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Cyclopentyl Methyl Ether: An Elective Ecofriendly Ethereal Solvent in Classical and Modern Organic Chemistry

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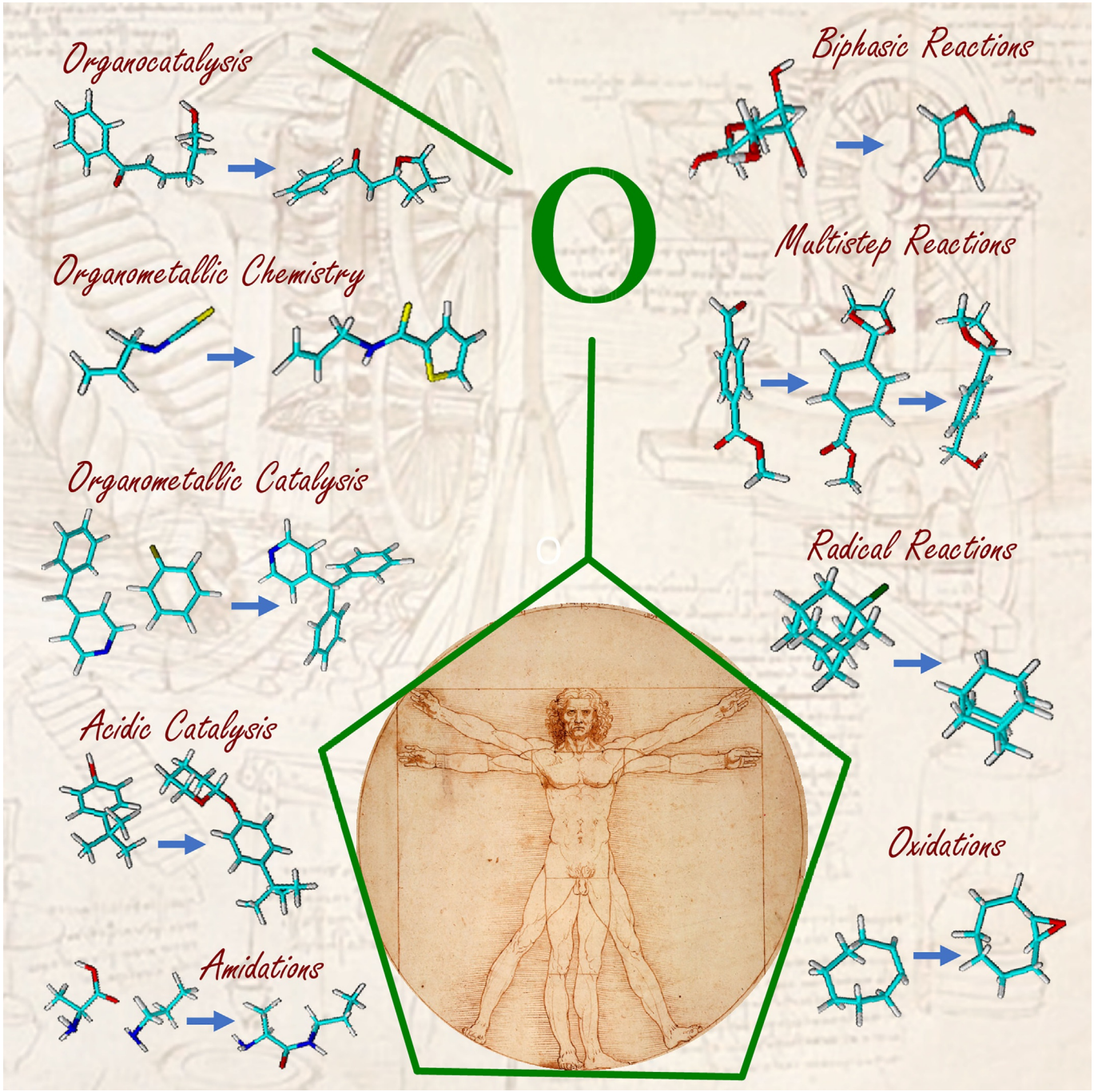
Dedicated to Professor Wolfgang Holzer on the occasion of his 62nd birthday



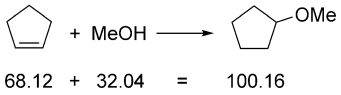
Solvents represent one of the major contributions to the environmental impact of fine-chemical synthesis. As a result, the use of environmentally friendly solvents in widely employed reactions is a challenge of vast real interest in contemporary organic chemistry. Within this Review, a great variety of examples showing how cyclopentyl methyl ether has been established as particularly useful for this purpose are reported. Indeed, its low toxicity, high boiling point, low melting point, hydrophobicity, chemical stability towards a wide range of conditions, exceptional stability towards the abstraction of hydrogen atoms, relatively low latent heat of vaporization, and the ease with which it can be recovered and recycled enable its successful employment as a solvent in a wide range of synthetic applications, including organometallic chemistry, catalysis, biphasic reactions, oxidations, and radical reactions.

1. Introduction

The use and disposal of solvents represents a major contribution to the environmental impact of fine-chemical industries. Indeed, the manufacture of active pharmaceutical ingredients (APIs) involves the use of more than 80% of solvents (organic solvents >50%; H_2O >30%),[1] employing about 60% of the overall energy to this aim and accounting for 50% of total post-treatment gas emissions.[2] Therefore, to meet environmental and economic goals simultaneously,[3] great attention is nowadays dedicated to the replacement of hazardous solvents with less dangerous ones, as well as to their recovery and reuse.[4] From this point of view, it is worth mentioning the great attention dedicated to the selection of solvents within the guidelines of the environmentally sustainable best practices in medicinal chemistry developed by the American Chemical Society's Green Chemistry Institute Pharmaceutical Roundtable (ACS GCI PR)[5] as well as by the Chemical Manufacturing Methods for the 21st Century Pharmaceuticals Industries (CHEM21), a European public–private partnership dedicated to the development of manufacturing sustainable pharmaceuticals.[6]

It is, however, worth noting that although solvent-selection guides[4b–d,5,6] represent a very useful primary source of information, the proper choice of a solvent requires up-to-date knowledge of literature data showing how its physical chemical properties match the requirements to set up a given reaction appropriately.

In 2007, a highly cited review by Watanabe et al. highlighted the most important physical–chemical properties of cyclopentyl methyl ether (CPME),[7] industrially produced through a 100% atom-economical reaction[7,8] by Zeon Corporation[8b] (Scheme 1), and the authors simultaneously reported its successful employment as a solvent in a variety of organic reactions.



Scheme 1. Zeon's process for the production of CPME.

Accordingly, CPME is characterized by a high boiling point (bp) and a low melting point (mp), as well as by hydrophobicity, a low heat of vaporization, and the formation of a positive azeotrope with H_2O (Table 1). Thanks to these physical properties, CPME can be employed as a solvent within a wide range of temperatures and, additionally, can be easily recovered, purified, and dried after aqueous workup.[7]

Table 1. Physical properties of CPME.[a]

bp [°C]	106
mp [°C]	<−140
density [g mL^{-1}, at 20 °C]	0.86
solubility in H_2O [g per 100 g, at 23 °C]	1.1
solubility of H_2O in CPME [g per 100 g, at 23 °C]	0.3
azeotropic bp with H_2O [°C]	83
azeotropic composition [CPME/H_2O, *w*/*w*]	83.7:16.3
dielectric constant (at 25 °C)	4.76
explosion range [vol%; lower limit–upper limit]	1.84–9.9
latent heat of vaporization [kcal kg^{-1}, at the bp]	69.2
ignition point [°C]	180
flash point [°C]	−1

[a] Adapted from Ref. [7,8].

