Aprotic, Polar and Hydrophobic Solvent
For Chemical Reactions and Extractions

MTHP

Chemical Name : 4-Methyltetrahydropyran
Synonym : 4-MeTHP
CAS No. : 4717-96-8

Kuraray
Isoprene chemicals Div.

2507-1

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Applications of MTHP

- ☐ Solvent for Chemical Reactions
- ☐ Solvent for Extractions
- ☐ Solvent for Polymerizations
- ☐ Solvent for Coatings

Chemical Reactions in MTHP

Organometallic Reactions	Reference #
Grignard	1), 4)
Lithiation of aryl bromide	6)
Anionic ortho-Fries rearrangement of carbamates with Lithium compound	6)
Alkylation of aldehyde with dialkyl zinc	6)
LAH Reduction	1)
Transition Metal Catalyzed Reactions	
Suzuki – Miyaura Coupling	7), 9)
Sonogashira-Hagiwara cross coupling	1), 7)
Palladium-Catalyzed three component coupling	8)
Nickel-Catalyzed Direct Arylation of Aliphatic Amides	2)
Platinum-Catalyzed cyclodimerization of alkynes	8)
Ruthenium-Catalyzed Hydrogenation of carbonyl compounds	5)
Olefin Metathesis	3), 7)
Substitute for halogenated solvent	
TEMPO catalyzed Oxidation	1), 4)
Dess-Martin Oxidation	1)
Swern Oxidation	1)
Epoxidation of allylic alcohol	1)
Amidation of Acid	1)
Ring-Closing-Metathesis	1)
Others	
Tin or Silicon radical-mediated addition and reduction	1)
Michael addition	1)
Wittig	1)
Dehydration condensation - Esterification and Acetalization	4)
Reduction	
Halogenation, Dehalogenation	
Protection & Deprotection for Peptide synthesis	10), 11)

See Slide 17 for the references

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Features of MTHP & Benefits with MTHP in Chemical reactions

Features

✓ Aprotic & Polar
✓ Hydrophobic

✓ B.P. is higher than THF
✓ Stable against Acids etc.
✓ Better Reaction yield depending on reaction

Benefits

- Good in balance of polarity/solvency and extraction yield
- Quick and clear phase separation with water
- No need to change the solvent throughout the entire process, reaction and washing/extraction
- Easy to recycle MTHP
- Less COD/BOD in wastewater
- Reduced CO_2 emission

- Higher in Reaction Rate
- Less by-products in Reaction & Quench.
  →Higher purity of target products
- Lower Raw Material Cost

