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Reviews

Cyclopentyl Methyl Ether as a New and Alternative Process Solvent

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Abstract:

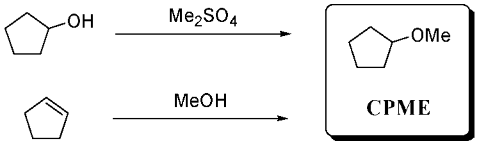
Cyclopentyl methyl ether (CPME) has become available in commercial quantities since November 2005 from Zeon Corporation with approval by the Toxic Substances Control Act (TSCA) and the European List of Notified Chemical Substances (ELINCS). A high boiling point (106 °C) and preferable characteristics such as low formation of peroxides, relative stability under acidic and basic conditions, formation of azeotropes with water coupled with a narrow explosion range render CPME an alternative to other ethereal solvents such as tetrahydrofuran (THF), 2-methyl tetrahydrofuran (2-MeTHF), dioxane (carcinogenic), and 1,2-dimethoxyethane (DME). Conventional drying is unnecessary for general organometallic reactions including Grignard reactions, enolate formation, Claisen condensation, general reductions, and Pd-based transformations.

Introduction

Despite many useful solvents available for routine organic reactions, it is not recommended to use certain organic solvents (halogenated solvents, low-boiling ethers, or hazardous solvents) for contemporary plant synthesis (or process development). In this context, the necessity for a new ethereal solvent has long existed in the synthetic community.

Typical ethereal solvents such as Et_2O, THF, DME, and dioxane have been widely used in synthesis. However, they have the drawbacks of low boiling point, easy peroxide (PO) formation, and solubility in water, thus resulting in inefficient recovery. To overcome these disadvantages, methyl *tert*-butyl ether (MTBE) has been used. MTBE, however, also has some demerits such as low solubility, instability under acidic conditions, and low flash point. 2-MeTHF has also been used as an alternative to THF. It also has the drawbacks of easy PO formation, insufficient recovery from water, instability under acidic conditions, and low flash point. In such a situation, cyclopentyl methyl ether (CPME) has proven to be quite useful as a process solvent for organic synthesis because it is free from those drawbacks that are associated with the classical ethereal solvents.[1]

Scheme 1. **Practical synthesis of CPME**



1. Practical Synthesis of CPME

CPME can be manufactured by the methylation of cyclopentanol or the addition of MeOH to readily available cyclopentene (Scheme 1).[2,3] The former process is a nucleophilic substitution which produces byproducts as wastes, whereas the latter (addition reaction) produces no apparent waste.

2. General Property of CPME

The general properties of CPME along with those of other ethereal solvents are summarized in Table 1.[3] The advantageous features of CPME are: (1) high hydrophobicity and thus very easy to dry, (2) suppressed formation of PO byproducts, (3) relatively stable under acidic and basic conditions, (4) low vaporization energy, and (5) narrow explosion range. All of these characters highlight CPME as an optional process solvent for future investigations, as detailed below.

2.1. Hydrophobicity and Facile Drying. Anhydrous ether solvents with long shelf lives are of particular interests for contemporary synthesis. When the recovery of the solvent is facile by usual extractive procedures, it becomes much more useful from the viewpoint of a green sustainable solvent. Water removal by MS-4A is summarized in Figure 1. After standing overnight, the moisture in THF cannot be reduced to less than 200 ppm. In comparison, the moisture in CPME is reduced to less than 100 ppm in 3 h and to 30 ppm or less uponstanding overnight. This indicates the advantage of CPME for anhydrous reactions.

2.2. Formation of Peroxide (PO). Safety concerns for ethereal solvents closely relate to its explosive nature arising

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(1) *CPME Catalog & Technical Data*; Zeon Corporation, Specialty Chemicals Division, 2006.

(2) Watanabe, K.; Goto, K. *Synth. Org. Chem., Jpn.* **2003**, *61*, 806.

(3) Watanabe, K.; Kogoshi, N.; Miki, H., *Fain Kemikaru* (*CMC*) **2006**, *35* (6), 14.

10.1021/op0680136 CCC: $37.00

Table 1. **Physical properties of CPME and other ethereal solvents**

	CPME^a	THF	2-MeTHF^a	MTBE^a	Et$_2$O	dioxane
density (20 °C)[g/cm^3]	0.86	0.89	0.85	0.74	0.71	1.03
vapor specific gravity (air = 1)	3.45	2.49	2.97	3.1	2.56	3.3
boiling point[°C]	106	65	80	55	34.6	101
melting point[°C]	<−140	−108.5	−136	−110	−116.3	11.8
viscosity (20 °C) [cP]	0.55	0.55	0.6(25 °C)	0.35	0.2448	1.31
surface tension (20 °C) [mN/m]	25.17	26.4	unknown	19.8	17.3	33.74
vaporization energy (bp) [kcal/kg]	69.2	98.1	89.7	81.7	86.08	98.6
specific heat (20 °C) [kcal/kg•K]	0.4346	0.469	unknown	0.51	0.5385	0.41
refractive index (20 °C)	1.4189	1.407	1.406	1.369	1.353	1.422
solubility parameter [cal/mL]	8.4	9.5	8.52	unknown	7.4	unknown
dielectric constant (25 °C)	4.76	7.58	7	2.6	4.197	2.227
dipole moment [*D*]	1.27 (calcd)	1.7	unknown	1.4	1.12	0.45
azeotropic point with water [°C]	83^b	64	71^c	52.9^d	34.2	87.8
solubility in water [g/100 g]	1.1 (23 °C)	∞	14	4.8	6.5	∞
solubility of water in the solvent [g/100 g]	0.3 (23 °C)	∞	4.4	1.4	1.2	∞
flash point [°C]	−1	−14.5	−11	−28	−45	12
ignition point [°C]	180	205	270	224	180∼90	180
Log Pow	1.59	0.47	unknown	0.94	0.89	−0.42
explosion range [vol %]	1.1−9.9	1.84−11.8	1.5−8.9	1.6−8.4	1.85−48	2−22

^{a} Azeotrope (wt %). ^{b} Composition = CPME: 83.7, H$_2$O: 16.3. ^{c} Composition = MeTHF: 89.4, H$_2$O: 10.6. ^{d} Composition = MTBE: 96.5%, H$_2$O: 3.5.

