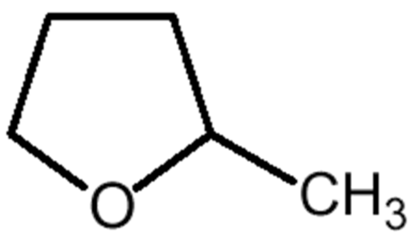
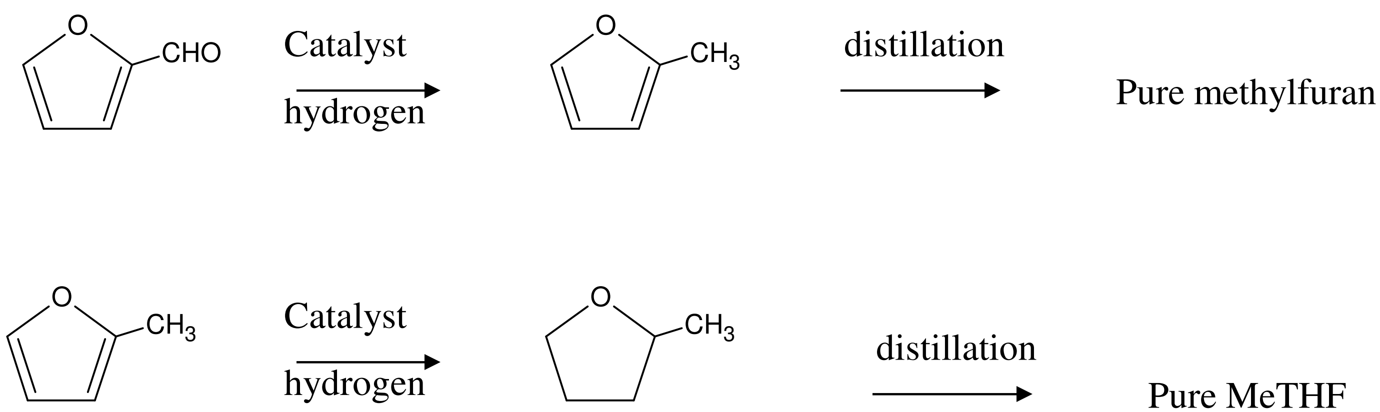
METHYLTETRAHYDROFURAN