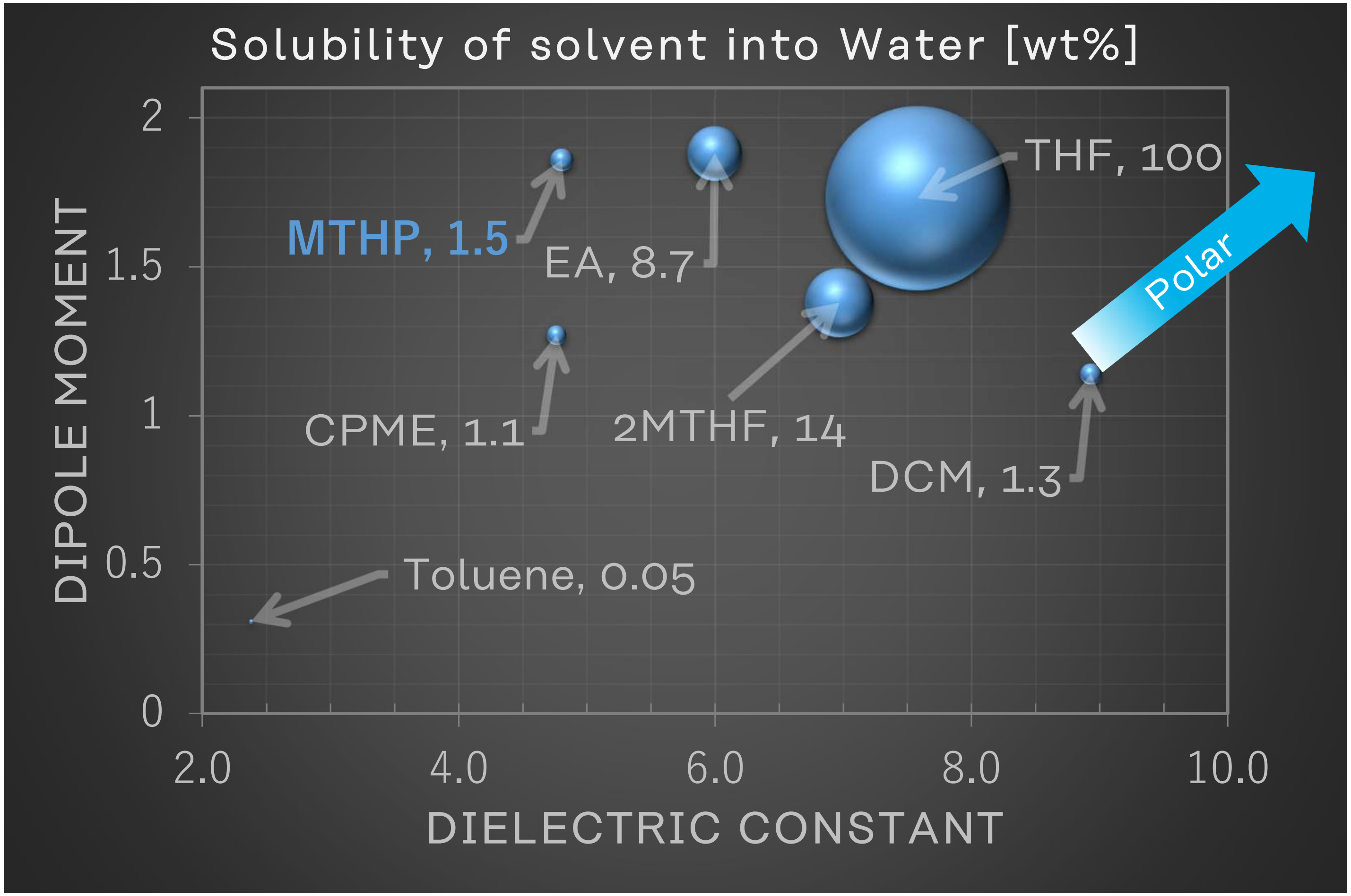
Physical Properties

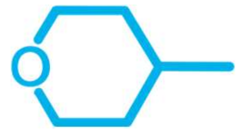
Solvents are arranged in order of increase of "Solubility of solvent into water".

	B.P. [°C]	M.P. [°C]	Density [20°C]	Viscosity [mPa·s]	F.P. [°C]	Solubility of solvent into Water [wt%]	Solubility of Water into Solvent [wt%]	Azeotrope with Water [°C], Water wt%	Log Pow
Toluene	111	-95	0.87	0.56	4.4	0.05	0.03	85, 20	2.73
CPME	106	-140	0.86	0.55	-1	1.1	0.3	83, 16	1.59
DCM	40	-97	1.32	0.44	---	1.3	0.2	40, 5	1.25
MTHP	105	-92	0.86	0.78	6.5	1.5	1.4	85, 19	1.90
EA	77	-84	0.90	0.43	-4	8.7	3.3	70, 8	0.73
2MTHF	80	-136	0.85	0.6	-11	14	4.4	71, 11	0.77
THF	65	-109	0.89	0.55	-15	∞	∞	64, 6	0.46
Water	100	0	1		---	∞	∞	---	---