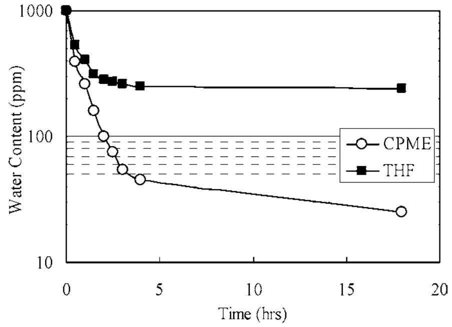

Figure 1. **Drying of CPME (in comparison with THF).**

from the concomitant PO generation. Accordingly, the formation of PO from CPME was carefully investigated and compared with those from other ethereal solvents, as shown in Figure 2.

In diisopropyl ether (IPE) and THF, quick formation of the corresponding PO in the absence of 2,6-di-*tert*-butyl-4-methyl phenol (BHT) was observed. The PO formation in CPME was very sluggish as was that of MTBE, which hardly generates PO under these conditions.

We speculate that in the autooxidation of ethers, the slowest rate-determining step is supposedly the formation of the ether radical from the original structure.[4] As the ether radical is more stable, more PO is accumulated during the storage. The ether radical of CPME is unstable compared to that of IPE. It is thus concluded that the peroxide formation from CPME is very slow compared to that of other ethers. For further safety reasons, however, CPME is commercially supplied with about 50 ppm BHT as a peroxide inhibitor, while the commercially available THF contains 250 ppm BHT.

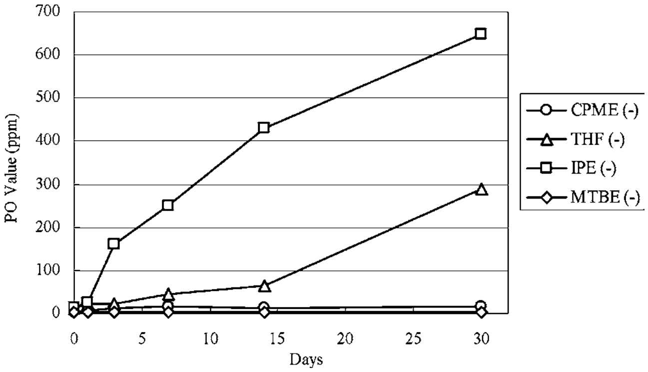

Figure 2. **Peroxide formation of ether solvents.**

3. Stability under Acidic and Basic Conditions

In general, many ethers are susceptible to acidic conditions. MTBE is cleaved into alcohols. THF is prone to ring opening followed by a facile polymerization. In contrast, CPME is relatively stable to acids in both homogeneous and heterogeneous conditions as detailed below.[5]

3.1. Under Homogeneous Acidic Conditions. In a typical homogeneous condition, 0.1 M camphorsulfonic acid (CSA) in CPME was heated at reflux for 8 h, revealing ∼0.2% of decomposition products that were easily identified as cyclopentene and methanol without any polymerization

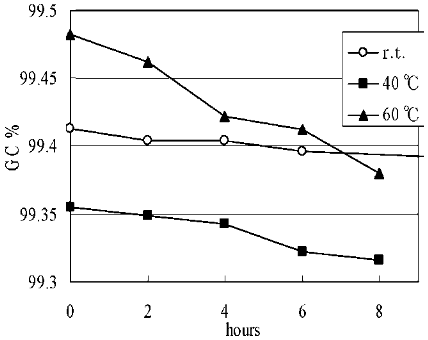

Figure 3. **Anhydrous HCl in CPME.**

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(4) Kubo, H.; Sakakibara, K.; Yoshizawa, K.; Watanabe, K.; Yuzuri, T. *The 85th Spring Meeting of Chemical Society of Japan*; **2005**.

(5) Torisawa, Y.; Aki, S.; Minamikawa, J. *Fain Kemikaru* (*CMC*), **2006**, *35* (10), 53.