System Advantages in Organometallic Chemistry and Biphasic Reactions



Agenda

MeTHF Process



MeTHF Impurities

MeTHF Manufacturing Specification

- Minimum 99% assay
- 150-400 ppm BHT
- Less than 300 ppm water

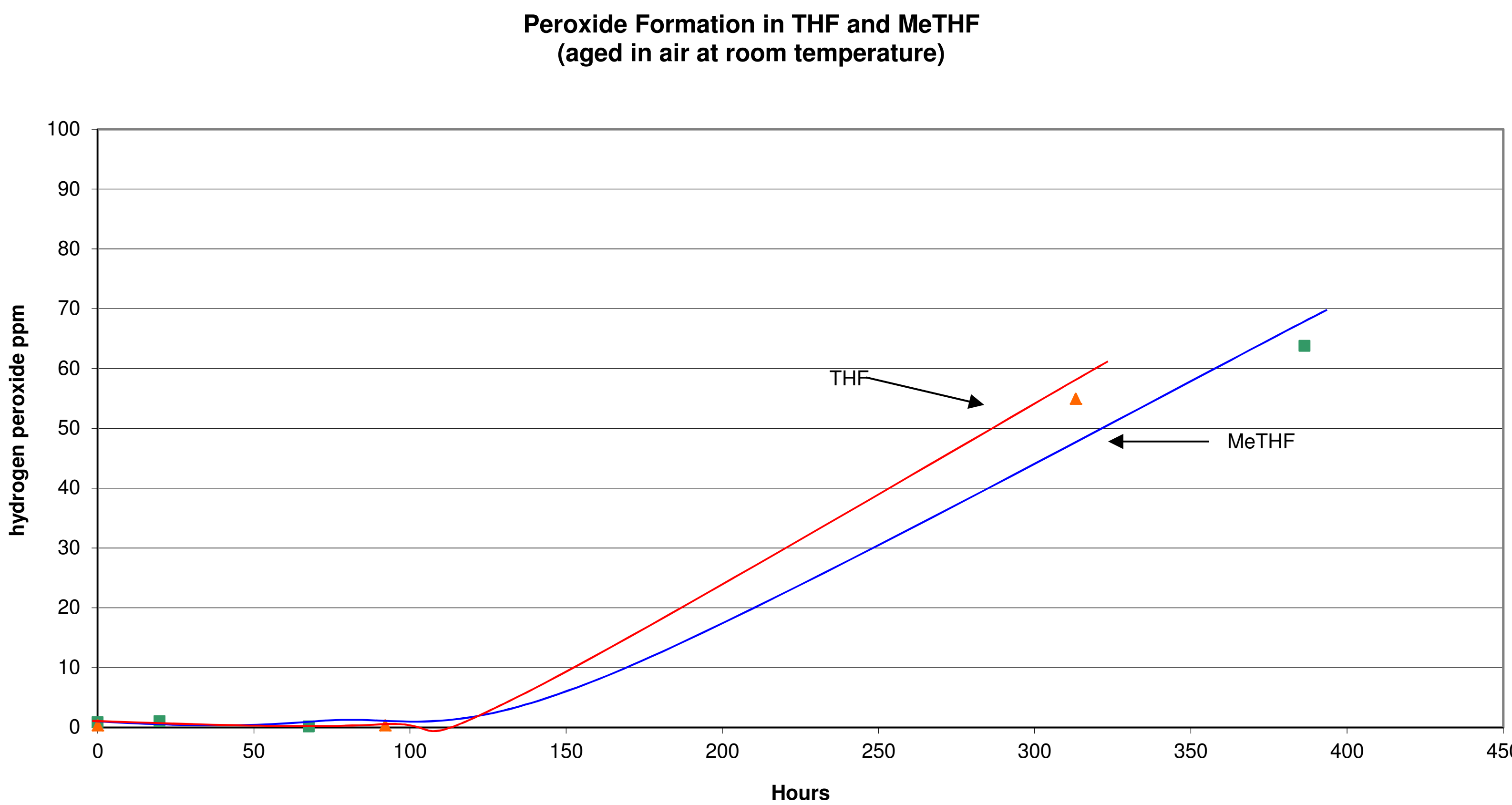
MeTHF Stability

Peroxide formation rate in unstabilized MeTHF is similar to THF

MeTHF is more stable to acid degradation than THF

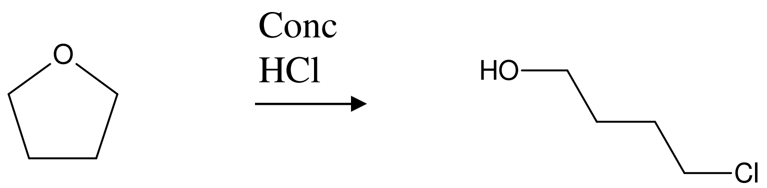
MeTHF is more stable to strong base than THF

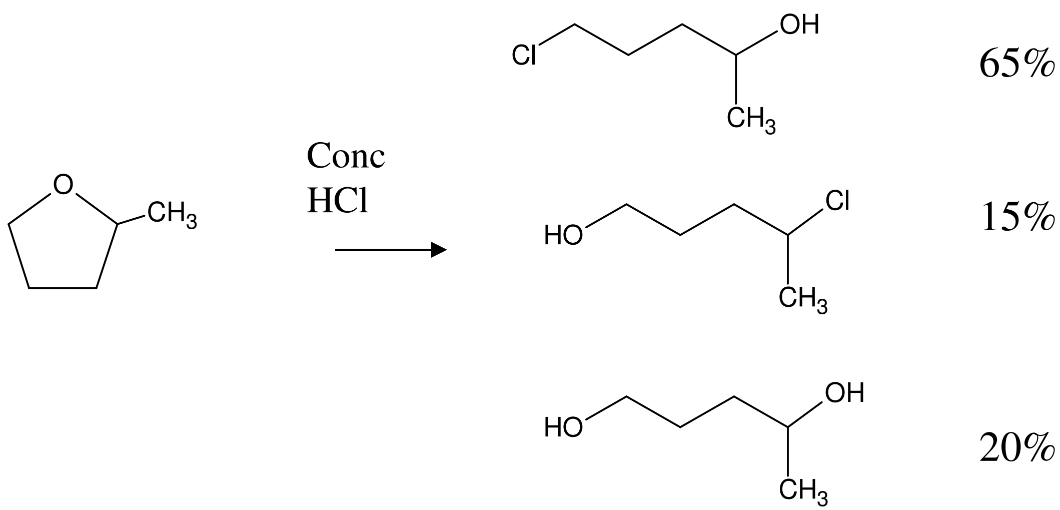
MeTHF Peroxide Formation



Acid Degradation

THF and MeTHF will ring open with strong acids





Acid Degradation

THF and MeTHF both degrade in concentrated HCl

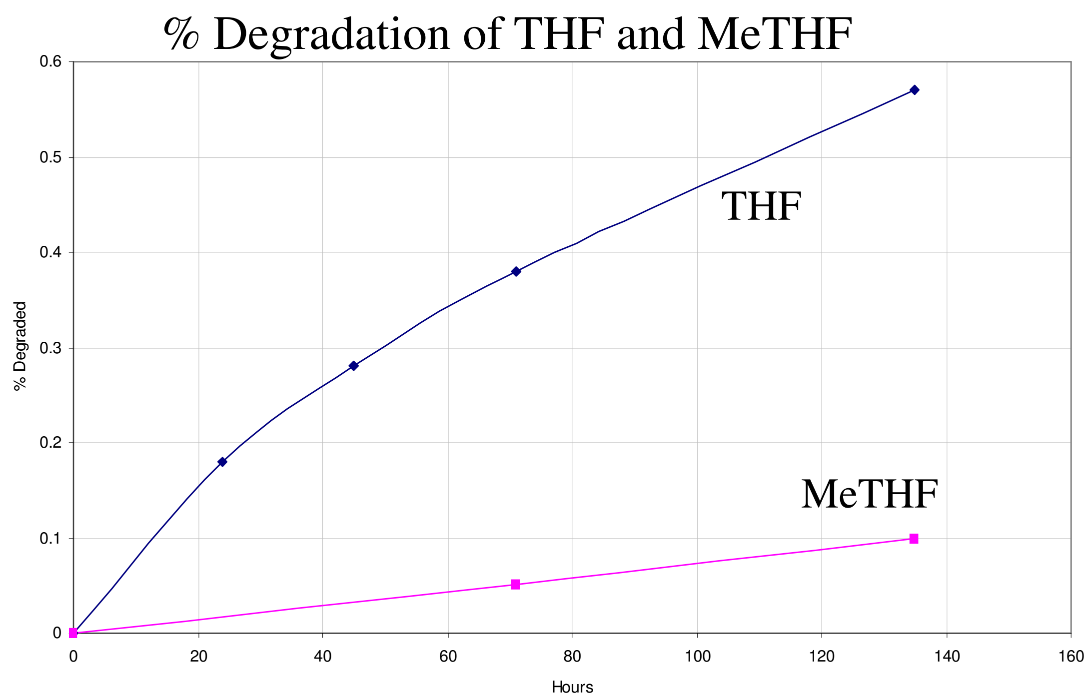
THF degrades about 3 times faster than MeTHF in 18% (5N) HCl