From the point of view of storage and handling safety, one of the most serious drawbacks of ethereal solvents is the formation of peroxides (POs). At variance with solvents such as THF and 2-methyltetrahydrofuran (2-MeTHF), CPME shows a particularly high resistance to PO formation,[7] which can be correlated to an unusually high bond dissociation energy (BDE) of the secondary α-C–H bond.[9] The stability of CPME towards autoxidation under an oxygen atmosphere has additionally been highlighted within a theoretical investigation of the factors influencing the identification of solvents suitable for the development of rechargeable Li–air batteries.[10]

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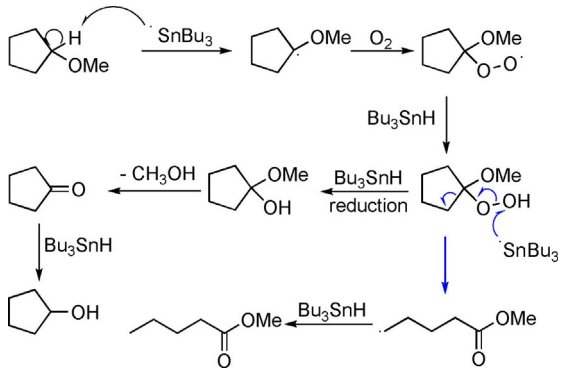
Accordingly, commercial CPME is usually stabilized with a relatively small amount of a peroxide inhibitor [butylated hydroxytoluene (BHT), 50 ppm], and the value is less than that used to stabilize, for example, THF and 2-MeTHF (250 ppm). Furthermore, by using stabilized CPME, it is possible to run reactions at high temperatures exposed to air through a $CaCl_2$ tube without observing the formation of any peroxides.[11] Coupled with its narrow explosion range, these characteristics make CPME a particularly safe-to-store and safe-to-handle ethereal solvent, although a note of caution is due as a result of its relatively low autoignition temperature (Table 1).[7]

Concerning the range of applications of CPME as a solvent, its high stability towards both Brønsted and Lewis acids, for example, camphorsulfonic acid, H_2SO_4, HCl, and $TiCl_4$, is notable.[7] CPME is additionally particularly stable towards strong bases and nucleophilic reagents, such as Grignard reagents and organolithium derivatives, and as a result is, for example, more stable than THF and diethyl ether (Et_2O) towards *n*-butyllithium (*n*BuLi).[7]

Ugo Azzena was born in Sassari (Italy) in 1954. After graduating in chemistry at the University of Sassari in 1979, he completed his Ph.D. studies at the ETH Zürich (CH) working under the guidance of Prof. P. L. Luisi. He then moved back to the University of Sassari, where he is an associate professor of organic chemistry. His current research interests focus on the set up of widely employed reactions under environmentally friendly conditions, on the employment of tunable synthetic equivalents of sodium metal in organic synthesis, and on the chemical modification of vegetable oils.

Vittorio Pace received his Ph.D. degree in chemical sciences cum laude from the Complutense University of Madrid in 2010. After postdoctoral training at Vienna (Prof. Holzer), Manchester (Prof. Procter), and Stockholm (Prof. Olofsson), he obtained a group leader position at the University of Vienna, followed by a tenure track professorship in drug synthesis in 2018. In 2016, he received the habilitation in pharmaceutical chemistry from the University of Vienna, and in 2017, he received the habilitation for full professor of organic chemistry. He has received several awards, including the Ciamician Medal of the Italian Chemical Society, the Caglioti Prize of the Accademia Nazionale dei Lincei, and the Young Investigator Award of the Faculty of Life Sciences at Vienna. His research core is focused on the design and development of new transformations with functionalized organolithiums.

The chemical inertia of the secondary α-C–H bond is a particular advantage if CPME is employed as a solvent for radical reactions (see below). Indeed, it has been shown by GC-MS analysis that CPME, recovered by extraction and distillation from the addition reaction of nBu$_3$SnH to 4-pentyn-1-ol promoted by 2,2′-azobis(isobutyronitrile) (AIBN, 0.2 equiv., 2 h, 90 °C), can be recycled up to four times with only a slight decrease in its purity from (99.9 to 99.4 %) and moderate effect on the yield of the product in subsequent experiments. The formation of trace amounts of byproducts such as cyclopentanone, cyclopentanol, and methyl pentanoate suggests the formation of a methoxy-substituted carbon radical as a key intermediate of this very slow solvent-degradation pathway (Scheme 2).[12]



Scheme 2. Suggested degradation pathway of CPME under radical-addition conditions.

Although some precautions have to be taken in handling every solvent for obvious reasons, it is notably that, from a toxicological point of view, CPME shows low acute or subchronic toxicity, with moderate irritation and negative genotoxicity and mutagenicity.[13]

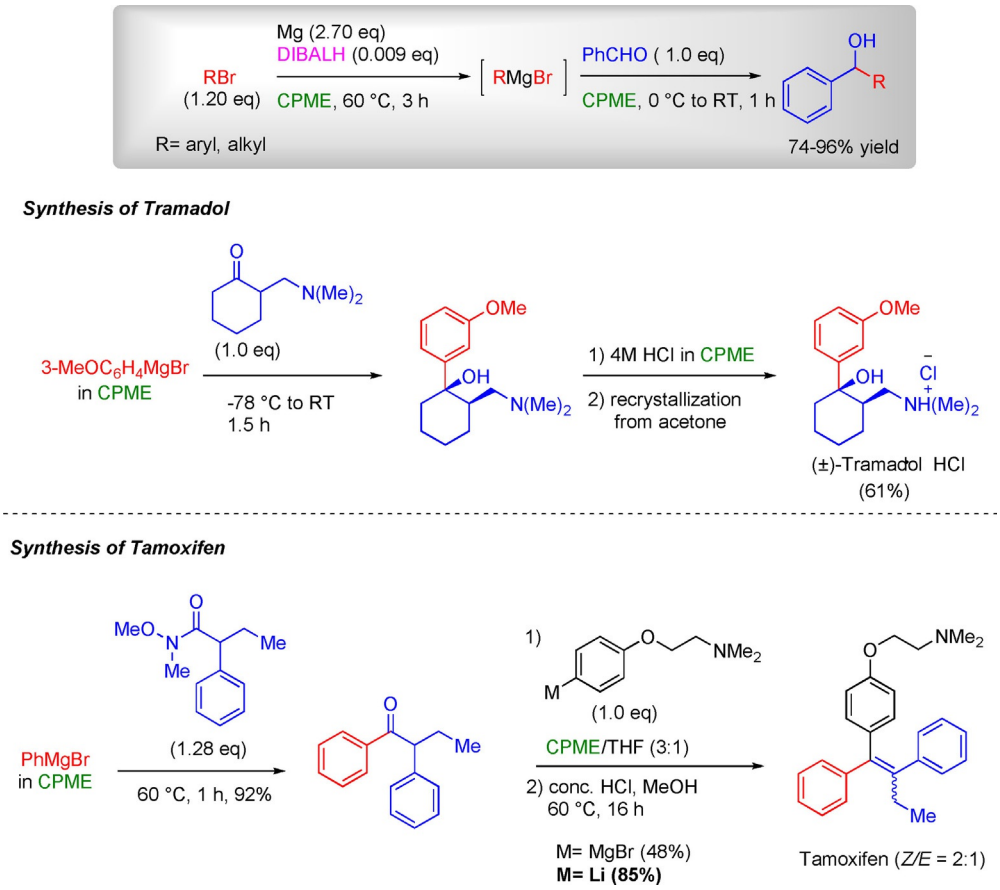
According to these ecofriendly properties and in spite of its origin from nonrenewable resources, CPME can be considered to have low environmental impact, and it competes with 2-MeTHF[14] as a green alternative to more problematic ethereal solvents such as Et_2O, THF, 1,2-dimethoxyethane (DME), dioxane, and methyl *tert*-butyl ether (MTBE). As a result, applications of CPME as a solvent in organic synthesis have multiplied within the last 10 years.