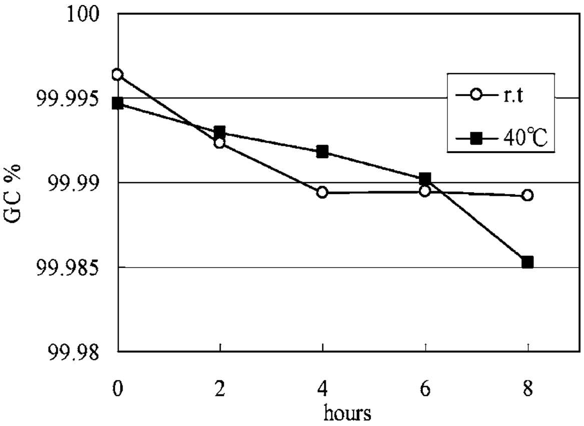


Figure 4. **Concentrated H_2SO_4 in CPME.**

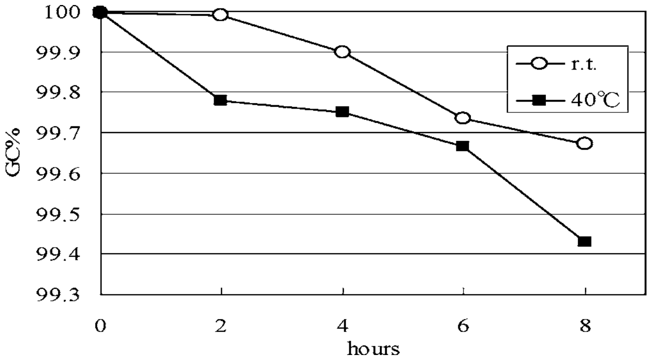


Figure 5. **62% H_2SO_4 in CPME.**

product. Therefore, CPME can be applied for dehydration reactions under acidic conditions, provided the two above byproducts do not interfere with the reaction.

The stability of CPME in anhydrous HCl is summarized in Figure 3 to show that CPME is almost intact with anhydrous HCl at room temperature. Consequently, up to 4 M HCl in CPME is now available from Watanabe Chemical Co., Ltd. Some utilities of this HCl solution are summarized under section 6.7. Additionally, CPME forms a homogeneous solution when mixed with 36% HCl in the form of oxonium complex.

The stability of CPME to concentrated H_2SO_4 is demonstrated in Figure 4. It shows only trace decomposition at room temperature. In Figure 5, very little decomposition was observed with 62% H_2SO_4 at 40 °C. Such acidic mixtures are often employed in the workup stage of some organometallic reactions such as Grignard- (as detailed later) and organolithium-based transformations.

3.2. Under Heterogeneous Acidic Conditions. In typical heterogeneous conditions, Figure 6, CPME was heated with 18% HCl at 100 °C for 8 h. Acidic decomposition was not a major problem (a very sluggish reaction) because of an oil−water separation (two-phase) mixture.

3.3. Under Basic Conditions. Ether solvents are very good partners for strongly basic organometallic reagents such as organolithium, organomagnesium, and organozinc reagents; all of them are very useful synthetic tools. Half-lives of *n*-BuLi in various ethereal solvents (THF, ether, CPME) were compared to ascertain their utility under basic conditions. As often noted, *n*-BuLi cannot be compatible with THF at higher temperature because of the undesired deprotonation followed by ring opening. On the contrary, *n*-BuLi in CPME has sufficient half-life even at 40 °C (Figure 7). Thus, CPME exhibits superior stability at ambient temperature when compared to THF and is stable like ethyl ether.

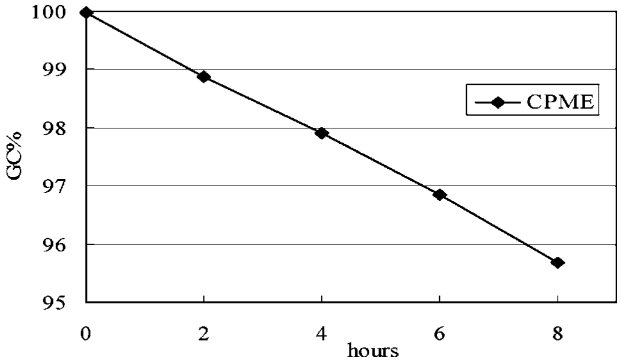


Figure 6. **18% HCl in CPME.**

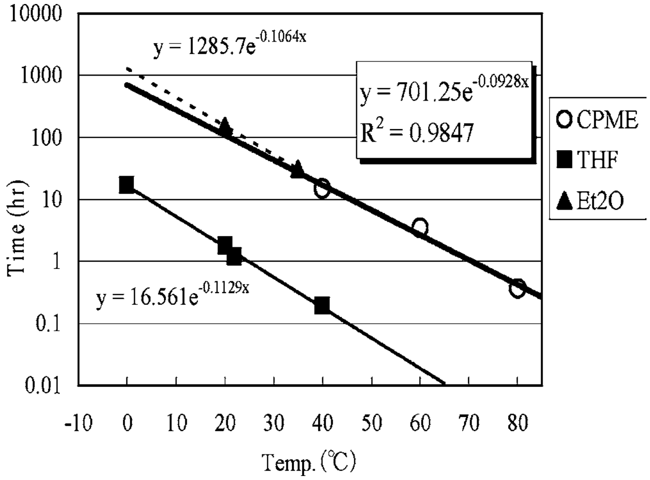


Figure 7. **Half-lives of *n*-BuLi in various ethers.**

4. Low Heat Energy for Vaporization

As already shown in Table 1, CPME has the lowest evaporation energy, and thus, facile recovery through distillation can be attained because of its high boiling point which is similar to that of toluene. These are obviously advantageous for its recovery followed by recycle in a plant-scale application.

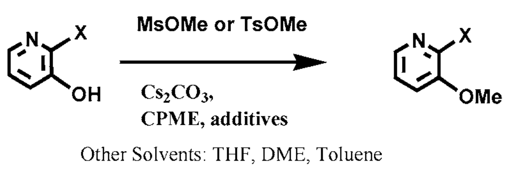
5. Narrow Explosion Range

Table 1 also indicates a relatively narrow explosion range of CPME, and this shows a facile handling during many conventional organic transformations as detailed in the following sections.

