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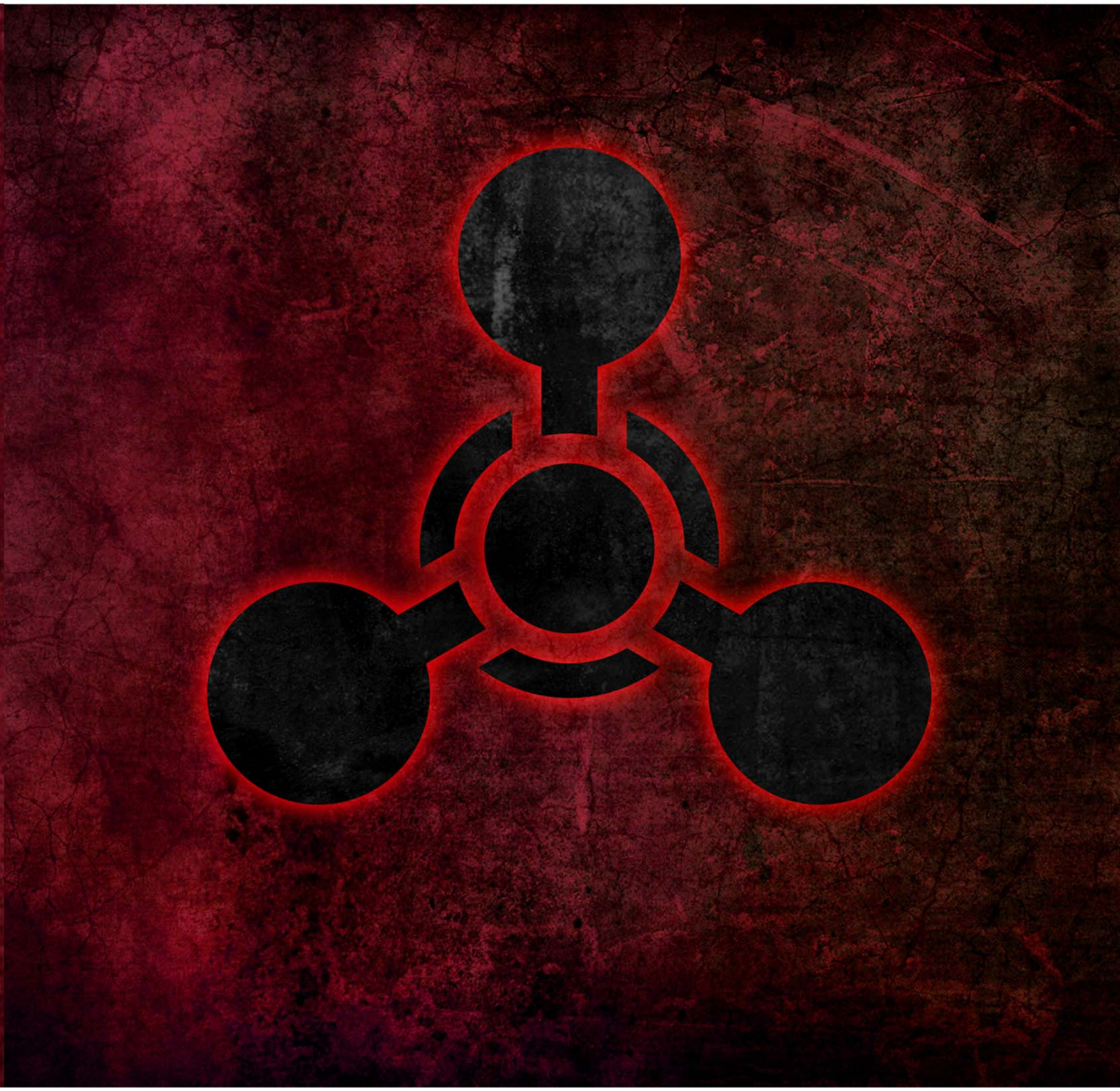

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Greener Chemical Processes by Regioselective Aromatic Substitution Reactions of Simple Aromatics

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Abstract

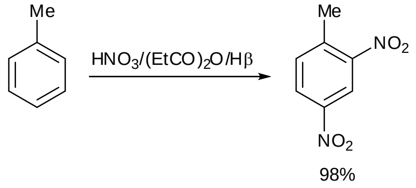
Our research has been oriented towards the development of greener processes for the synthesis of commercially important products, especially in the area of selective electrophilic aromatic substitution reactions, which are of major industrial importance but are traditionally often very unselective reactions. For example, we have shown that reusable zeolite catalysts can have advantages in *para*-regioselective nitration, halogenation, acylation and alkylation reactions of simple aromatics and heteroaromatics. On the other hand use of directed lithiation reactions allows regioselective *ortho*-substitution.