It is the aim of this Review to present the most significant achievements in this field from 2008 to 2018, with a particular focus on organometallic chemistry and catalysis, as well as on the set up of some widely employed reactions under environmentally friendly conditions. More emphasis is given to work in which CPME is proven to be superior to other solvents to promote a given reaction and/or in which it is successfully employed as an alternative to environmentally less-friendly solvents.

2. Synthetic Applications

2.1. Use of CPME in polar organometallic reactions

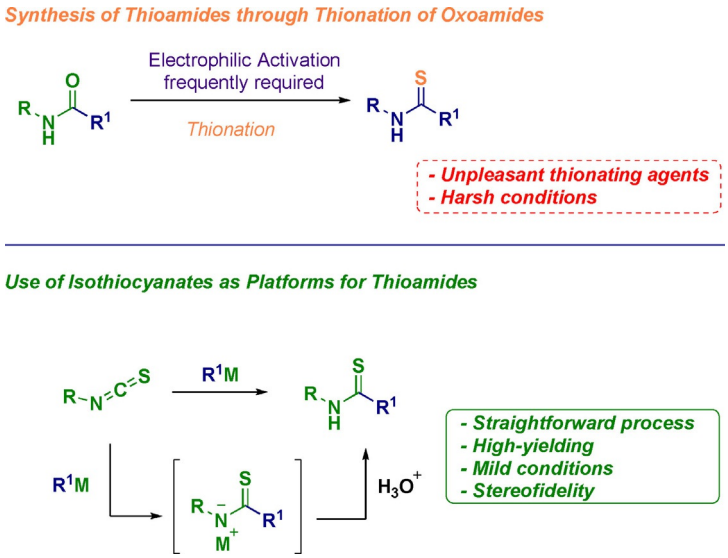
Considering the ethereal nature of CPME and the well-established employment of solvents with analogous features in reactions involving organometallic species,[15] with the aim to improve the sustainability of such processes, CPME has become a popular solvent in the field. In particular, two main issues often plague chemistry in classical ethereal solvents: 1) degradation with strongly basic organometallic reagents (e.g., organolithiums); 2) low sustainability–safety profile owing to the formation of peroxides, risk of flammability, and requirement for additional organic solvents during workup procedures. Kobayashi reported the first detailed and comprehensive study on the generation and employment of these organometallics in CPME (Scheme 3).[16] Diisobutylaluminum hydride (DIBALH) is the optimal activator for the reductive magnesiation of aryl and alkyl bromides with Mg metal, and this reaction results in the formation of the corresponding Grignard reagents upon heating to approximately 60 °C. Some points merit note: 1) the procedure is wide in scope as documented with over 20 cases and, thus, constitutes a reliable method to access benzylic-type alcohols upon quenching with PhCHO; 2) the deleterious Wurtz coupling of Grignard reagents can be advantageously minimized or suppressed by proper selection of the metalation conditions (i.e., order of addition); 3) only notoriously unstable or problematic Grignards (e.g., 2-ClC_6H_4MgBr, 2-FC_6H_4MgBr, propargyl) cannot be prepared through this method; 4) the stability of Grignards in CPME is assured for at least 3 months at 0 °C; 5) the use of cheaper alkyl chlorides as precursors is allowed, though the corresponding aryl chlorides are not. This latter point is intriguing, as it appears that CPME has a negative effect on the metalation of aryl chlorides, which thus suggests the requirement for a co-solvent. Substantial immiscibility with water (1.1 g/100 g at 23 °C)—in analogy to 2-MeTHF—renders it suitable for almost full recovery after running reactions, and this is an indicator of its robustness and stability to basic Grignard reagents. Kobayashis's study documents the high performance of organomagnesiums in the expeditious synthesis of important biologically active drugs such as the analgesic opioid tramadol and the antiestrogenic tamoxifen. Accordingly, upon magnesiation of 3-methoxyphenyl bromide in CPME in the presence of DIBALH, the resulting Grignard stereoselectively adds to a cyclic β-amino ketone to furnish the corresponding racemic alcohol that is a direct precursor of tramadol HCl. Analogously, tamoxifen can be prepared starting from phenyl bromide, which is first metalated to the corresponding Grignard and then added at 60 °C to a Weinreb amide to yield a congested ketone. The addition of a second organometallic



Scheme 3. Generation of Grignard reagents in CPME and their use in synthesis. Cy = cyclohexyl, Tol = toluene, dba = dibenzylideneacetone, NIXANTPHOS = 4,6-bis(diphenylphosphino)-10*H*-phenoxazine.

to this ketone followed by dehydration to the fully substituted olefin (i.e., tamoxifen) is challenging with a Grignard reagent (48% yield) but is straightforward with a more nucleophilic organolithium (85% yield). Notably, the lithiation process has to be realized in the presence of THF as a co-solvent (CPME/THF 3.3:1, *v/v*) to ensure complete metalation. The methodology affords a 2:1 *Z/E* mixture of olefins, from which the pure active *Z* isomer can be obtained by recrystallization.

Scientists at Novartis—in the course of investigations towards dipeptidyl peptidase-4 inhibitors with antidiabetic activity—found it highly beneficial to perform the addition of a benzyl Grignard reagent to an Ellmann's sulfinimine in a medium containing CPME (Scheme 4).[17] The solvent displays a remarkable effect not only in optimizing the diastereoselectivity of the process up to 85:15 (which can even be maximized up to 99.8:0.2 by subsequent crystallization) but also in stabilizing the same Grignard reagent.



Scheme 5. Concept of generating thioamides starting from isothiocyanates under more sustainable conditions than classical sulfurizing procedures.

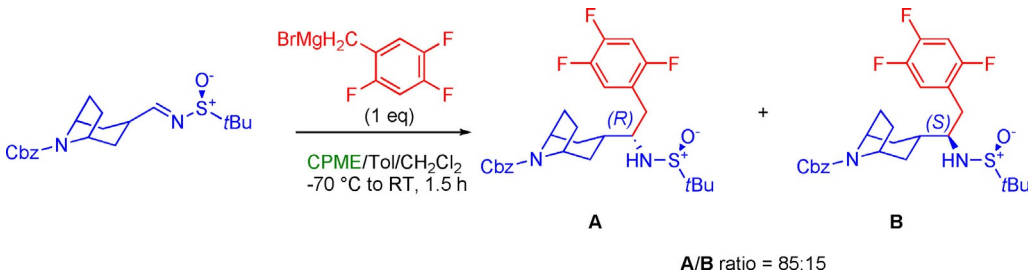
During their re-investigation of using heterocumulenes as precursors of amide-type linkages,[18] Pace et al. have developed a straightforward synthesis of secondary thioamides starting from widely available isothiocyanates and organolithium reagents (Scheme 5).[19] In fact, considering the success of their previous studies on the reaction between isocyanates and lithium carbenoids,[20] they detail the synthesis of thioamides through a conceptually simple and direct approach that circumvents the limitations affecting the synthesis of these building blocks with standard highly contaminating and toxic thionating procedures.[21]

Optimization studies have indicated the feasibility of this approach, and CPME is the optimal medium for accomplishing the reaction. The procedure is versatile and flexible and is, thus, applicable to different combinations of isothiocyanates and organolithiums (commercially available or prepared): pure thioamides are obtained in excellent yields after simple recrystallization from the same solvent (Scheme 6). By transmetalating the lithium carbanion to a Gilman reagent (R_2CuLi)—again in CPME—it is possible to obtain chemoselectively a functionalized thioamide featuring an ester group, which thus limits the addition of the carbanion to the isothiocyanate.