6. Application in Synthesis

CPME has attracted many synthetic chemists in challenges from the bench study to plant-scale application. In this section, recent applications and comments in the literature are collected. CPME can thus supplant THF, DME, or other ethereal solvents as a reaction medium under basic conditions, but furthermore, CPME can participate as a crucial extractive tool. Sometimes, it can assist the isolation and crystallization of the products. Some examples are listed in recent reviews by the authors as are patents by the company

Scheme 2. *O*-Methylation of 3-hydroxypyridine



X	additive (solvent)	Yield
Cl	DMF	80
Br	DMF	70
COOMe	DMF or DMI	60

researchers. In this article, however, useful transformations are extracted from the recent events with polar substrates, as often encountered in the research of drug substances.

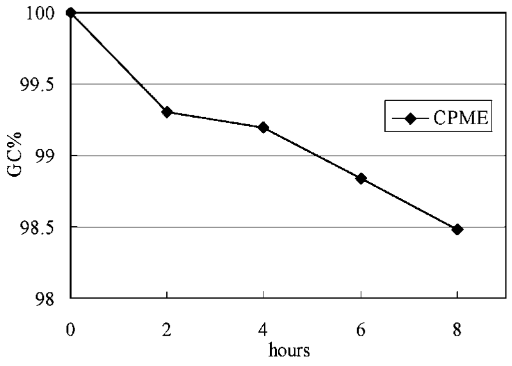
6.1. Reactions with Alkylating Agents. Among others, general conditions for classical nucleophilic substitution by heteroatoms (alcohols and amines) are illustrative and summarized in the following schemes. It should be noted that some *polar additives* are necessary for satisfactory conversions in CPME; otherwise, incomplete reactions or unsuccessful results were obtained in our hands. Useful additives for alkylation (or acylation) reaction in the CPME are worthy of comments.

In the presence of strong bases (NaH, NaOMe, NaO^{t}Bu, MHMDS: M = Li, Na, K) as well as mild inorganic bases (K_2CO_3, Cs_2CO_3, CsOH), we have utilized a system of CPME plus amide cosolvent (DMF, DMA, NMP, DMI) for a facile *O*-methylation (*O*-alkylation) (Scheme 2). The system often resulted in a cleaner mixture and easy separation of the products.[6]

As for methylating agents, the utility of methyl mesylate (Me-OMs) was investigated, rather than methyl tosylate (Me-OTs). We sometimes prepared Me-OMs from MsOH and MeOH under conventional dehydrating conditions (P_2O_5) followed by distillation. This methylating agent can be applied for the synthesis of CPME itself.

With methyl triflate (Me-OTf), another powerful methylating agent, the decomposition of CPME is also sluggish at room temperature as indicated in Scheme 3. Thus, methylation with Me-OTf in CPME will be an additional option for alcohol methylation. Another utility of Me-OTf in CPME is noted later in relation to Imamoto reduction conditions (Me-OTf and LAH in CPME) for phosphine oxides.[7]

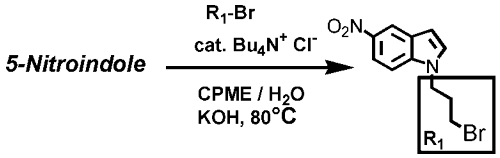
Scheme 3. Stability of CPME toward 10% TfOMe



In addition to the amide solvents, some amine additives such as DBU, DABCO, and tris-[2-(2-methoxyethoxy)ethyl]amine (TDA-1) are useful for alkylation and acylation in CPME which, after the reaction is completed, can be removed through extractive isolation from the products quite easily. In the related study, it was found that CPME was applicable to some phase transfer catalyst (PTC) conditions. During these alkylation reactions, DBU, DABCO, and TDA-1 can form quaternary ammonium salts (with alkylating agents) and thus work as PTC does. It should be noted that in the CPME−H_2O mixture some reactions were faster (and cleaner) than in toluene−H_2O system.

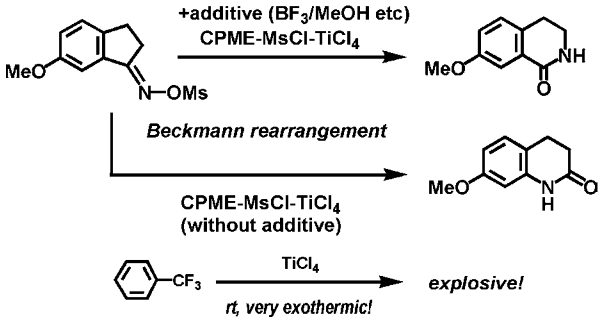
PTC alkylation conditions are very useful for heteroatom manipulation, because of its high regioselectivity (among many reaction centers) and thus facile isolation of the single desired product. Scheme 4 demonstrates regioselective *N*-alkylation of indoles under mild conditions (X = Cl or Br).[8] In these alkylations, addition of amines (without the addition of ammonium salt) is also effective, because they can be transformed into ammonium salts under reaction conditions. Such two-phase PTC system (PTC/CPME/H_2O) is easily applicable to typical Pd-based transformations such as Heck, Suzuki and related reactions, as mentioned later.