Time (hours)	% MeTHF Degraded	% THF Degraded
4	0.54	1.52
7.5	0.83	2.24

4% in 5N HCl at 60 C

Acid Degradation

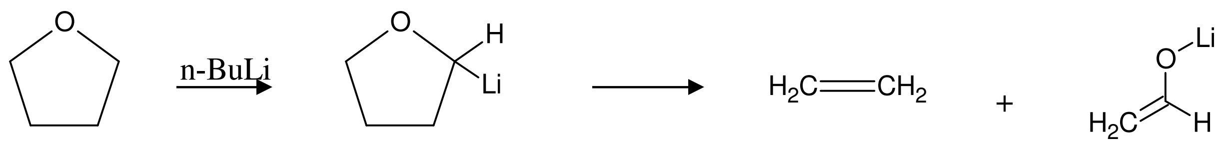
With typical process conditions, MeTHF degrades about 6 times slower than THF



Conditions: 50:50 THF/MeTHF: 2 N HCl at 60 C

Strong Base Stability

THF reacts with n-butyllithium



The reaction of n-butyllithium with MeTHF is slower

Compound	Half life at 35 C minutes
THF	10
MeTHF	70

R. Bates, J. Org. Chem. (1972) 37(4), p560.

General Comparison of MeTHF vs THF

MeTHF behaves like THF in most reactions

- Partial water miscibility and easy drying make it a useful solvent for product recovery
- Polar properties make it a useful solvent in biphasic reactions and for extraction of polar compounds from water

Lewis Base Strength of MeTHF

MeTHF is between THF and Ethylether in Lewis Base strength and polarity

Property	MeTHF	THF	Et_2O
dielectric const	6.97	7.5	4.42
dipole moment, Debye	1.38	1.69	1.11
water solubility, g/100g	4	mis	1.2
Hildebrand, $MPa^{1/2}$	16.9	18.7	15.5
solvation energy, kcal/mol	0.6	0	2.3
Donor Number	18	20.5	19.2

Properties of MeTHF

molecular weight	86.1
bp (ºC)	80.2
mp (ºC)	-136
vapor press at 20 ºC (mm)	102
density at 20 ºC (g/ml)	0.854
viscosity at 25 ºC (cp)	0.46
viscosity at -70 ºC (cp)	1.85
refractive index at 20 ºC	1.408
flash point ºC	-11
heat of vaporization (cal/g) at bp	87.1
solubility in water 20 ºC g/100g	14
solubility water in MeTHF 20 ºC g/100g	4
azeotrope bp ºC	71
azeotrope % water	10.6

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Solubility of Magnesium Salts

	MeTHF 25 C	MeTHF 80 C	THF 25 C	THF 60 C
MgCl2	<0.1	<0.13	<0.1	2
MgBr2	>40	>50	5	14.5
MgI2	10		<0.1	

Solubility in g/100g

Diethylether forms two phases at high $MgBr_2$ concentrations

Grignard Reagent Solubility

Grignard-Reagents in 2-MeTHF available from Chemetall

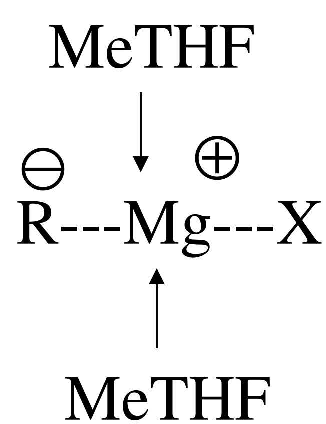
R-MgBr	W/W%	Mol/liter	W/W%	Mol/liter
Methyl-MgBr	35	3.2	15	1.2
Ethyl-MgBr	40	3.4	8	0.6
Phenyl-MgBr	45	2.9	17	0.9

MeTHF Azeotropes

Compound	Azeo bp ºC	% Compound in Azeo
methanol (64.7 ºC bp)	62.8	57
ethanol (78.5 ºC bp)	74.4	34
n-propanol (97.2 º bp)	79.5	1
2-propanol (82.3 ºC bp)	77	18
toluene (110.6 ºC bp)		no azeo
Water (100 ºC bp)	71	10.6

Grignard Reagents in MeTHF

- For most Grignard reagents, formation and reaction in MeTHF are similar to THF
- MeTHF behaves more like ethylether in the formation and reaction of some Grignard reagents (weaker Lewis Base)