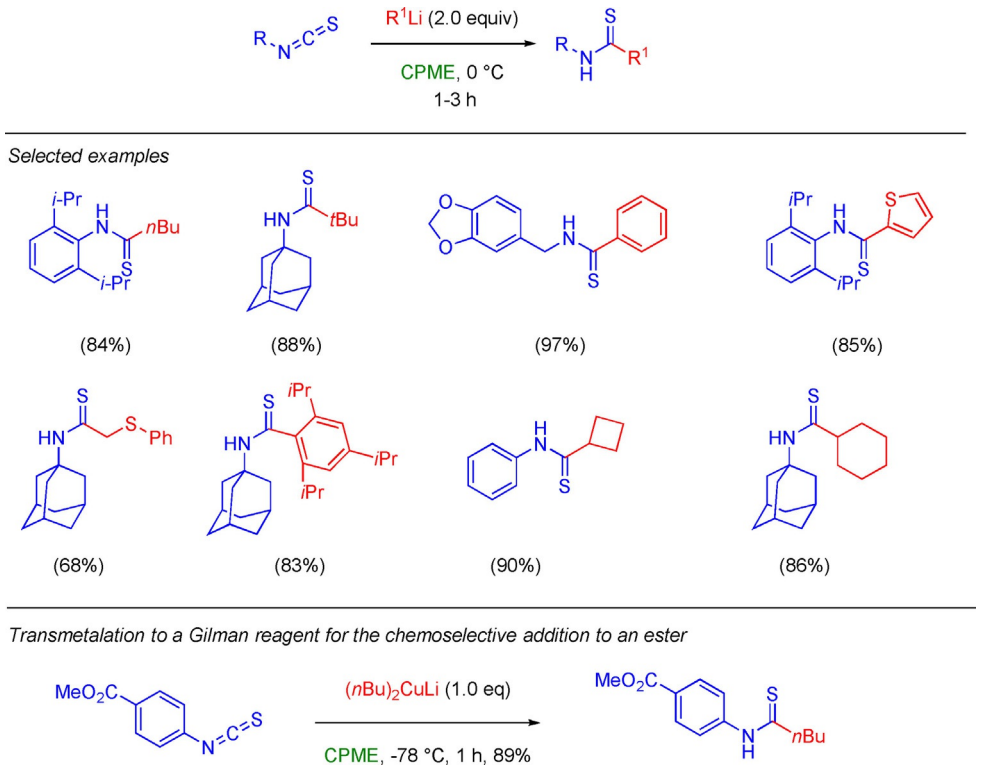
The stereochemical information of the starting isothiocyanate can be fully delivered to the thioamide,[19] in agreement with previous reports on similar isocyanates (Scheme 7).[20c] In the (−)- or (+)-sparteine-mediated preparation of enantiopure reagents in CPME, such as lithiated *N*-Boc-pyrrolidine (Boc = *tert*-butoxycarbonyl) and Hoppe's carbamate, enantio- and diastereopure thioamides are obtained. By simply switching from one enantiomer of sparteine to the other, both enantiomers of a given thioamide can be accessed with excellent optical purity.

Capriati and co-workers employ CPME as a convenient medium for the regioselective lithiation/functionalization of 2,2-diaryltetrahydrofurans in which the THF moiety serves as an effective directing group for metalation (Scheme 8).[22] The *ortho*-lithiation reaction performed with *t*BuLi as the base at 0 °C, followed by electrophilic quenching is more efficient and selective in CPME than in diethyl ether for different cases.

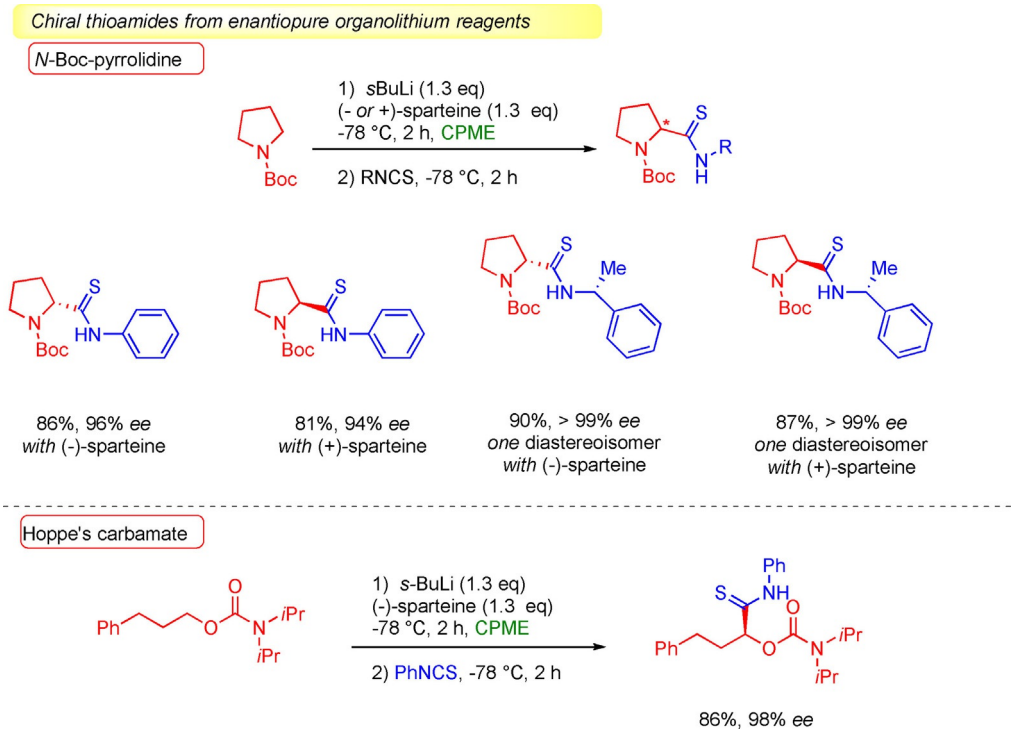
The same Capriati group has discovered an unexpected highly regioselective "greener" alkylative ring-opening reaction of *o*-tolyltetrahydrofuran derivatives with concomitant formation of new C–C bonds as the result of a directed lateral lithiation (DLL) reaction triggered by bases such as *s*BuLi, *i*PrLi, and *t*BuLi (Scheme 9).[23] This reaction provides a new method for the synthesis of functionalized primary alcohols and can be performed efficiently in CPME and protic eutectic mixtures consisting of choline chloride (ChCl)/glycerol (Gly) (1:2) at 0 °C in air competitively with protonolysis. However, under these conditions, only trapping reactions with electrophiles such as a



Scheme 4. Beneficial effect of CPME during the diastereoselective addition of a Grignard reagent to a sulfinimine.



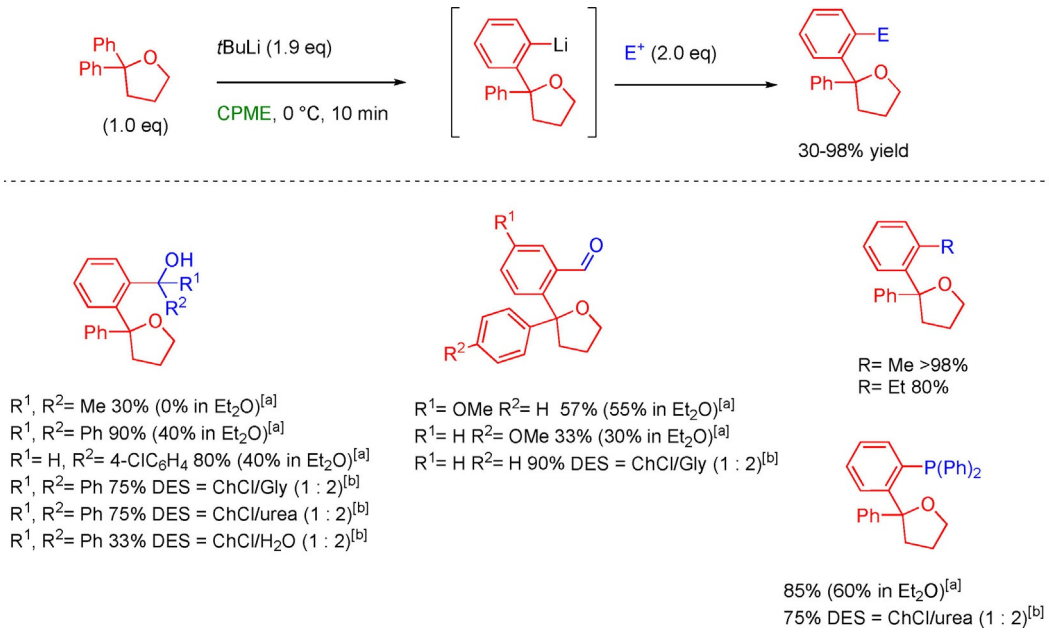
Scheme 6. Generation of thioamides from isothiocyanates and organolithiums in CPME.