Scheme 4. PTC alkylation



6.2. Lewis Acid-Mediated Reactions. *6.2.1. Beckmann Rearrangement.* Improvement of the classical Beckmann rearrangement (BR) highlights two important aspects: (1) new catalyst for regiocontrolled rearrangement and (2) waste and *solvent optimization*. In this context, we refer to the solvent systems for BR and other Lewis acid transformations. *Benzotrifluoride* (BTF, Scheme 5) was reported to behave as a useful substitute for CH_2Cl_2 in some classical synthetic transformations.[9] It is however, *not* very often employed in transformations with Lewis acid catalysts such as $AlCl_3$ and $TiCl_4$. We attempted the BR of indanone oxime with TiX_4

Scheme 5. Beckmann rearrangement of indanones



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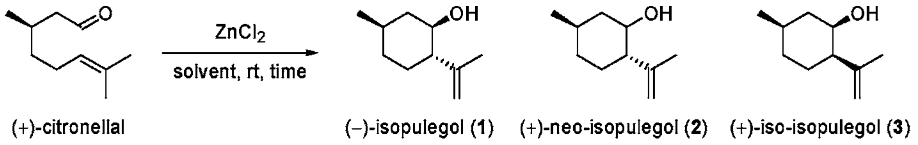
(6) Torisawa, Y.; Fujita, N.; Furuta, T.; Aki, S.; Minamikawa, J. *Summer Symposium of the Japanese Society for Process Chemistry*; **2005**.

(7) Shimada, T.; Suda, M.; Nagano, T; Kakiuchi, K. *J. Org. Chem.* **2005**, *70*, 10178.

Scheme 6. **Intramolecular carbonyl-ene reaction**



solvent	phase	time (hr)	yield (%)	product (**1**:**2**:**3**)	note
CPME	heterogeneous	18	**60**	85:11:4	
THF	homogeneous	18	trace	-	recovery of citronellal : 93 %
toluene	heterogeneous	10	23	86:10:4	

in BTF, which resulted in exothermic reactions with decomposition. CPME, however, can participate in the selective conversion to the two quinolinone products, as shown in Scheme 5, demonstrating the two Beckmann pathways to the carbostyril and its isomeric isocarbostyril by the difference in the additives.[10] Usually, these transformations can be achieved with halogenated solvents such as ethylene dichloride (EDC) and dichloromethane (CH_2Cl_2), to exert enough Lewis-acid activity. Thus, CPME is a rare ether solvent to be used in Beckmann rearrangements.

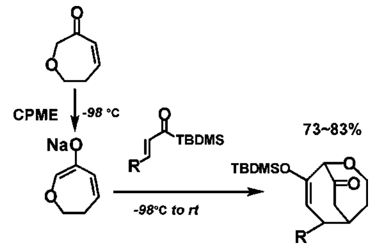
CPME may substitute for CH_2Cl_2 or EDC in some (not all) $TiCl_4$-based transformations. Through these experiments, *BTF offered almost no synthetic utility for Lewis acid-mediated reactions*, as it spontaneously reacted with $TiCl_4$ at room temperature in an explosive manner, while CPME can exert its unique stability towards mild Lewis-acid catalysts such as $TiCl_4$ and $TiBr_4$.

6.2.2. Friedel−Crafts Type Reactions. Friedel−Crafts (FC) reaction also requires Lewis-acid catalyst and halogenated solvents. In order to improve and facilitate this process in view of atom-economical green chemistry, new acid catalysts have evolved, and metal triflates are one of them. *Bismuth triflate* [Bi(OTf)$_3$] is one of the emerging catalysts for FC reactions, and we have surveyed its utility in the field of process research.[11] It is, however, difficult to achieve very efficient (i.e., regiocontrolled) FC acylation with substrates containing heteroatoms.

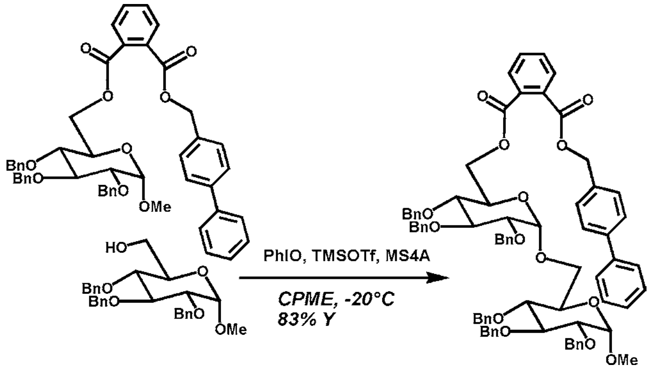
Nonetheless, we studied a few transformations using the combination CPME−Bi(OTf)$_3$. The separation of the catalyst (i.e., bismuth wastes) at the workup stage was feasible by simple filtration. In this system, a relatively high temperature can be applied for the triflate reaction. Because CPME can attain very anhydrous conditions, it is useful to keep anhydrous reaction media for metal triflates or prevent from decaying. It is further apparent that CPME cannot be compatible with a strong Lewis-acid catalyst ($AlCl_3$). As far as we surveyed, some Ti Lewis acids are recommendable with CPME.

The FC-type reaction with Zn Lewis acid is also feasible, but in these reactions substrates are restricted to those containing favorable substituents for FC. It is, however, emphasized that mild Lewis acid-catalyzed transformations are possible as in the case of the ene reaction of acid-promoted cycloaddition reactions as shown in the next section.

Scheme 7. **[3 + 4] Annulation reaction**



Scheme 8. **Selective glycosylation**



6.2.3. Ene-Type and Cycloaddition Reactions. Mild reaction conditions are preferable for typical cycloaddition and related reactions, which can be carried out in CPME as a solvent. Onaka's group has revealed the utility of CPME in an intramolecular carbonyl-ene reaction of citronellal using *zinc chloride*, which was conducted in various ethereal solvents.[12] It was shown that the reaction did not occur in THF, whereas the best results were obtained in CPME as shown in Scheme 6.

Takeda's group demonstrated new [3 + 4] cycloaddition reactions in CPME, which revealed the unique solvent effect of CPME in the formation of reactive enolate derivatives (Scheme 7).[13] This result indicates that CPME can keep the unstable enolate participating in the unusual cycloaddition reaction. This study also revealed that the utility of CPME is unfortunately limited in other synthetic sequences.

