Commercial liquid and solid starting materials were respectively purified by fractional distillation or recrystallization before use. Dichloroanisoles were obtained from the corresponding commercial phenols following standard phase-transfer catalysed procedures.[17]

All silica gels and zeolites were obtained from a commercial source and dried respectively in an oven at 150 °C or a furnace at 400 °C. Partially proton-exchanged sodium zeolites were obtained by reflux for one hour in a 1 M ammonium chloride solution (10 ml for 1 g), filtration, washing with distilled water until the washings were chloride free, and then drying in a furnace at 500 °C.

Chlorination over silica; general procedure

Solvent (10 ml), silica (3.76 g), decane (76 mg, as GC standard), aromatic substrate (5.0 mmol) and chlorinating agent (5.0 mmol) were gently stirred together at the stated temperature in a 50 ml round-bottomed flask. After completion of the reaction, the mixture was filtered and the silica was washed with more solvent. The combined filtrates were analysed on GC without any further purification.

Chlorination over zeolite; *tert*-butyl hypochlorite procedure

Solvent (10 ml), zeolite (1.5 g), decane (76 mg, as GC standard), aromatic substrate (2.5 mmol) and *tert*-butyl hypochlorite (2.5 mmol) were gently stirred together at the stated temperature in a 50 ml round-bottomed flask. From time to time, aliquots were taken and filtered through cotton wool. The zeolite was washed with more solvent and the combined filtrates were analysed on GC without any further purification.

Chlorination over zeolite; sulfuryl chloride procedure

Solvent (10 ml), zeolite (1.5 g), decane (76 mg, as GC standard), aromatic substrate (2.5 mmol) and sulfuryl chloride (7.5 or 12.5 mmol—see text) were gently stirred together at room temperature in a 50 ml round-bottomed flask. From time to time, aliquots were taken and filtered through cotton wool. The zeolite was washed with more solvent and the combined filtrates were analysed on GC without any further purification.

Preparative chlorination of chlorobenzene using *tert*-butyl hypochlorite and HX

To partially proton-exchanged sodium faujasite X (20 g) was added acetonitrile (54 ml) and chlorobenzene (3.83 g, 34 mmol). In a separate vessel, *t*-BuOCl (34 mmol) was dissolved in acetonitrile (82 ml). This solution was added to the first mixture, the flask was fitted with a reflux condenser, and the mixture was heated to 40 °C in a thermostatically controlled water bath, whilst gentle stirring was maintained. After 14 days, the mixture was cooled and filtered. The separated solid was washed with more acetonitrile (50 ml), pentane (2 × 50 ml) and water (50 ml) and the combined filtrates were placed in a separating funnel. The pentane layer was separated and then washed with water (2 × 20 ml) and dried with magnesium sulfate. Evaporation of the solvent under reduced pressure gave a white semi-solid material in almost quantitative yield. GC analysis showed the material to consist of 1,4-dichlorobenzene (97%) and 1,2-dichlorobenzene (3%). This material was further purified by kugelrohr distillation (*ca.* 55 °C/10 Torr) to give a colourless crystalline distillate which, according to GC analysis, was almost pure 1,4-dichlorobenzene containing just a trace of 1,2-dichlorobenzene; yield: 4.60 g (92%), mp = 50–51 °C (ref:[18] mp = 53°C).

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