Scheme 7. Formation of optically active organolithium reagents in CPME for the preparation of enantiopure thioamides.

deuterium source (MeOD) and simple alkyl halides (MeI and EtI) are clean and effective in allowing the creation of an all-carbon quaternary stereogenic center. The only exception is DMF, which gives the formylated adduct.

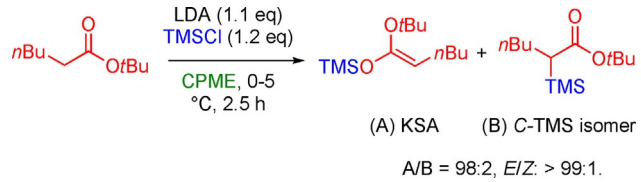
Okabayashi and co-workers have screened the influence of different ethereal solvents such as Et_2O, THF, dioxane, and DME in the regio- and stereoselective preparation of synthetically valuable intermediates such as (*E*)-ketene trimethylsilyl acetals



Scheme 8. Capriati's functionalization of diaryltetrahydrofurans in CPME. DES = deep eutectic solvent, ChCl = choline chloride, Gly = glycerol. Conditions [a]: 0 °C, 30 min; conditions [b]: DES, RT, under air.

(KSAs) starting from *tert*-butyl esters in the presence of lithium diisopropylamide (LDA)/TMSCl at 0–5 °C (Scheme 10).[24] The stereochemistry (*E*/*Z*) of the KSAs, which subtly depends on the molar ratio, temperature, and solvent, is fundamental, because it profoundly affects the subsequent diastereo- and enantioselective C–C bond-forming events. Therefore, the use of a suitable reaction temperature range, from −20 to 20 °C, and considering that a bulky *tert*-butyl group would be useful to enhance the *E* selectivity, the best result in terms of both yield and regioselectivity is achieved with CPME, whereas Et_2O, THF, dioxane, and DME provide poor regioselectivity, thus promoting undesirable *C*-silylation.

Takeshi and co-workers describe a method for the highly diastereoselective addition of γ,γ-disubstituted allyltitanocenes species, generated from γ,γ-disubstituted allyl sulfides, to aliphatic and aromatic ketones (Scheme 11).[25] This methodology allows the practical construction of a variety of acyclic systems

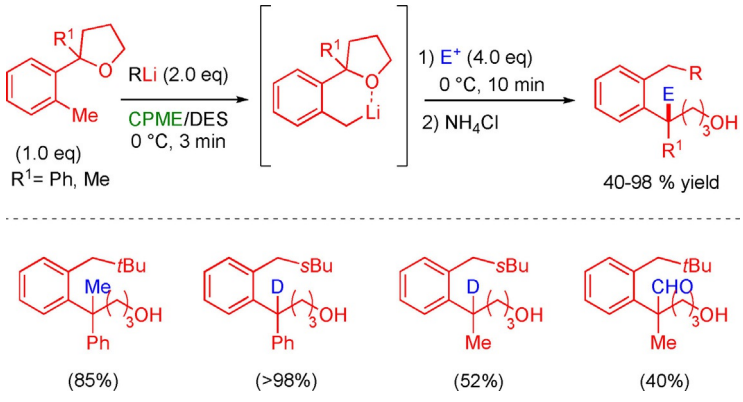


Scheme 10. Selective enolization of esters to ketene acetals in CPME.

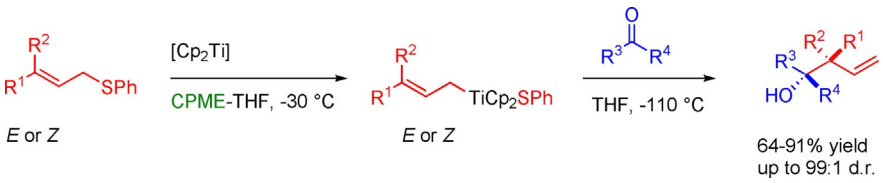
having two adjacent quaternary carbon centers. The use of CPME as a co-solvent is indispensable for achieving good yields and high diastereocontrol.

Sugimura disclose the employment of CPME as a valuable solvent for Simmons–Smith cyclopropanation chemistry (Scheme 12): comparative studies with diethyl ether highlight the better performance of the former, thus allowing reactions to reach completion approximately 10 times faster.[26] The higher boiling point of CPME together with its apolarity are considered keys for understanding the better efficiency, also in light of improvements in the yields and diastereocontrol in some instances. Notably, CPME stabilizes the labile $IZnCH_2I$ carbenoid during its generation.

Molander et al. outline the development of convergent approach to synthesize disubstituted 2,1-borazaronaphthalenes from *N*-substituted 2-aminostyrenes and potassium organotrifluoroborates as the nucleophiles through an annulation/aromatization reaction (Scheme 13).[27] Starting from aryl-, heteroaryl-, alkynyl-, alkenyl-, and alkyltrifluoroborates, a large number of highly functionalized 2,1-borazaronaphthalenes are synthesized in one step under mild, transition-metal-free conditions. The addition



Scheme 9. Synthesis of functionalized primary alcohols through a DLL reaction on substituted THF analogues in CPME.



Scheme 11. Diastereoselective addition of allylmetal species to ketones.Cp = η^5-cyclopentadienyl.

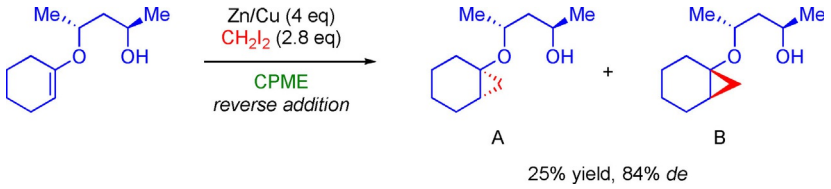
of CPME as a coordinating solvent leads to an increase in the yield relative to that obtained in toluene, and a 1:1 mixture of toluene/CPME is the most effective for accomplishing the reaction. Analogous chemistry has been further optimized under microwave irradiation, again with the use of CPME as the solvent.[28]