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(8) Torisawa, Y., *Synth. Org. Chem. Jpn.* **2003**, *61*, 454.

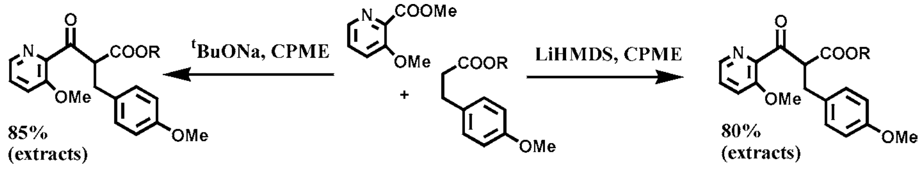
(9) Ogawa, A.; Curran, D. P., *J. Org. Chem.* **1997**, *62*, 450.

(10) Torisawa, Y.; et al., *Bioorg. Med. Chem. Lett.* **2006**, doi:10.1016/j.bmcl.2006.10.022.

(11) Torisawa, Y.; Nishi, T.; Minamikawa, J.-i. *Org. Process Res. Dev.* **2001**, *5*, 84 and references cited therein.

(12) Onaka, M. Private communication.

Scheme 9. **Claisen−Schmidt condensation**



Other Bases: NaH, KHMDS
Other Solvents: THF, DME, Toluene, EtOH

Kitamura's group reported unique benzyne generation and trapping in CPME media, which can be effected comparably in THF, toluene, and CH_2Cl_2, starting from hypervalent iodine precursors.[14]

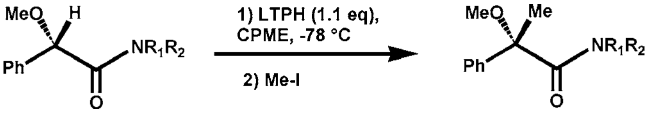
6.2.4. Glycosylation Reaction. Fukase's group has disclosed *almost complete* α*-selective glycosylation*, which was effected by virtue of the solvent effect of CPME and the long-range assistance of bulky protective groups at −20 °C (Scheme 8).[15] High α-selectivity was obtained by the use of CPME in comparison with conventional diethyl ether. This paper obviously indicates further potential of CPME in the related glycosylation, because a variety of promoters are developed with the combination of a particular solvent system. In the manipulation of these sugar derivatives, low solvent polarity of CPME may have no significant disadvantages.

6.3. Reactions Using Basic or Organometallic Reagents. *6.3.1. Claisen Condensation.* Aldol and Claisen condensations are typical transformations under basic media, thus compatible with CPME. A classical example of Claisen−Schmidt condensation with a pyridine derivative is feasible in CPME with the proper base catalysis as shown in Scheme 9,[6] demonstrating a facile entry into the 2-acylpyridine skeleton from 2-picolinate esters. Among many methods available for the acylpyridine derivatives, these are the most simple combinations of organometallic reagents. These base-catalyzed reactions clearly indicate the usefulness of CPME for general condensation reactions.

It also should be noted here that the desired product can be isolated by the simple extraction from CPME, leaving the polar starting materials (starting picolinate and acids) in aqueous solution. Thus, CPME makes the workup process very easy in operation.

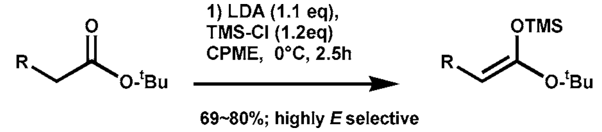
6.3.2. Enolate Chemistry. From the survey of recent reports, an interesting solvent effect of CPME emerged during enolate formation and further reactions. While many ethereal solvents are involved in conventional enolate formation with a strong base, CPME has demonstrated its unique participation as described in the following examples. Kawabata's group reported an asymmetric methylation (chirality transfer reaction; Scheme 10), which might be manifested through the formation of a rigid enolate from *O*-methyl mandelic acid in the medium of CPME. Aggregated enolate formation is controlled by the interference of CPME with base or enolate itself.[16]

Scheme 10. **Chirality transfer methylation**



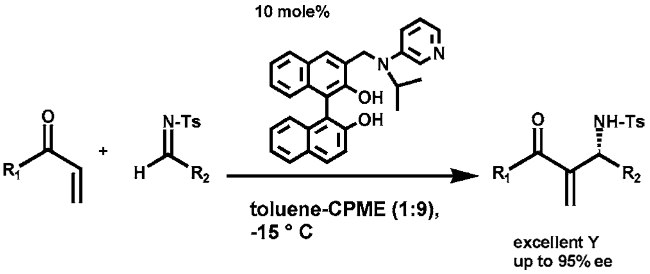
Tanabe's group also described a controlled formation of TMS enolate of the esters (i.e., ketene silylacetals) by utilizing CPME as key solvent component. Enolate formation is again controlled in the presence of CPME (Scheme 11).[17]

Scheme 11. **Selective KSA formation**



Sasai's group disclosed asymmetric aza-Morita−Baylis−Hilman reaction with the new BINOL catalyst, which can produce an effective asymmetric organization of the substrates under the influence of CPME and toluene medium (Scheme 12).[18]

Scheme 12. **Asymmetric aza-Morita−Baylis−Hillman reaction**



6.3.3. Grignard and Related Conversions. Because CPME can maintain anhydrous conditions without any particular precautions, it is a preferred solvent for Grignard-type reactions. In fact, a number of applications have been investigated, and some of them are already in the literature or patents. Here we disclose some attempts with pyridine derivatives, because these compounds are useful intermediates for antiinflamatory drug substances. Grignard additions to nitriles are effective entries to carbonyls (acyl heterocycles), and active cyanopyridines are very good substrates for such conversions, as illustrated in Scheme 13.[6]

Useful information was obtained whenthe Mg-ate complex in CPME was treated with free acid derivatives,

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(13) Sawada, Y.; Sasaki, M.; Takeda, K. *Org. Lett.* **2004**, *6*, 2277.