DCM : Dichloromethane 2MTHF : 2-methyltetrahydrofuran
EA : Ethyl Acetate

Polarity and Compatibility with water





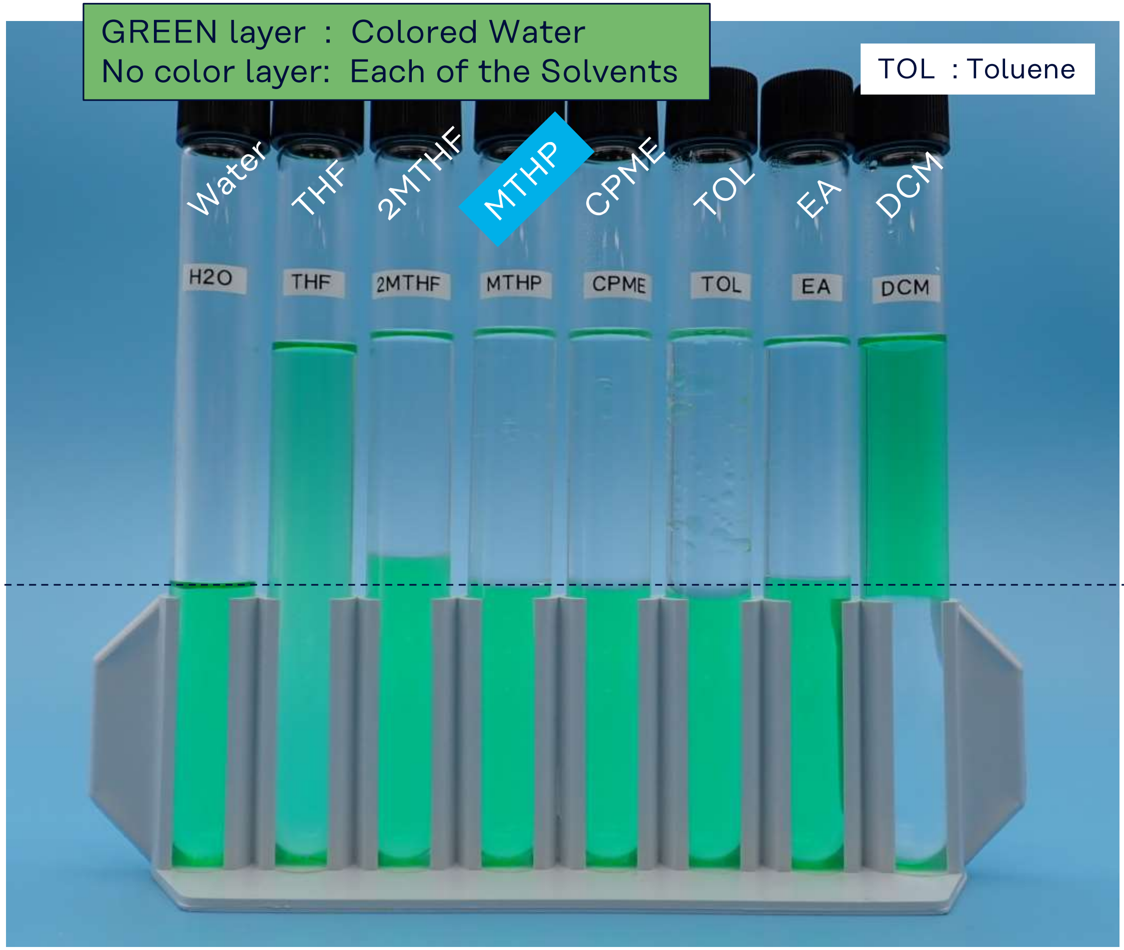
MTHP

Despite its high polarity,
MTHP also exhibits high hydrophobicity.

The unique property of MTHP
are presumed to be derived from
its six-membered cyclic ether structure.

Source : Shoji Kobayashi et al., Chem. Asian J. **2019**, 14, 3921 – 3937

Phase separation with water -1



<Test Method >
Added 15ml of water colored green to each test tube.

Added 15ml of each of different solvents to each test tube.

The test tubes were set to the holder, shaken together for about 20 sec. and left to stand for about 3 hours at 23°C / 73°F.

THF : No phase separation with water.

2MTHF and Ethyl Acetate:
The level of water layer was elevated.

MTHP : No change in the level of water layer.