2.2. Use of CPME in transition-metal-catalyzed chemistry

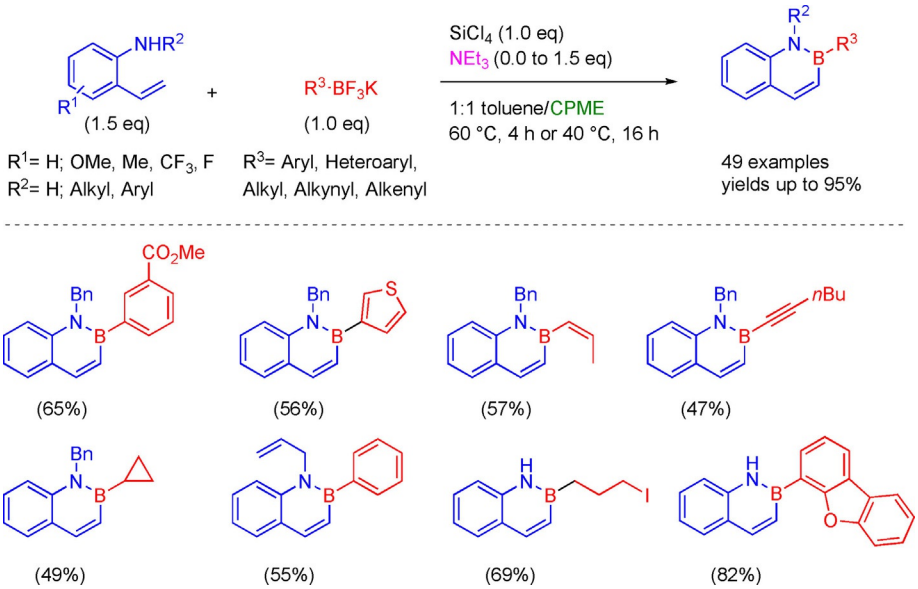
Catalysis heavily relies on the capability of a reaction medium to sustain (and not interfere with) a given catalytic cycle. Indeed, as recently underlined by Dyson and Jessop, interactions of the solvent with the catalyst, the substrates, and the products influence both the speed and the selectivity of reactions.[29] The tremendous impact that transition-metal-catalyzed processes has in organic synthesis has evidently been the result of careful optimization protocols that highlight the paramount importance of solvents in tuning the selectivity and efficiency of a given process:[30] recent applications of CPME as a particularly useful solvent in catalysis are discussed in Sections 2.2–2.5.

Denmark notes the beneficial effect of CPME in the highly selective Fe-catalyzed cross-coupling of aryl Grignards with secondary alkyl thioethers featuring a pyridyl directing group; this method is a sustainable alternative to C–C bond formation (Scheme 14).[31] This protocol can also be applied to analogous sulfones, though the concomitant presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) dramatically increases the efficiency.

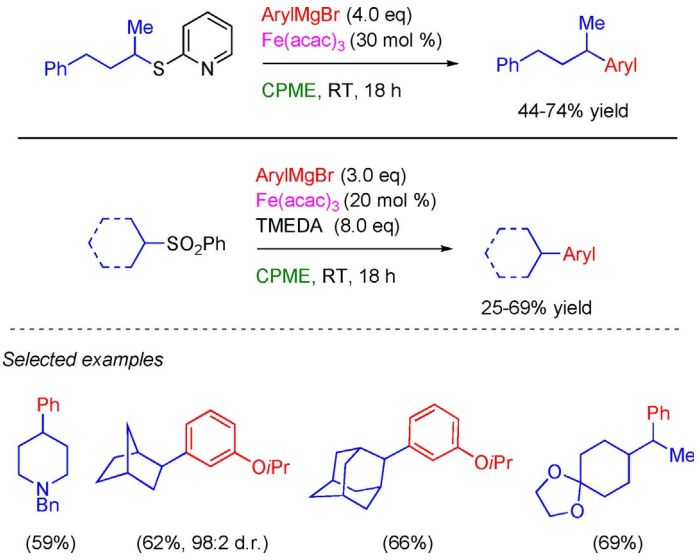
Feringa et al. delineate a procedure for the iron-catalyzed hydrogen borrowing direct coupling of amines and alcohols (Scheme 15).[32] The scope of the method includes the monoalkylation of anilines and benzylamines with a wide range of alcohols and the use of diols in the formation of five-, six-, and



Scheme 12. Simmons–Smith cyclopropanation in CPME.



Scheme 13. Molander's synthesis of 2,1-borazaronaphthalenes in CPME with organotrifluoroborates.



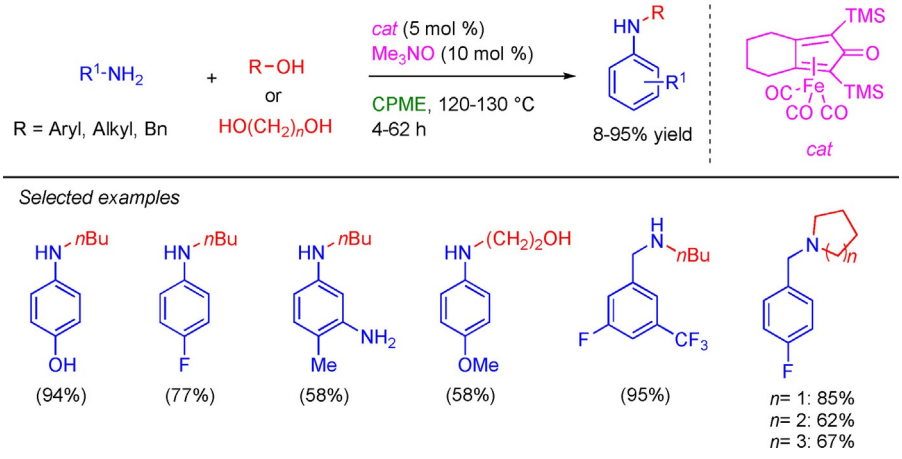
Scheme 14. Fe-catalyzed cross-coupling of aryl Grignard reagents with secondary thioethers and sulfones. acac = acetylacetonate.

seven- membered nitrogen heterocycles, which are important motifs in pharmaceuticals. The use of the green solvent CPME is strategic for the outcome of this transformation, together with the use of a bifunctional iron–cyclopentadienone complex catalyst.

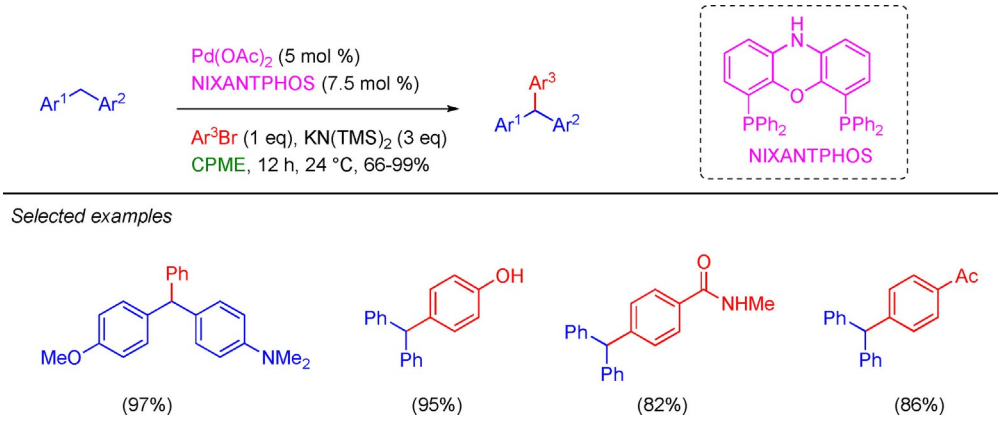
In 2012, Dreher and Walsh developed a robust, high-yielding, and scalable method for the preparation of valuable triarylmethanes through the Pd-catalyzed deprotonative cross-coupling (DCC) of simple diarylmethanes at room temperature in CPME, thus circumventing traditionally challenging methods to access these valuable motifs, such as the use of low-temperature deprotonation conditions or high-temperature cross-couplings (Scheme 16).[33] The reaction shows a significant level of chemocontrol and has been optimized after deep investigations that have identified—inter alia—the excellent performance of CPME and NIXANTHOS as the phosphine ligand. However, CPME is less efficient than THF if employed for the preparation of triaryl(heteroaryl)methanes under analogous conditions.[34]

Walsh and co-workers have also realized an effective method for the chemo- and regioselective Pd-catalyzed arylation of aryl bromides and allylbenzene in the presence of a phosphine and a base in CPME (Scheme 17).[35] Although this is the classic recipe for a Heck-type process, the authors note that the nature of the base is critical and conclude that $LiN(TMS)_2$ is the most effective in accomplishing reversible deprotonation, followed by transmetalation with the catalyst, which thus inhibits the Heck pathway. Overall, this deprotonative cross-coupling constitutes an excellent method to access α-arylated 1,1-diarylprop-2-enes, and the positive effect of CPME as the solvent has been evidenced.