(14) Kitamura, T.; Abe, T.; Fujiwara, Y.; Yamaji, T. *Synthesis* **2003**, 213.

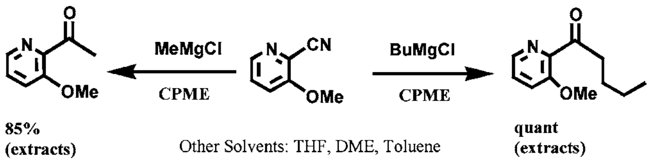
(15) Tokimoto, H.; Fujimoto, Y.; Fukase, K.; Kusumoto, S. *Tetrahedron: Asymmetry* **2005**, *16*, 441.

(16) Kawabata, T.; Ozturk, O.; Chen, J.; Fuji, K. *Chem. Commun.* **2003**, 162.

(17) Okabayashi, T.; Iida, K.; Takai, K.; Tanabe, Y. *Summer Symposium of the Japanese Society for Process Chemistry*; **2005**.

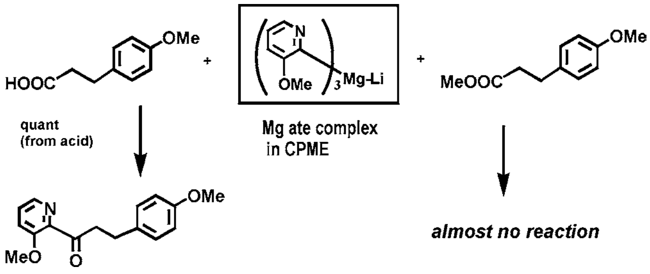
(18) Matsui, K.; Tanaka, K.; Horii, A.; Takizawa, S.; Sasai, H. *Tetrahedron: Asymmetry* **2006**, *17*, 578; Matsui, K.; Tanaka, K.; Horii, A.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680.

Scheme 13. **Grignard addition reactions in CPME**



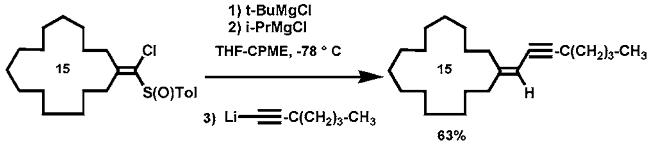
resulting in a new conversion to acylpyridine from the free acid as shown in Scheme 14.

Scheme 14. **New Grignard addition reactions in CPME**



Application of CPME in carbenoid chemistry has been noted by Satoh's group, who developed an unusual vinylic addition via magnesium alkylidene carbenoids (Scheme 15).[19]

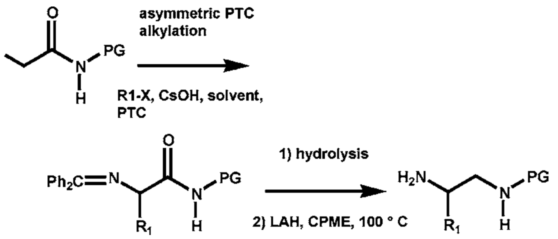
Scheme 15. **Carbenoid reaction**



CPME can successfully participate in the reaction as in THF, but often, THF was proved to be a solvent of choice. Further experimentation will accumulate useful knowledge about the selection of ether solvents.

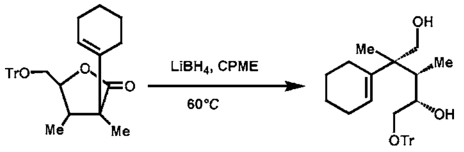
6.4. Oxidation and Reduction Conditions. Useful applications of CPME for reduction reactions are disclosed in recent literatures, while not many examples are found for oxidation in CPME. In an interesting application, lithium aluminum hydride ($LiAlH_4$, LAH) reduction of chiral amides in CPME has often been utilized by Maruoka's group to obtain vicinal diamines efficiently (Scheme 16).[20] While this LAH protocol seems to be very effective at small scales, further precaution to LAH conditions should be taken in case of a large-scale operation at high temperature.

Scheme 16. **LAH reduction**



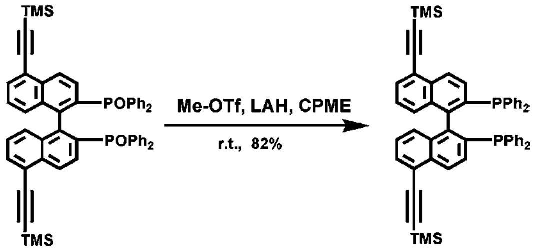
Borohydride reduction in CPME was surveyed by Tatsuta's group, demonstrating interesting reductive cleavage of a sugar lactone into diol as shown in Scheme 17.[1]

Scheme 17. **LBH reduction**



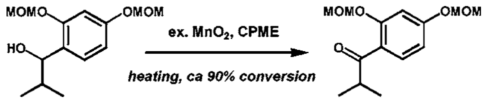
Shimada's group also mentioned the Imamoto reduction[21] in CPME, which was carried out at room temperature to reduce phosphine oxides chemoselectively into phosphines by the combination of LAH and MeOTf (Scheme 18).[7]