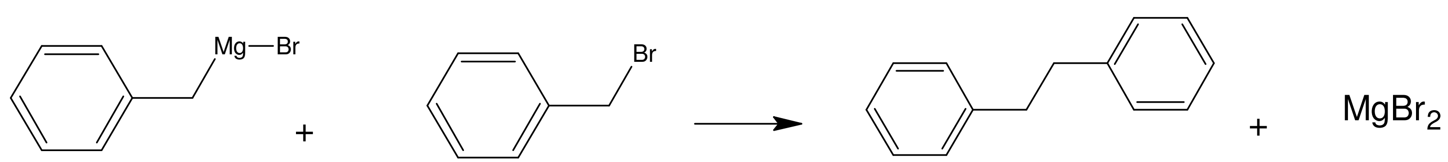


MeTHF: Higher Yield in Grignard Formation

Benzyl and allyl Grignard Reagents

- Benzyl and allylmagnesium halide reagents are used in many agricultural and pharmaceutical synthesis

- In THF, formation of by-product dimer dramatically reduces yields of the Grignard reagent



MeTHF: Higher Yield in Grignard Formation

#	Reagent	Solvent	Organomagnesium Yield	Yield Difference
1	benzyl chloride	THF	85%	**14%**
		MeTHF	99%	
2	benzyl bromide	THF	83%	**15%**
		MeTHF	98%	
3	o-methylbenzyl chloride	THF	78%	**19%**
		MeTHF	97%	
4	o-chlorobenzyl chloride	THF	20%	**66%**
		MeTHF	86%	
5	allyl chloride	THF	73%	**16%**
		MeTHF	89%	

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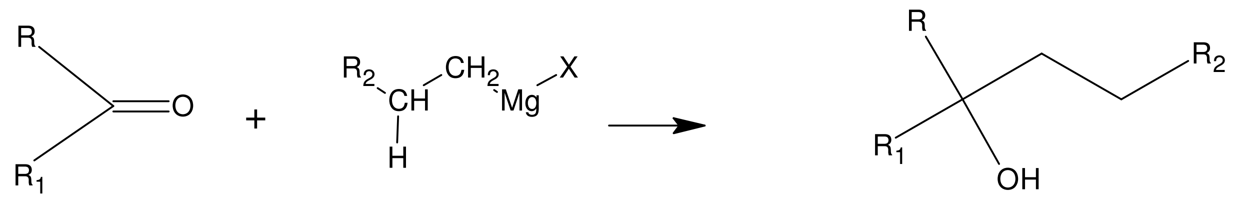
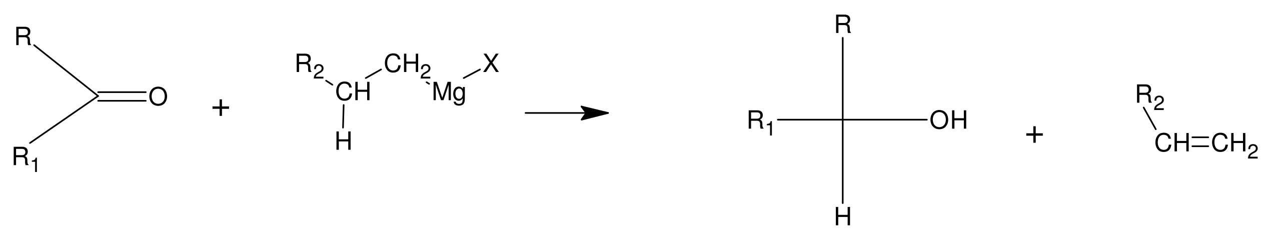
MeTHF: Improved Yield of Grignard Reactions

- Like ethyl ether, MeTHF gives less reduced product for Grignard reagents that contain beta hydrogens

More addition product with MeTHF



More reduction product with THF



Better Extraction in the Grignard Work-up

- MeTHF gives clean phase separations in the acid quench step whereas THF needs addition of non-polar solvents (toluene) in large excess
- Toluene addition gives milky emulsions and rag layers often difficult to separate
- MeTHF is a far better extracting solvent for a wide range of extract polarities