Phase separation with water -2

Length of time after the shaking
for the emulsion layer to disappear

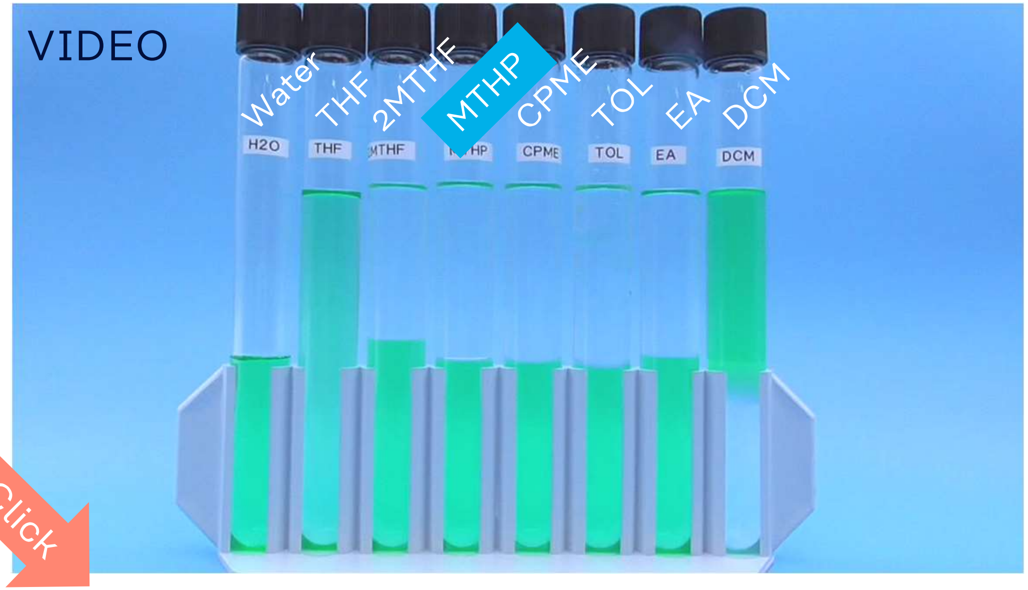
Solvent	Time [Seconds] 23°C No Salt	40°C No Salt	40°C With NaCl 20wt% to Water
THF	No Phase Separation with Water		
2MTHF	30	20	10
MTHP	5	2	<1
CPME	2		
Toluene	8		
Ethyl Acetate	16		
DCM	>60		

<Test Method >
Added 15ml of water colored green to each test tube.

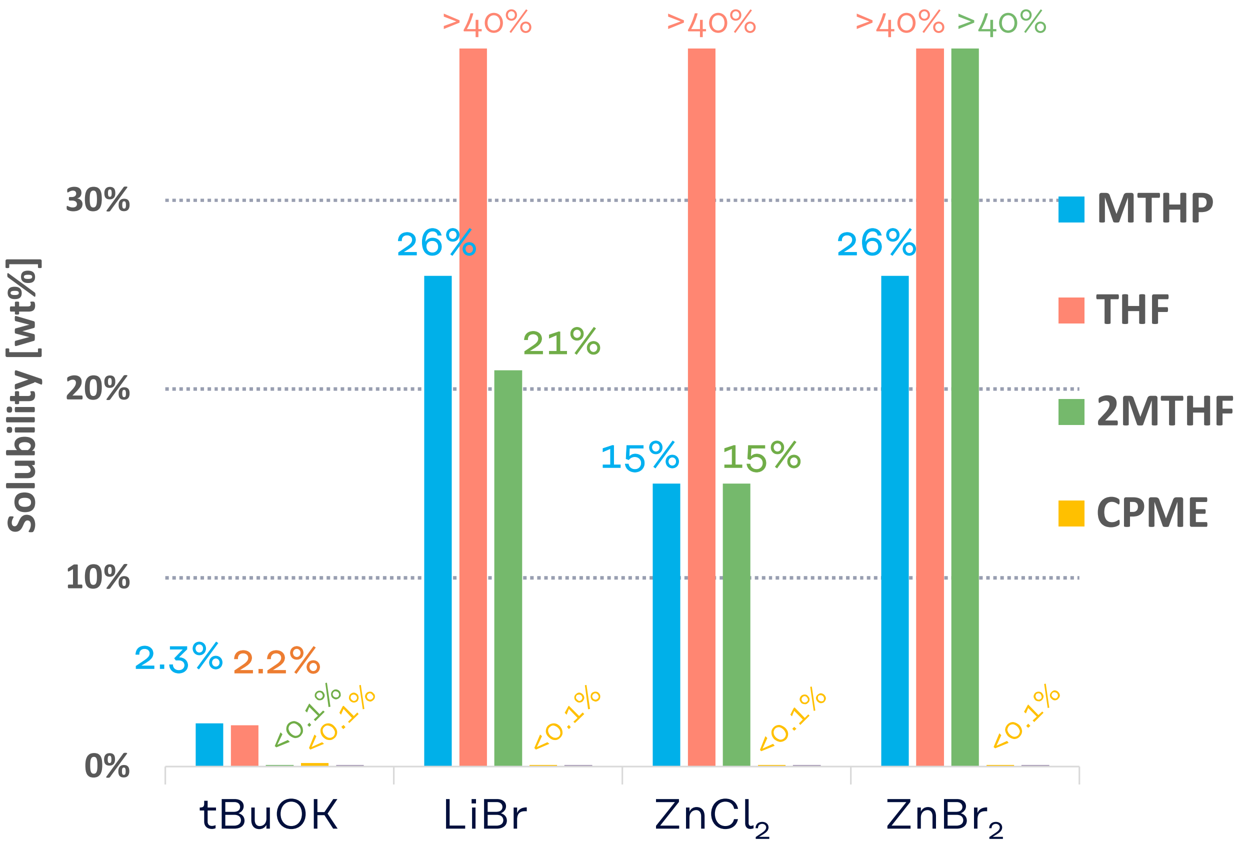
Added 15ml of each of different solvents to each test tube.