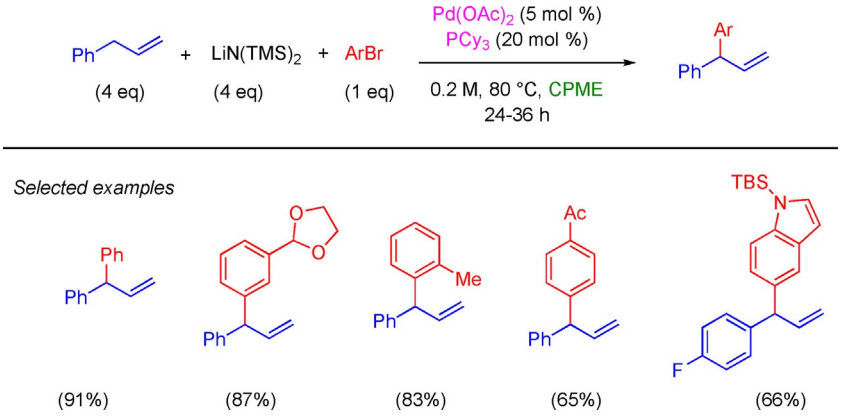
Subsequent studies by the same group have identified (again) CPME as the solvent of choice for the first chemoselective tandem $C(sp^3)$–H arylation/[1,2]-Wittig rearrangement of pyridylmethyl ethers under Pd-catalysis conditions (Scheme 18).[36] Optimization studies have revealed the critical role played by the base/solvent/temperature and have thus allowed the design of a divergent synthesis of tertiary and quaternary adducts. Accordingly, the tandem process becomes highly selective by selecting the $LiN(TMS)_2$/CPME/45 °C triad, whereas the corresponding sodium base in DME at 23 °C furnishes the simple arylated product. The inherent synthetic potentiality of this method is evident, as the three simple reaction parameters can be fine-tuned to reach different products. As an extension of the (hetero)arylation of benzylic C–H groups, this methodology is also a suitable platform for the generation of quaternary 4-pyridylmethyl ethers through the monoarylation of tertiary ethers or the diarylation of secondary ones.[37] Extension of the scope to α-alkenylation processes—with the use of CPME as the solvent—has also been demonstrated to be feasible.[38] As illustrated very recently by this group, switching to more sustainable Ni catalysis is permitted without affecting the chemoselectivity or the efficiency. Moreover, scale-up of the process can be easily realized, and in various circumstances, cheaper aryl chlorides can be conveniently used for the transformation.[39]



Scheme 15. Fe-catalyzed direct coupling of amines and alcohols.

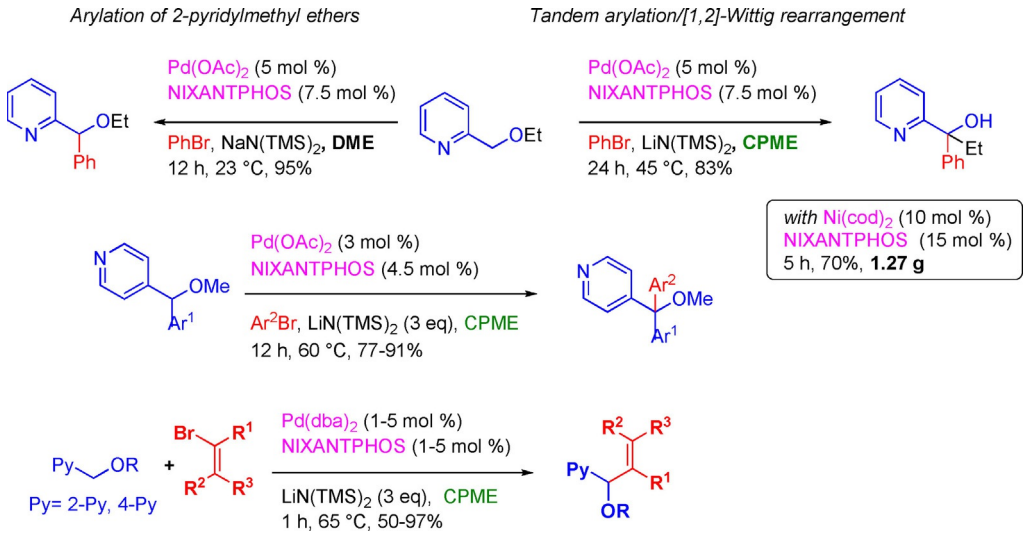


Scheme 16. Pd-catalyzed arylation of benzylic groups en route to triarylmethanes.

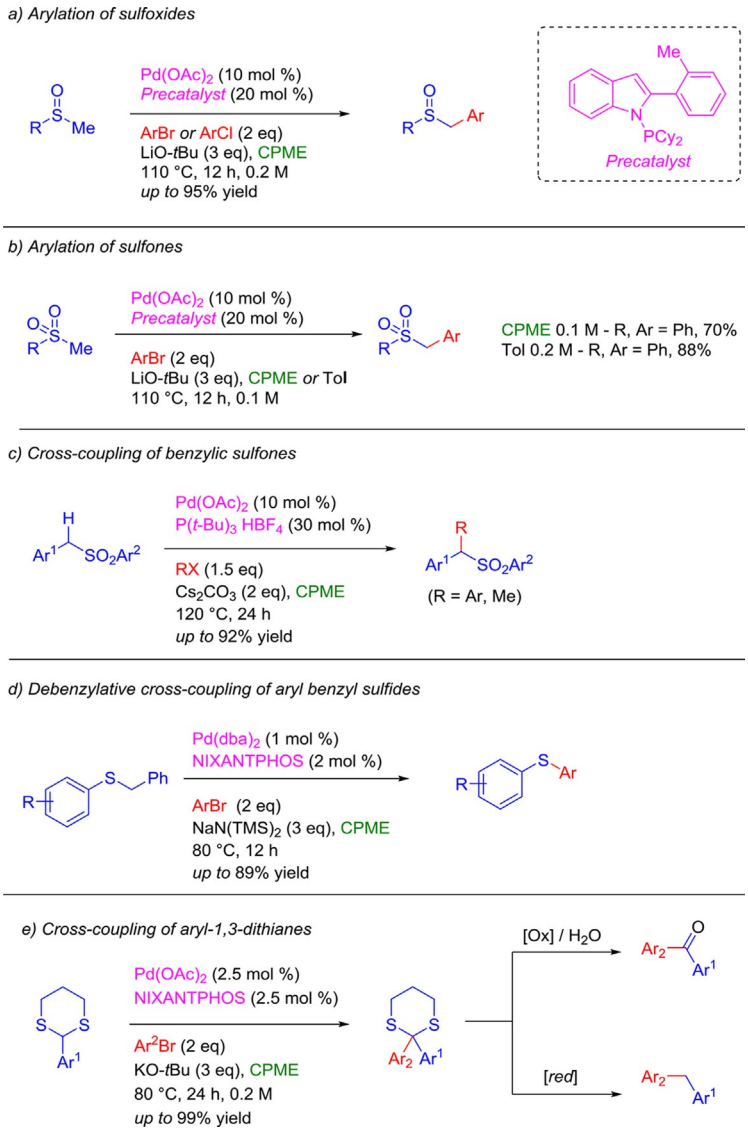


Scheme 17. Walsh's Pd-catalyzed deprotonative cross-coupling of allylarenes and aryl bromides.

The versatility of Pd-catalyzed arylation processes in CPME is further documented by the functionalization of the challenging methyl fragments of sulfoxides[40] and sulfones (Scheme 19).[41] In fact, analogous operations with these materials are often problematic because of the need for strong alkali bases, the compatibility of which with coupling partners and catalysts is rather limited. The reaction is suitable for unactivated alkyl and aryl sulfoxides with aryl bromides in the presence of a Buchwald-type second-generation precatalyst (with water as an additive) in CPME (Scheme 19a). Aryl chlorides can



Scheme 18. Walsh's switchable Pd-catalyzed arylation and tandem arylation/[1,2]-Wittig rearrangement. cod = cycloocta-1,5-diene.