Scheme 18. **Modified LAH reduction**



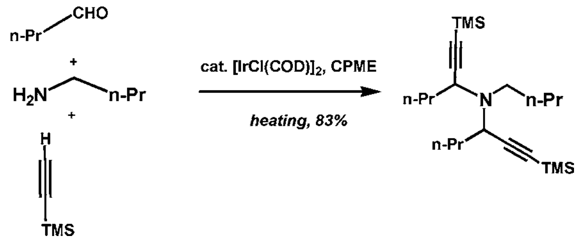
MnO_2 oxidation in CPME has attempted by Tatsuta's group. However, a rather slow oxidation was observed (Scheme 19).[1]

Scheme 19. **MnO_2 oxidation to aldehyde**

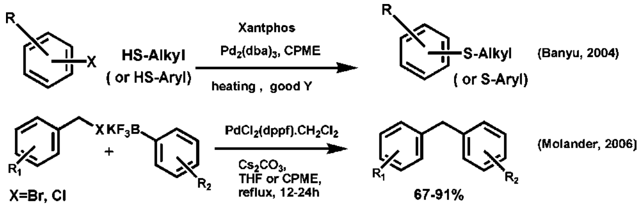


6.5. Reactions with Transition Metal Catalysts. Ethereal solvents are good partners for transformations with transition metal catalysts (Pd, Ni, Rh, Ir). Scattered examples are found in the literature. In particular, high reaction temperature is preferable for such catalytic reactions, and anhydrous conditions are useful for multicomponent couplings, as demonstrated by Ishii's group in Scheme 20.[22]As in the report from Mino's group, CPME can also take part in the Pd-catalyzed asymmetric allylic alkylation in the same manner as for other ethers (THF) and toluene.[23] It is obvious that the two-phase PTC system (PTC/CPME/H_2O) mentioned earlier is easily

Scheme 20. **Multicomponent coupling**



Scheme 21. **Some Pd-based transformations**



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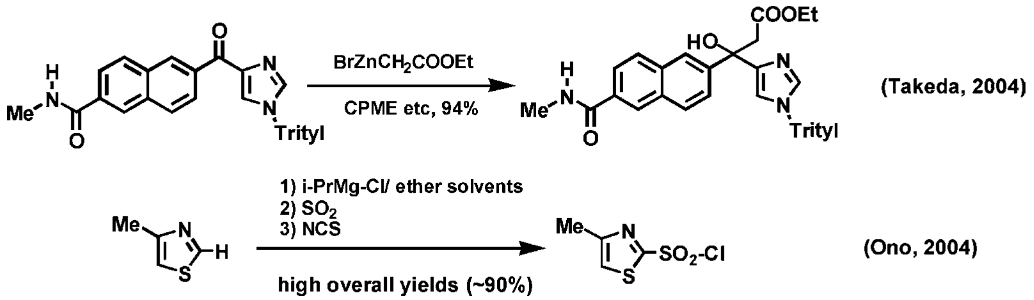
(19) Watanabe, M.; Nakamura, M.; Satoh, T. *Tetrahedron* **2005**, *61*, 4409.

(20) Ooi, T.; Takeuchi, M.; Kato, D.; Uematsu, U.; Tayama, E.; Sakai, D.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 5073.

Scheme 22. **Patented transformations**



applicable to typical Pd-based transformations such as Heck, Suzuki, and related reactions.

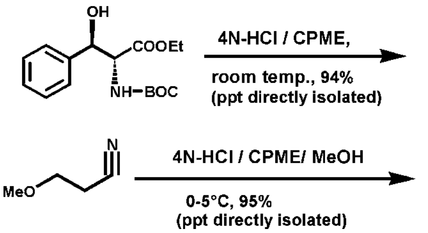
Pd-catalyzed couplings of aryl halides with heteroatom functionality (amine, alcohol, and thiol) are, of course, feasible in CPME. In the example reported by the Banyu group in Scheme 21, CPME supplanted for conventional ethereal solvents such as THF and dioxane.[24] A high boiling point of CPME is capable of making such coupling reactions reach completion within short time.

Molander's group reported the modified Suzuki-type coupling with fluoroborates. CPME was successfully employed as the solvent. The unique property of CPME was manifested in this coupling, presumably through a strong coordination to the metal center. High boiling points and easy workup made the overall reaction sequence very effective and convenient (Scheme 21).[25]

6.6. Selected Patented Transformations. Classical transformations utilized in the pharmaceutical company have been renewed by the use of CMPE as a solvent, as seen in patent applications. Two examples are shown in Scheme 22, which demonstrated the utility of CPME in the manipulation of the heterocyclic intermediates. A note should be added here that mixed ether solvents were employed in the transformations.[26,27]

6.7. Reactions with 4 N HCl in CPME. Commercially available 4 N HCl in CPME is useful in the conventional transformations, particularly in the isolation of the precipitated products as shown in Scheme 23.[28]

Scheme 23. **Reactions with 4N-HCl/CPME**



Concluding Remarks

It is now obvious that CPME is compatible with both classical and modern reaction conditions, emerging therefore as a new ethereal solvent for both bench-size and plant-scale applications with particular emphasis on the easy handling (low PO formation and high boiling point) and future prospects for attaining green sustainable processes (facile recovery and recycle). Comparison with other solvents will further throw light on the advantageous profile.

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(24) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587.
(25) Molander, G. A.; Elia, M. D. *J. Org. Chem.* **2006**, *71*, 9198.
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