The test tubes were set to the holder, shaken together for about 20 sec. and left to stand at 23°C / 73°F.

The time was measured for the emulsion layer to disappear and For the interface level stabilize.



Solubility of Organic & Inorganic salts into each solvent at 22°C



Compatibility of the solvents
with Organic salts & Inorganic salts

THF >> 2MTHF ≒ MTHP > CPME

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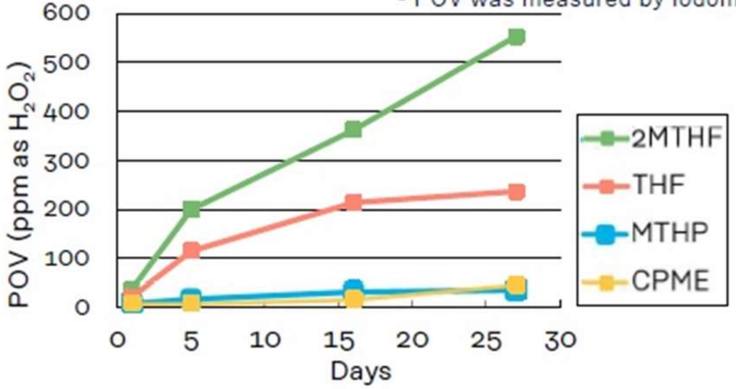
Stability of solvents

Autoxidation

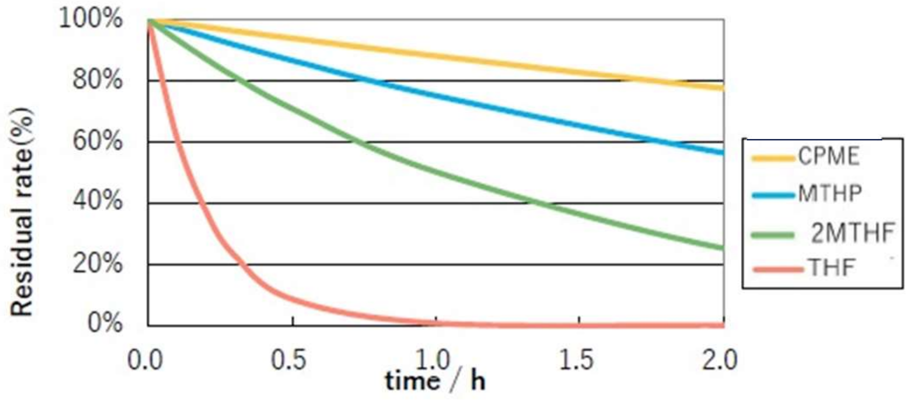
<Test condition>

- Under air at 25°C, without stabilizer.
- POV was measured by Iodometry method.



Residual rate of NBL(n-butyl lithium)