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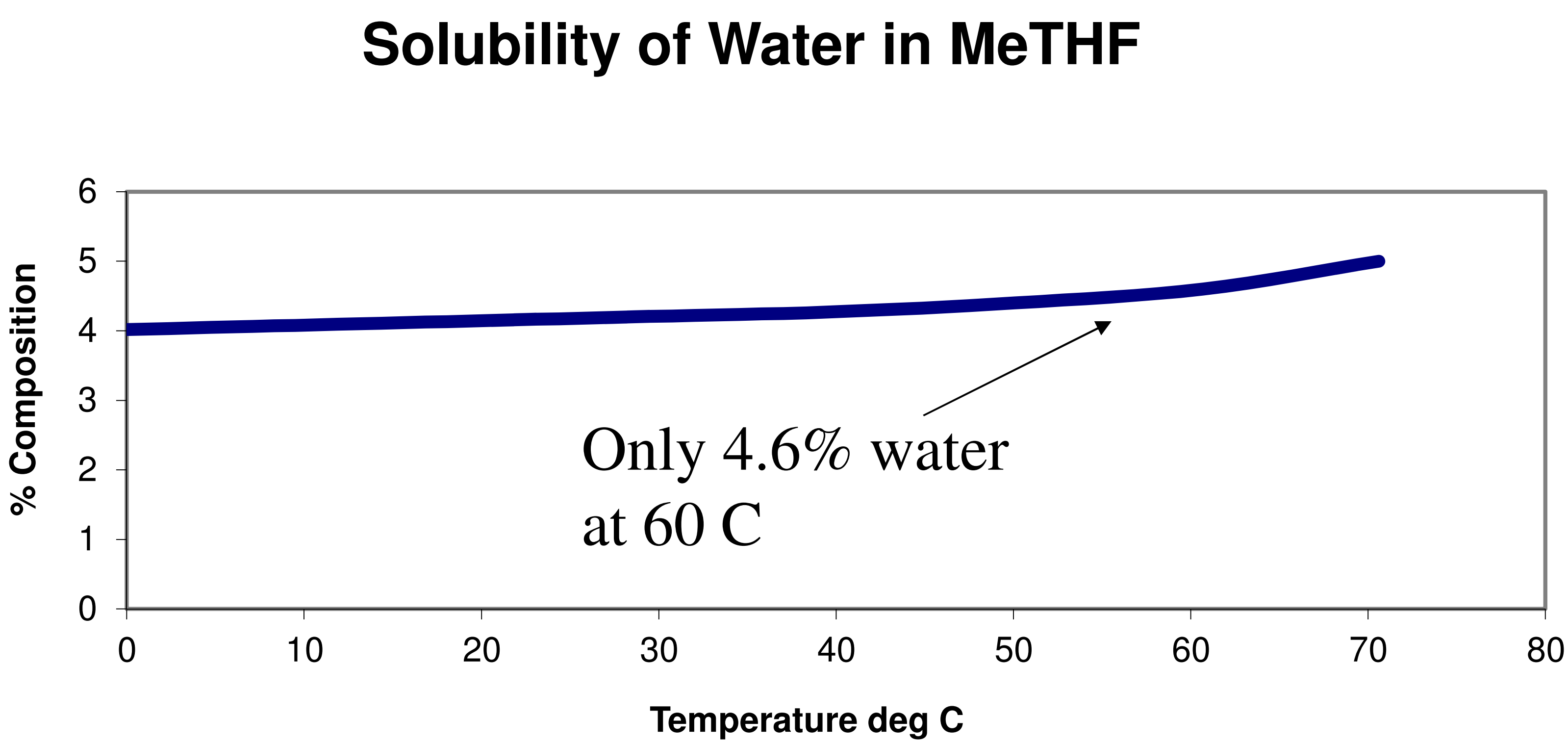
MeTHF: Easy Solvent Recycling

- Several properties make MeTHF easy to recycle versus THF

Property	MeTHF	THF
Boiling point (C)	80	66
Water solubility in solvent (% at 20 C)	4.1	infinite
Water azeotrope composition (% water)	10.6	6.7

MeTHF: Easy Solvent Recycling

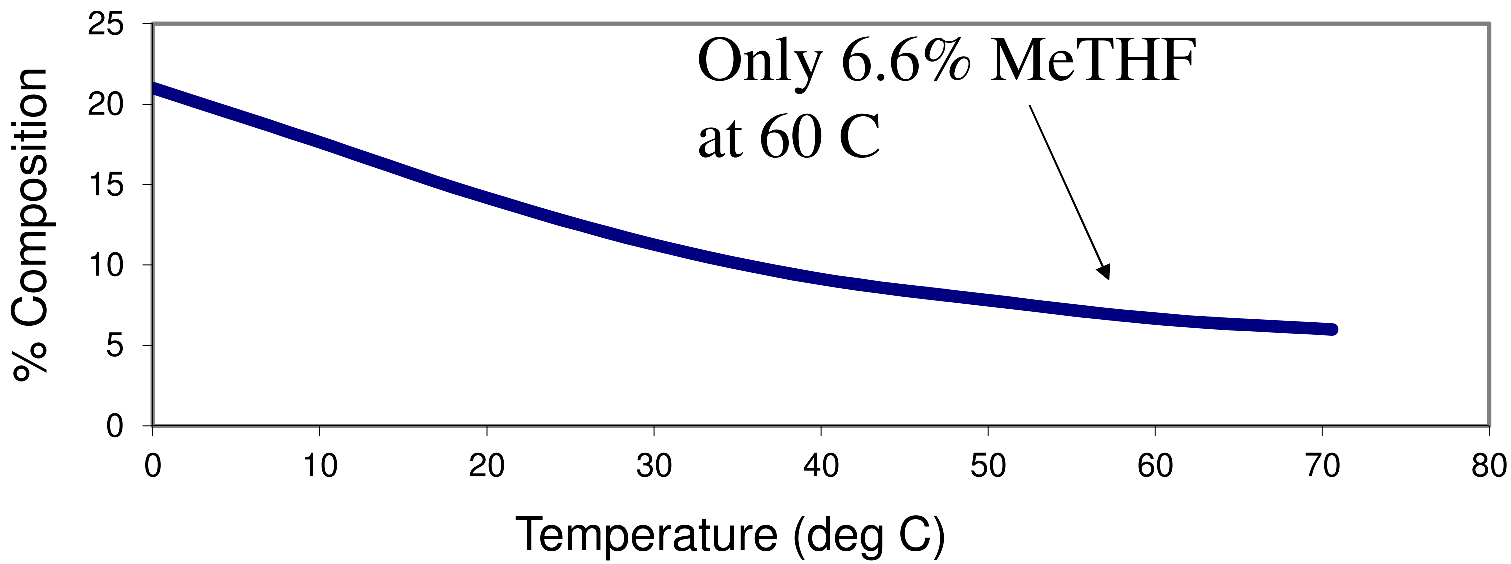
- The solubility of water in MeTHF increases only slightly as temperature increases