Introduction

Electrophilic substitution of aromatic compounds is an important process for the synthesis of aromatic compounds, some of which are useful intermediates for the synthesis of valuable industrial and pharmaceutical compounds. Traditionally, electrophilic substitution reactions of aromatic compounds often require the presence of acid or Lewis acid activators.[1,2] Unfortunately, use of such activators creates a number of environmental limitations. The activators may be needed in more than stoichiometeric quantity because of complexation to starting materials and/or products. Work-up usually involves hydrolysis, which may lead to generation of large amounts of corrosive and toxic waste products and loss of the activator. Moreover, reactions are often not clean and lead to the production of mixtures of isomers with poor selectivity. Much effort has therefore been made to find more environmentally friendly processes for aromatic substitution reactions.[3]

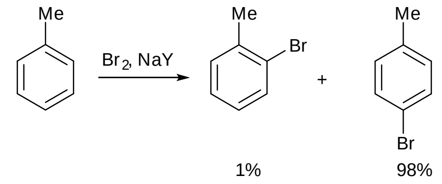
We have had a great deal of success, particularly by the use of recoverable and regenerable solid catalysts such as zeolites or by directed lithiation to overcome some of the limitations associated with use of activators such as metal halide Lewis acids, with the added advantage of providing regioselectivity.[4–7]

Selective Nitration

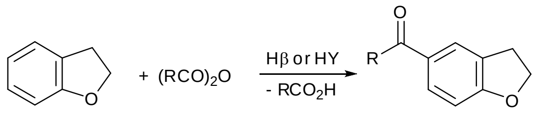


Aromatic nitro compounds represent versatile feedstock for various industrial products. Recently, we have reported the quantitative dinitration of toluene using a mixture of propanoic anhydride and nitric acid over zeolite Hβ to give 2,4-dinitrotoluene in 98% yield, with a 2,4-:2,6-dinitotouene ratio of over 120.[8] This represents the most selective quantitative process for 2,4-dinitrotolune from double nitration of toluene. Also, the catalyst is re-usable, solvent is not needed and an aqueous work-up is not required.[8]

Selective Halogenation



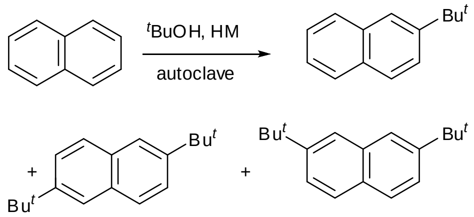
Halogeneated aromatic compounds are valuable intermediates for pharmaceutical chemicals. Bromination of mono-substituted benzenes of moderate activity with bromine in the presence of zeolite NaY at room temperature provides a high yielding and highly regioselective process for the synthesis of *para*-brominated products.[9] For example, bromination of toluene over Br_2/Hβ system gave 4-bromotoluene in 98% yield along with 1% of 2-bromotoluene.[9] Heating the mixture of HY and NaBr produced drives off HBr and NaY can be recovered for use again.



Selective Acylation

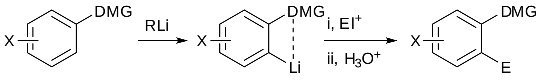
Acylation of aromatic compounds is an important reaction for the synthesis of various agrochemicals, pharmaceuticals and fragrances. Zeolite catalysts are efficient catalysts for the acylation of activated aromatic compounds with unhindered acid anhydrides in a solvent-free system. For example, acylation of 2,3-dihydrobenzofuran over zeolite Hβ or HY gave the corresponding 5-acylated products selectively in high yields.[10]

Selective Dialkylation of Naphthalene



There is considerable interest in the use of zeolites to control regioselective dialkylation of naphthalene to produce 2,6-dialkylnaphthalenes, potential precursors of naphthalene-2,6-dicarboxylic acid (NDA), which is needed for production of poly(ethylenenaphthalate; PEN). We have achieved highly regioselective dialkylation of naphthalene using various alcohols over zeolites.[11,12] For example, *tert*-butylation of naphthalene with *tert*-butyl alcohol over a dealuminated HM zeolite gave 2,6-di-*tert*-butylnaphthalene in 60% yield with a 2,6/2,7 ratio of over 50.[11]

Selective *ortho*-Lithiation



While zeolites offer approaches to *para*-disubstituted products *via* shape selectivity, an alternative process is needed when *ortho*-disubstituted products are needed. Organolithiums can play an important role in such cases. We have shown that organolithium reagents are useful intermediates for the synthesis of more complex *ortho*-substituted aromatics.[13] We have also shown that *ortho*-lithiation can be applied to more complicated heterocycles to produce derivatives that are difficult to prepare by other routes.[14]

Conclusions

New strategies are required in order to reduce the waste generated by traditional aromatic substitution reactions. Shape-selective effects of zeolite catalysts and directed lithiation reactions represent two useful approaches for enhancement of selectivity, all of which have been explored successfully.

Acknowledgements

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