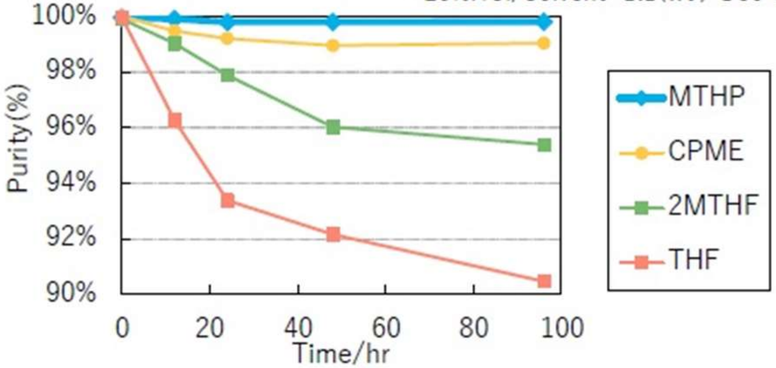
50℃



Acidic condition

<Test condition>

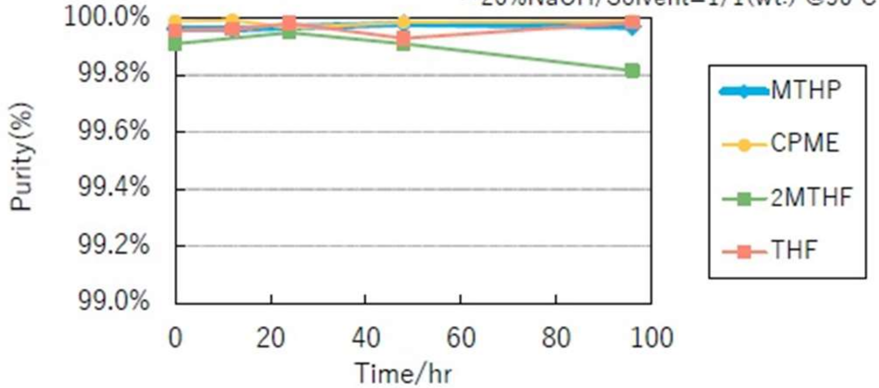
- 20%HCl/Solvent=1:1(wt.) @50°C



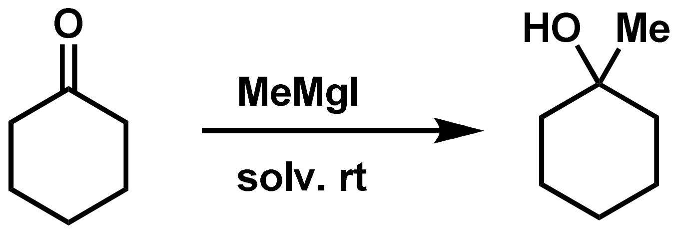
Basic condition

<Test condition>

- 20%NaOH/Solvent=1/1(wt.) @50°C



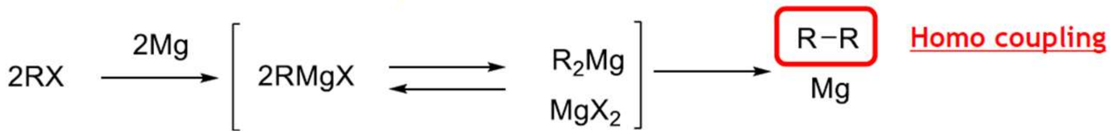
Chemical Reaction : Grignard



Solvent	Yield [%] In Org. layer	In Aqua. Layer	Total
THF	0.0	0.0	0.0
2MTHF	70.5	2,5	73.0
MTHP	83.9	0.9	84.9

MeCl(b.p.-24°C), MeBr(b.p.4°C) are not easy to handle because of their low b.p. though MeI(b.p.42°C) is high enough in b.p. to handle.

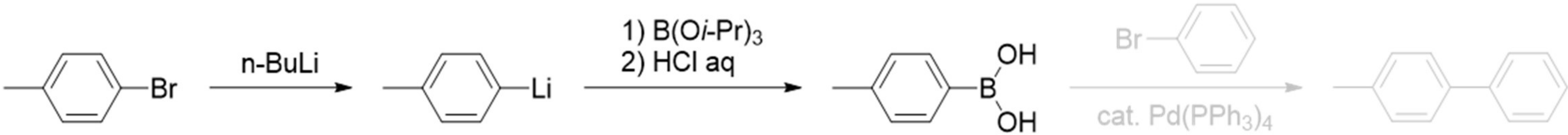
However, in the reaction of methyl iodide and magnesium in THF, the methyl Grignard reagent cannot be prepared in a high yield due to side reactions.