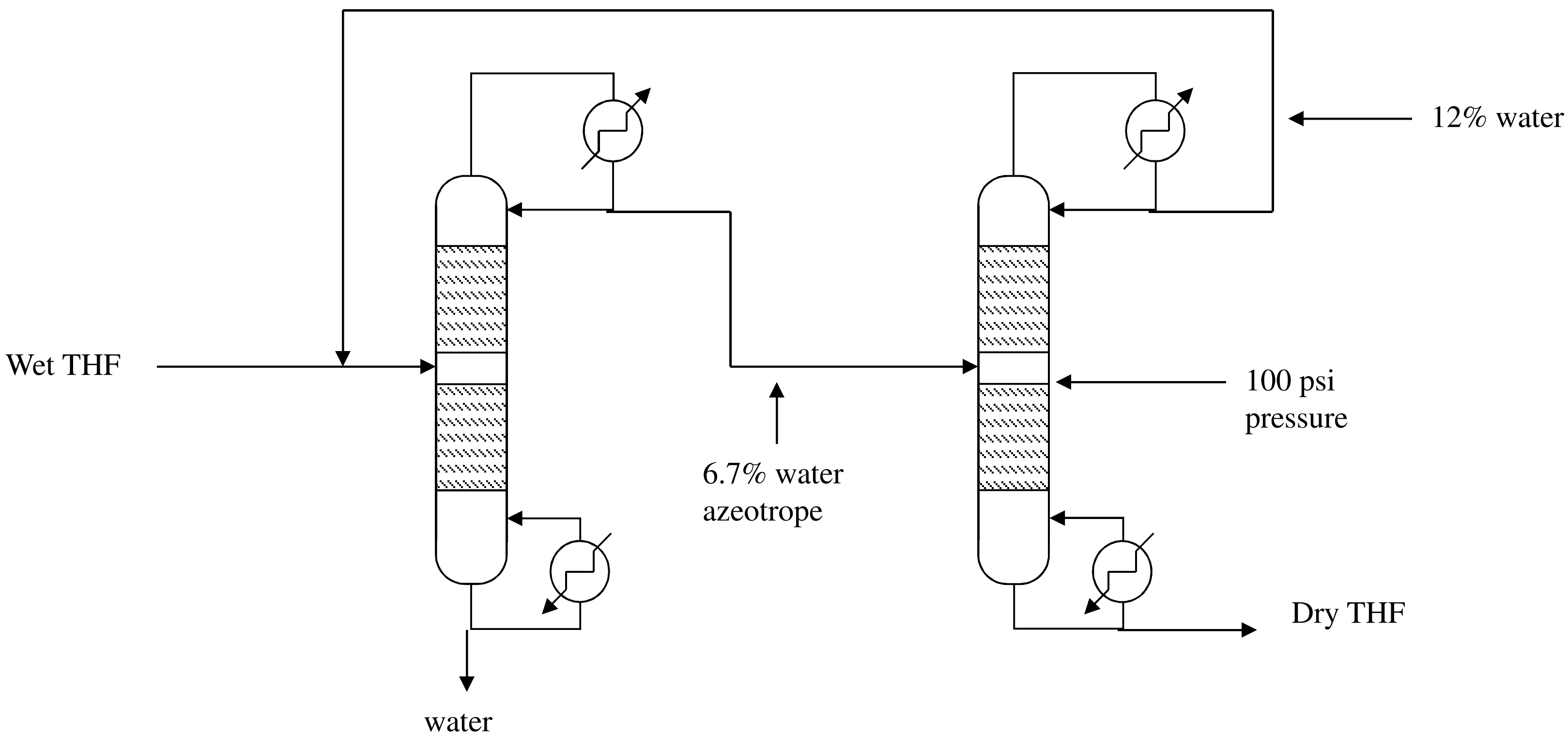
MeTHF: Easy Solvent Recycling

- The solubility of MeTHF in water decreases quickly as temperature increases

Solubility of MeTHF in Water

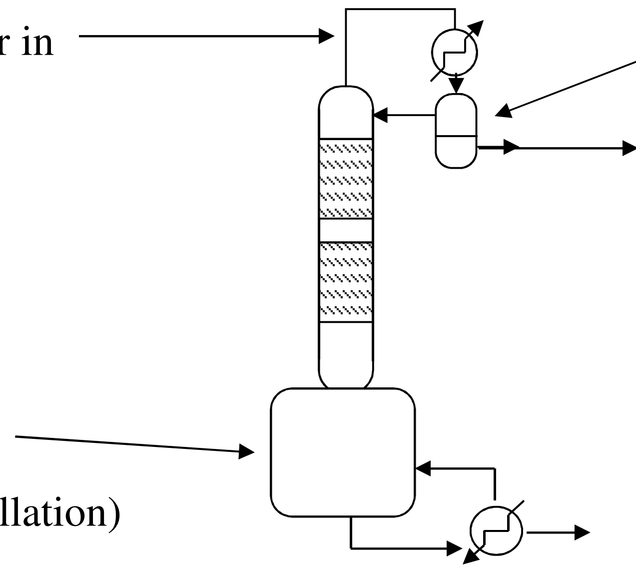


Process to Dry THF



MeTHF: Easy Solvent Recycling

- Dry MeTHF can be recovered in a simple batch distillation



Conclusions on the Use of MeTHF vs. THF

- MeTHF is the choice over THF for allyl and benzyl Grignard reagents
- MeTHF allows formation of bromo Grignard reagents at high concentration
- MeTHF minimizes side reactions in Grignard chemistry
- MeTHF provides for easy work-up of the Grignard
- MeTHF improves the extraction yield in Grignard work-up
- MeTHF can be used to azeotropically dry the product before isolation
- MeTHF can be easily recovered and recycled
- MeTHF saves money

