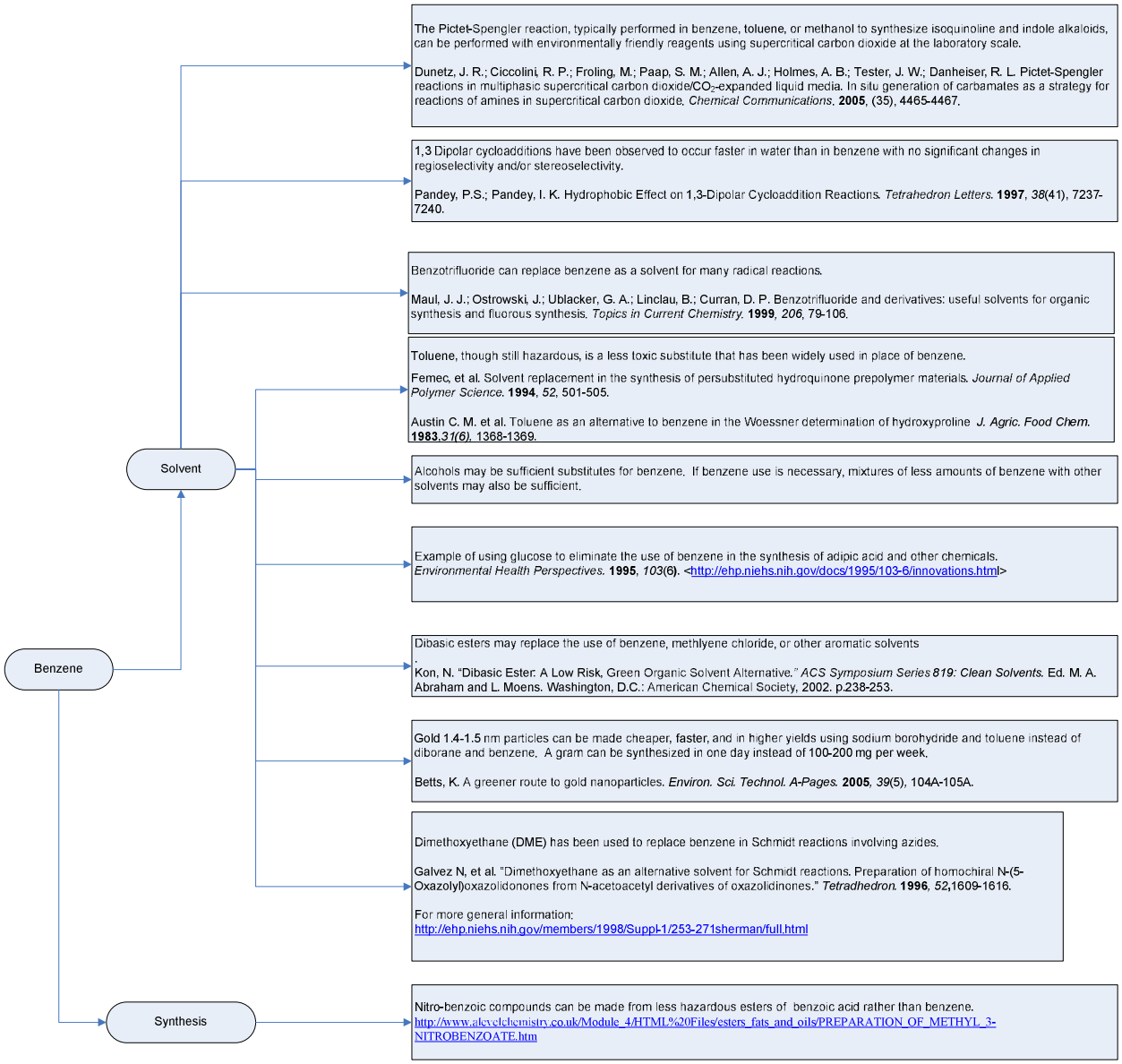
Benzene
Solvent
Synthesis
The Pictet-Spengler reaction, typically performed in benzene, toluene, or methanol to synthesize isoquinoline and indole alkaloids, can be performed with environmentally friendly reagents using supercritical carbon dioxide at the laboratory scale.
Dunetz, J. R.; Ciccolini, R. P.; Froling, M.; Paap, S. M.; Allen, A. J.; Holmes, A. B.; Tester, J. W.; Danheiser, R. L. Pictet-Spengler reactions in multiphasic supercritical carbon dioxide/CO_2-expanded liquid media. In situ generation of carbamates as a strategy for reactions of amines in supercritical carbon dioxide. *Chemical Communications*. **2005**, (35), 4465-4467.
1,3 Dipolar cycloadditions have been observed to occur faster in water than in benzene with no significant changes in regioselectivity and/or stereoselectivity.
Pandey, P.S.; Pandey, I. K. Hydrophobic Effect on 1,3-Dipolar Cycloaddition Reactions. *Tetrahedron Letters*. **1997**, *38*(41), 7237-7240.
Benzotrifluoride can replace benzene as a solvent for many radical reactions.
Maul, J. J.; Ostrowski, J.; Ublacker, G. A.; Linclau, B.; Curran, D. P. Benzotrifluoride and derivatives: useful solvents for organic synthesis and fluorous synthesis. *Topics in Current Chemistry*. **1999**, *206*, 79-106.
Toluene, though still hazardous, is a less toxic substitute that has been widely used in place of benzene.
Femec, et al. Solvent replacement in the synthesis of persubstituted hydroquinone prepolymer materials. *Journal of Applied Polymer Science*. **1994**, *52*, 501-505.
Austin C. M. et al. Toluene as an alternative to benzene in the Woessner determination of hydroxyproline *J. Agric. Food Chem.* **1983**,*31(6)*, 1368-1369.
Alcohols may be sufficient substitutes for benzene. If benzene use is necessary, mixtures of less amounts of benzene with other solvents may also be sufficient.
Example of using glucose to eliminate the use of benzene in the synthesis of adipic acid and other chemicals. *Environmental Health Perspectives*. **1995**, *103*(6). <http://ehp.niehs.nih.gov/docs/1995/103-6/innovations.html>
Dibasic esters may replace the use of benzene, methlyene chloride, or other aromatic solvents
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Kon, N. "Dibasic Ester: A Low Risk, Green Organic Solvent Alternative." *ACS Symposium Series 819: Clean Solvents*. Ed. M. A. Abraham and L. Moens. Washington, D.C.: American Chemical Society, 2002. p.238-253.
Gold 1.4-1.5 nm particles can be made cheaper, faster, and in higher yields using sodium borohydride and toluene instead of diborane and benzene. A gram can be synthesized in one day instead of 100-200 mg per week.
Betts, K. A greener route to gold nanoparticles. *Environ. Sci. Technol. A-Pages*. **2005**, *39*(5), 104A-105A.
Dimethoxyethane (DME) has been used to replace benzene in Schmidt reactions involving azides.
Galvez N, et al. "Dimethoxyethane as an alternative solvent for Schmidt reactions. Preparation of homochiral N-(5-Oxazolyl)oxazolidonones from N-acetoacetyl derivatives of oxazolidinones." *Tetradhedron*. **1996**, *52*,1609-1616.
For more general information:
http://ehp.niehs.nih.gov/members/1998/Suppl-1/253-271sherman/full.html
Nitro-benzoic compounds can be made from less hazardous esters of benzoic acid rather than benzene.
http://www.alevelchemistry.co.uk/Module_4/HTML%20Files/esters_fats_and_oils/PREPARATION_OF_METHYL_3-NITROBENZOATE.htm