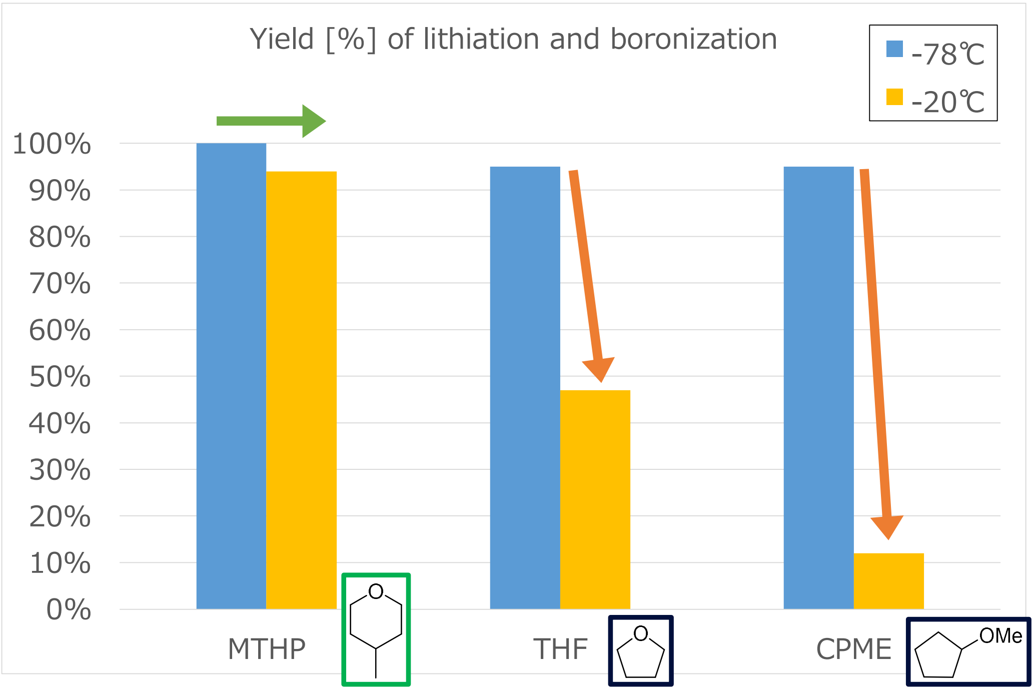


The side reaction was inhibited, and target compound was produced in good yield with MTHP.

Chemical Reaction : Lithiation and Boronization

- Preparation of Raw material for Suzuki-Miyaura coupling -

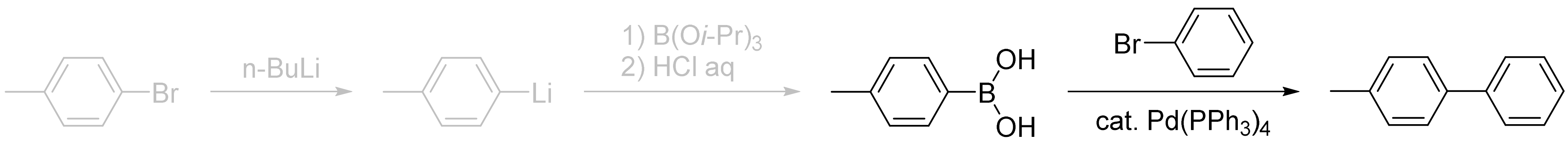




Yield of boron compound were good no matter which solvent is used when the reaction was conducted at -78°C, Which is too low to conduct on a commercial scale.

Only MTHP system had good yield of boronic acid When the reaction was conducted at – 20°C, Which is feasible temperature on a commercial scale.

Chemical Reaction : Suzuki – Miyaura Coupling



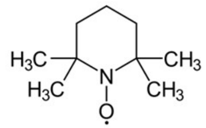
Solvent	Reaction Temp. * [℃]	Reaction time [hrs]	Yield Of coupling compounds
THF	62	8	70
2MTHF	70	4	82
MTHP	82	2	93
CPME	82	2	89
Toluene	84	2	88