$LiAlH_4$ Reductions with MeTHF

- $LiAlH_4$ solubility in MeTHF is at least 1.8 M (7.7 g/100 g)
- A survey of aldehydes, esters and acids gave similar product yields for reductions run in MeTHF versus THF
- Product recovery is improved with MeTHF versus THF
  - No additional solvent needed for product recovery
  - High efficiency for recovery of water soluble or partially water soluble compounds
  - Fieser procedure can be used to remove salts
  - Clean water-organic phase splits
  - Can be used to dry product for next reaction step

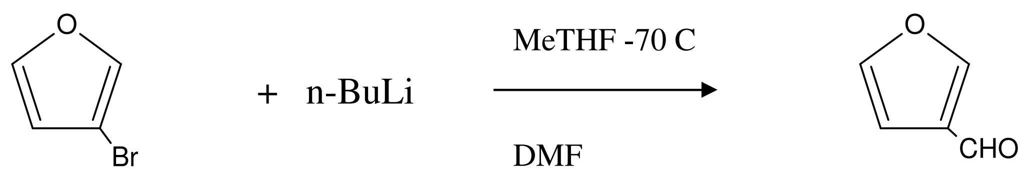
$LiAlH_4$ Solubility

Solvent	grams/100 grams
MeTHF	>7.7
THF	13
Ethyl ether	25
Dibutyl ether	2
Dioxane	0.1

Lithiation Solvent

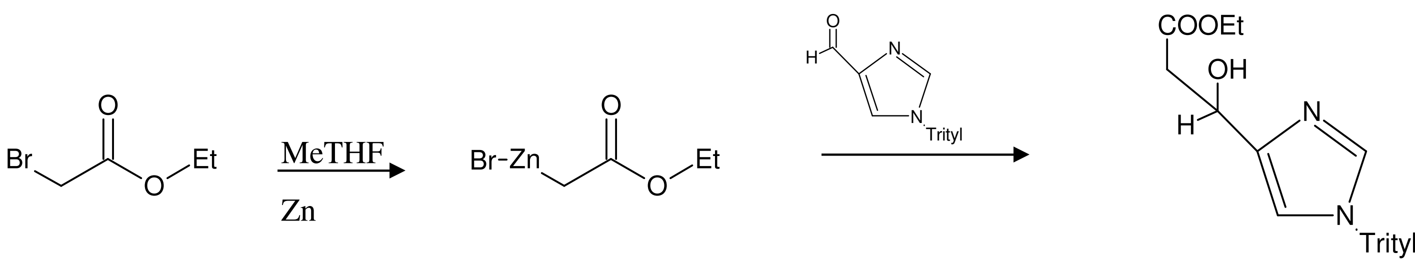
MeTHF can be used to replace THF in low temperature reactions with n-BuLi

MeTHF has a low mp (forms an organic glass at –136 C) and has low viscosity at –70 C



Zinc Chemistry

MeTHF can be used in place of THF in the Reformatsky reaction



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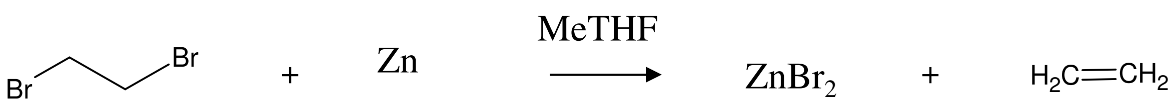
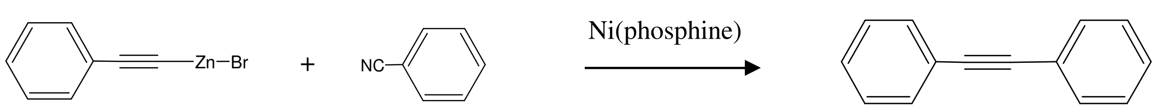
Anhydrous $ZnBr_2$ can be made in MeTHF with a solubility of >50 g/100g



MeTHF was used in the Ni catalyzed coupling of alkynlzinc bromide with nitriles[2]



1. Nuwa, S.; Handa, S.; Miki, S., US 20050043544. MeTHF was found to provide a stable solution and good yields in the Reformatsky reaction with ethylbromoacetate.
2. Miller, J., US 20050137402

MeTHF in Biphasic Reactions

- Limited miscibility with water facilitates easy product recovery
- Strong solvent for polar compounds typically soluble in DCM
- Very stable to basic conditions and stable to most acidic conditions
- In water systems, very clean phase separations are typically found
- Water washes decant from the reactor bottom versus DCM where water is the top layer
- Products in MeTHF can be dried in the reactor due to the favorable MeTHF azeotrope
- The 80 ºC b.p. allows condensing with cooling water with little vapor loss

MeTHF in Biphasic Reactions

- The higher apparent polarity of MeTHF in biphasic reactions is attributed to the dissolved water[1]

$$\mathrm{BnNH_2 + BzCl \xrightarrow{NaOH} BnNHBz} \qquad \text{88\% yield}$$

$$\mathrm{PhNH_2 + AcCl \xrightarrow{NaOH} PhNHAc} \qquad \text{94\% yield}$$

$$\mathrm{PhOH + o\text{-}FPhNO_2 \xrightarrow[TBABr]{NaOH} o\text{-}NO_2OPh} \qquad \text{95\% yield}$$

(1) David H. Brown Ripin, Synlett 2003, No. 15, p2353

MeTHF in Biphasic Reactions

The use of MeTHF in biphasic reactions is becoming more common in patents

Bayer Healthcare used MeTHF with toluene in a biphasic reaction of an acid chloride with an amine using NaHCO3 in synthesis of Rivaroxaban

Christian, T., WO2004060887.

