Tetrahydrofuran

Solvent

A solvent-free synthesis of dihydropyrimidinones using a ruthenium(III) chloride catalyst has both significantly increased yield and reduced reaction time while avoiding the use of solvents such as ethanol, acetonitrile, dichloromethane, and tetrahydrofuran.

De, S. K.; Gibbs, R. A. Ruthenium(III) Chloride-Catalyzed One-Pot Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-ones under Solvent-Free Conditions. *Synthesis*. **2005**, (11), 1748-1750.

Acylation of alcohols, amines, and thiols can be conducted under solvent and catalyst free conditions to give high yields and purity.

Ranu, B.; Dey, S.; Hajra, A. Highly Efficient Acylation of Alcohols, Amines, and Thiols under Solvent-free and Catalyst-free conditions. *Green Chemistry*. **2003**, *5*(1), 44-46.

Polymerization of molecules such as phenylacetylene have occurred at higher rates in super critical carbon dioxide than THF or hexane.

Hori, H.; Six, C.; Leitner, W. Rhodium-Catalyzed Phenylacetylene Polymerization in Compressed Carbon Dioxide. *Macromolecules*. **1999**, *32*(10), 3178-3182.

Reviewed in Leitner, W. Reactions in supercritical carbon dioxide. *Topics in Current Chemistry*. **1999**, *206*,107-132.

Alumina used in solventless reactions has similar regioselective properties as THF in anionic reactions.

Reviewed in: Loupy, A. Solvent-free reactions. *Topics in Current Chemistry*. **1999**, *206*, 153-208.

Diethoxymethane (DEM) has proven to be a good substitute for THF and dichloromethane in organometallic chemistry and phase transfer reactions. It does not need to be dry to be used in water sensitive reactions, it can be easily separated from water and recovered for reuse, and it is less susceptible to forming peroxides. It also has limited water solubility and can be used in phase-transfer catalyzed reactions.

Boaz, N. W.; Venepalli, Bhaskar. Applications of Diethoxymethane as a Versatile Process Solvent and Unique Reagent in Organic Synthesis. *Org. Process Res. Dev.* **2001**, *5*(2),127-131.

As mentioned in:
Macquarrie, D. *Green Chemistry*. **2001**, *3*(3), G35-G39.

Methyl tert-butyl ether can be used to replace tetrahydrofuran.

Stinson, S. C. *Chem Eng News*, 25 November 1996, p. 41.

THF derivatives, such as n-octyl tetrahydrofurfuryl ether, have been used instead of THF in the synthesis of the HIV protease inhibitor Crixivan. These derivatives are nonvolatile and water insoluble and, thus, can avoid THF contaminated aqueous solutions or energy intensive measures taken to separate THF and water.

Molnar LK. Polymer Based Solvents for Minimizing Pollution During the Synthesis of Fine Chemicals [PhD. dissertation]. Cambridge, MA:Massachusetts Institute of Technology 1996.

Molnar, L. K., Buchwald, S. L. and Hatton, T. A. Polymer based replacement solvents for minimizing pollution during the synthesis of fine chemicals. *Polymer Material Science Engineering*, **75**, 113-114, 1996.

Butyl diglyme (diethylene glycol dibutyl ether) is a good, high flashpoint solvent that has replaced THF and diethyl ether in Grignard reactions. It forms an easily removable water immiscible layer that dissolves $MgCl_2$. It has also been used in gold and other metal extractions.

http://www.glymes.com/butyldiglyme.php
or
http://www.ferro.com/Our+Products/Fine+Chemicals/Products+and+Markets/Glymes/Butyl+Diglyme+as+Grignard+Solvent.htm

Department of California's Hazard Evaluation System and Information Service (HESIS) finds that this is not as dangerous as other forms of glycol ethers
http://www.dhs.ca.gov/ohb/HESIS/solv_cht.htm

Aldol reactions in THF can run with no solvent using resusable ionic liquids
Zhu, A.; Jiang, T.; Wang, D.; Han, B.; Liu, L.; Huang, J.; Zhang, J.; Sun, D. Direct Aldol Reactions Catalyzed by 1,1,3,3-Tetramethylguanidine Lactate without Solvent. *Green Chemistry*. **2005**, *7*(7), 514-517.

Try a solventless reaction such as in the synthesis of dihydropyrimidinones

Ranu, B. C.; Hajra, A.; Dey, S. S. A Practical and Green Approach Towards Synthesis of Dihydropyrimidinones without any Solvent or Catalyst. *Org. Process Res. Dev.* **2002**, *6*, 817-818.