* Azeotropic reflux with Water, a co-solvent

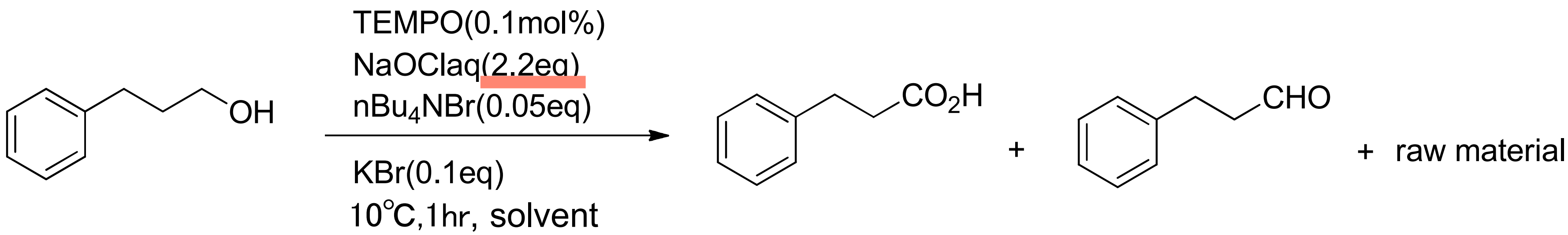
MTHP system was good
in both reaction rate and Yield
as Toluene system was,
which is a popular solvent for this reaction.

Chemical Reaction : TEMPO catalyzed Oxidation

- Substitute for DCM -



TEMPO



Solvent	Yield [%]			Notes
	Carboxylic Acid	Aldehyde	Alcohol Raw Material	
DCM	75	0.9	0.6	Low in Selectivity
CPME	64	15	13	Low in conversion
MTHP	89	8.5	0.9	

MTHP can be a substitute for DCM, Dichloromethane, which is a hazardous solvent.

General Information

- Product Name : MTHP
- CAS No. : 4717-96-8
- Package : Drum (Net 170kg)

Specifications

- Appearance :Colorless transparent
- Purity (%GC) : ≧ 99.0
- Water (ppm) : ≦ 200

* Contains Stabilizer : BHT 20ppm

Regulatory status

Government Inventory list	Status	Remarks
ENCS (Japan)	Present	
EU-REACH (Europe)	Registered	Registrant : Kuraray Europe GmbH (Importer) Tonnage Band 10-100 MT
TSCA (USA)	Registered	SNUR
IECSC (China)	Provisionally Registered	Tonnage Band : 1-10 MT
K-REACH (Korea)		OR registration Tonnage Band : 10-100 MT

Hazardous Information

	MTHP	THF	2MTHF
Pictogram			
Flammable liquids	Category 2	Category 2	Category 2
Skin corrosion/irritation	Category 1		Category 2
Serious eye damage/eye irritation	Category 1	Category 2	Category 1
Skin sensitization	Category 1		
Acute toxicity (oral)		Category 4	Category 4
Carcinogenicity		Category 2	
Specific target organ toxicity		Category 3	
Reference	SDS, Kuraray Dec 13, 2023	SDS, Thermo Fisher Scientific Dec 6, 2024	SDS, Thermo Fisher Scientific Sep 22, 2023

Dissolution of Resins in the different solvents

RESIN	MTHP	THF	2MTHF	CPME
ABS	**D**	**D**	**D**	**D**
Acrylic resin	**D**	**D**	**D**	**D**
Polystyrene	**D**	**D**	**D**	**D**
PVC	**D**	**D**	**D**	P
Polycarbonate	P	**D**	**D**	P
Fluoro rubber	P	P	**D**	P
SBR	P	P	**D**	P
Polyurethane	P	P	**D**	P
Butyl rubber	P	ND	P	ND
Nylon-6	ND	ND	ND	ND
Phenol resin	ND	ND	ND	ND
PP	ND	ND	ND	ND
HDPE	ND	ND	ND	ND
LDPE	ND	ND	ND	ND
Teflon	ND	ND	ND	ND

< Test Method >
Test panels of the resin were dipped into each solvent at 50°C for 7days. After the dipping, weight of the test panels were measured and compared with original one.

D : Dissolved completely

P : Dissolved 30% to less than 100%

ND : Dissolved 0% - 30%

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Note: The results may vary depending on the manufacturer and grade of the resin.

Reference

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3) Anna Kajetanowicz, Karol Grela et al., *ACS Sustainable Chem. Eng.*, **2020**, 8, 49, 18215-18223

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5) Yoichi Hoshimoto et al., *Tetrahedron Chem*, **2024**, 9, 100059

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10) Daniel Sejer Pedersen et al., *RSC Adv.*, **2020**, 10, 42457-42492

11) Hisata, Y., Washio, T., Takizawa, S. et al., *Nat Commun.,* **2024***,* 15, 3708

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