MeTHF used in reductive amination of sulfite-aldehyde with triacetoxyborohydride, gives higher yield than NMP/cyclohexane

Ragan, J., Organic Process Research Development (2003), 7(2), 155–160

Reaction of dimethylcarbonate with an amine in MeTHF since high losses of product to the water phase were found with other solvents

Ripin, D., Organic Process Research Development (2005), 9(1), 51-56

Methf as solvent to remove BOC amine blocker with sodium butoxide in two phase water system

Ripin, D., US 20050020625

MeTHF used in two phase displacement reactions with acid chloride and allylbromide

Ripin, D., US 20050026940

MeTHF-A Good Replacement for Dichloromethane

- Dichloromethane and dichloroethane are polar solvents that are used extensively in pharma and agri synthesis but are highly regulated chemicals
- MeTHF can often be used as a direct replacement for these chlorinated solvents
- High reactivities are found when MeTHF is used in biphasic reactions[1]
- MeTHF provides added value because it is derived from renewable resources and is readily biodegradable

(1) David H. Brown Ripin, Synlett 2003, No. 15, p2353

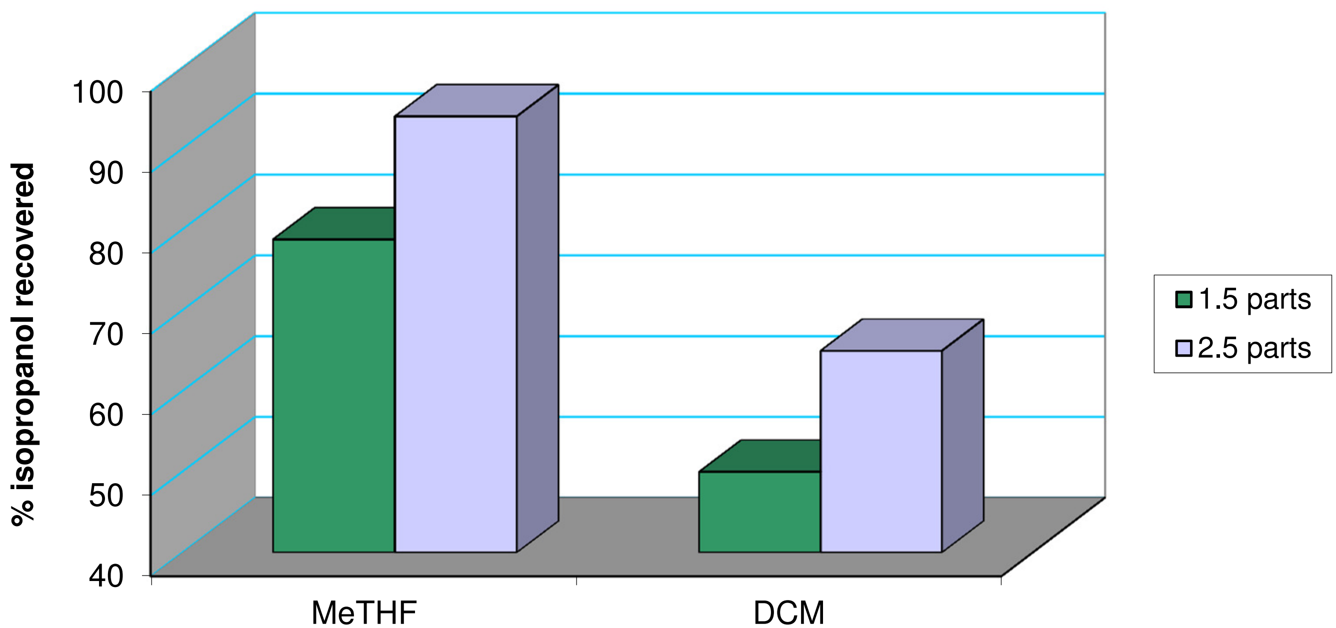
MeTHF and Dichloromethane Properties

- The low boiling point of dichloromethane (DCM) results in high losses to the atmosphere
- The high density of DCM means the water phase can not be directly decanted
- DCM can react with strong nucleophiles such as amines
- MeTHF gives clean organic-water phase separations
- The low water content in the DCM azeotrope means it is ineffective as a drying solvent

Property	**MeTHF**	**DCM**
Boiling point ºC	80	39.8
Density at 20 ºC	0.86	1.32
B.P. of azeotrope ºC	71	38
Wt % water in azeotrope	10.6	1.5

Extractions with MeTHF

- MeTHF removes water soluble compounds more efficiently than DCM



MeTHF Toxicity Tests

- NTP Genetic Toxicology study came back negative
- NTP Chemical Disposition tests showed MeTHF was quickly excreted
- NTP carcinogenicity study is on hold
- Listed as Class IV solvent by ICH
- Recent Merck study lists human daily exposure levels
  - Antonucci V; Coleman J; Ferry JB; Johnson N; Mathe M; Scott JP (2011). Toxicological Assessment of Tetrahydro-2-methylfuran and Cyclopentyl Methyl Ether in Support of Their Use in Pharmaceutical Chemical Process Development. American Chemical Society Publications. Org. Proc. Res. Dev., 15 (4), pp 939–941.