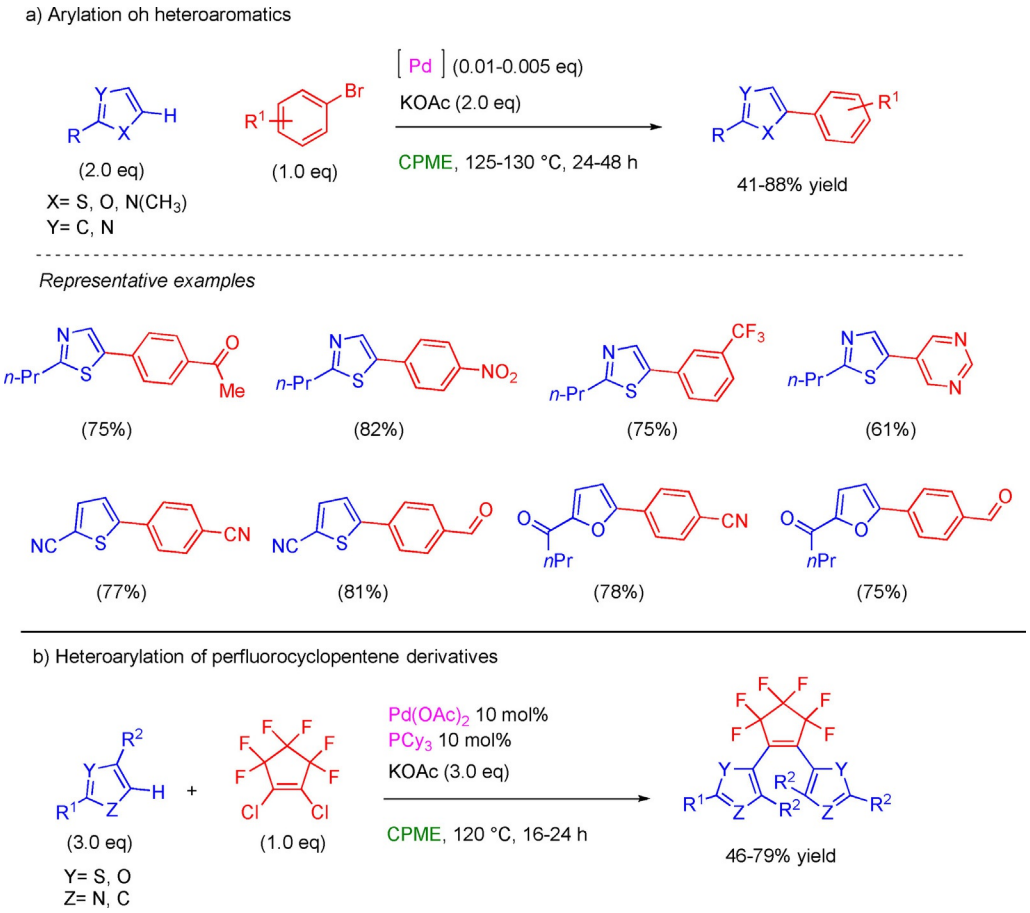
Scheme 19. Pd-catalyzed arylation processes on a carbon atom adjacent to a sulfur atom in CPME.

be used in the case of sulfoxides with all other parameters unchanged, whereas in the case of sulfones, toluene gave the best results (Scheme 19b). For the latter substrates, however, a significant concentration–solvent correlation exists: CPME maintains its superiority (over toluene) at 0.1 M, whereas a reversal effect is noticed at 0.2 M concentration. Conceptually related is the Pd-catalyzed derivatization of benzylic sulfones—again in CPME—developed by Crudden:[42] the protocol, which is also suitable for alkylation (with MeI), features a wide scope, as evidenced in the case of differently functionalized sulfone partners (Scheme 19c). During studies on the arylation of benzyl thioethers under similar conditions in CPME,[43] a debenzylative approach to diaryl sulfides from aryl benzyl sulfides and aryl bromides has been disclosed, and this enhances the portfolio of the chemistry accessible by using this promising solvent (Scheme 19d).[44] Schmink discloses the development of a method for the Pd-catalyzed cross-coupling of 2-aryl-1,3-dithianes, from which the products can be further derivatized into ketones or diarylmethanes (Scheme 19e).[45] By replacing the 2-aryl-1,3-dithianes with benzyl-type dithianes, new reactivity pathways paved on C–S bond-formation events can be similarly activated in CPME.[46] The versatility of Pd-catalyzed chemistry in CPME is also showcased in additional studies dealing with arylation processes at positions adjacent to amidic carbon atoms,[47] benzyl phosphonates,[48] benzylic phosphine oxides,[49] α-phosphonoacetates,[50] and cyclopropyl nitriles[51] under (almost) analogous conditions.

Doucet and Beydoun have developed an economically viable and environmentally attractive process in which CPME promotes the palladium-catalyzed direct arylation of heteroaromatics. In the presence of only 0.5–1 mol% of a palladium catalyst at 125–130 °C, the direct 5-arylation of thiazoles, thiophenes, and furans with the use of aryl bromides as coupling partners proceeds in moderate to high yields (Scheme 20).[52] A wide range of functional groups, such as acetyl, propionyl, formyl, ester, nitro, nitrile, trifluoromethyl, and fluoro, on the aryl bromide is well tolerated. Notably, the major byproduct of these couplings is innocuous KBr instead of the transition-metal salts obtained with more classical coupling procedures. The same group in 2012 developed a method for straightforward access to photochromic diarylethene derivatives through the palladium-catalyzed direct heteroarylation of 1,2-dichloroperfluorocyclopentene with a variety of heteroarenes in CPME.[53] The reaction proceeds with thiazole, thiophene, and furan derivatives and tolerates various substituents. This method offers direct access to symmetric and unsymmetric 1,2-di-(heteroaryl)perfluorocyclopentenes, and easy modification of the electronic structure of such derivatives enables tuning of their optical and photochromic properties.

Pd-catalyzed processes run in CPME have also been employed for carbon–heteroatom bond-formation events, such as in the Buchwald–Hartwig-type amination developed by Sajiki[54] and the enantioselective borylative migration of alkenyl nonaflates for the preparation of chiral piperidine derivatives (Scheme 21).[55] In this latter case, CPME affords the best results in terms of enantioselectivity with a low catalyst loading, though subsequent allylboration of the aldehyde is realized in toluene.

Knochel and co-workers have demonstrated the superiority of CPME over other solvents in the highly chemoselective $CrCl_2$-catalzyed cross-coupling reaction of dichlorinated aromatics with a series of functionalized arylmagnesium reagents (Scheme 22a).[56] Notably, full conversion is observed in CPME within only 1 h, whereas the reaction is very sluggish after 24 h in THF. Considering the intrinsic environmental limitations of using Cr-catalyzed processes in organic synthesis with regard to pharmaceutical applications, it is quite remarkable that the authors report effective removal of the salt prior to



Scheme 20. Pd-catalyzed (hetero)arylation in CPME developed by Doucet.

further transformations. Chemoselective arylation chemistry on aminoazaheterocycles can also be done by the Pd-catalyzed Suzuki–Miyaura reaction in CPME followed by reduction in COware apparatus, as introduced by Watson for the preparation of biologically active tetrahydropyrimidine derivatives (Scheme 22 b).[57]

In some instances, running organometallic reactions in CPME has a beneficial effect in terms of stereocontrol, as evidenced in Pd-catalyzed asymmetric allylic substitutions[58] and in the catalytic enantioselective monofluorination of α-keto esters in the presence of chiral Pd complexes.[59] The excellent performance of the solvent is also noted in the construction of quaternary α-amino acids containing pyrrolidines through the 1,3-dipolar cycloaddition of azomethine ylides to α-aminoacrylates under Ag/ferrocenyl-type catalysis (Scheme 23).[60]

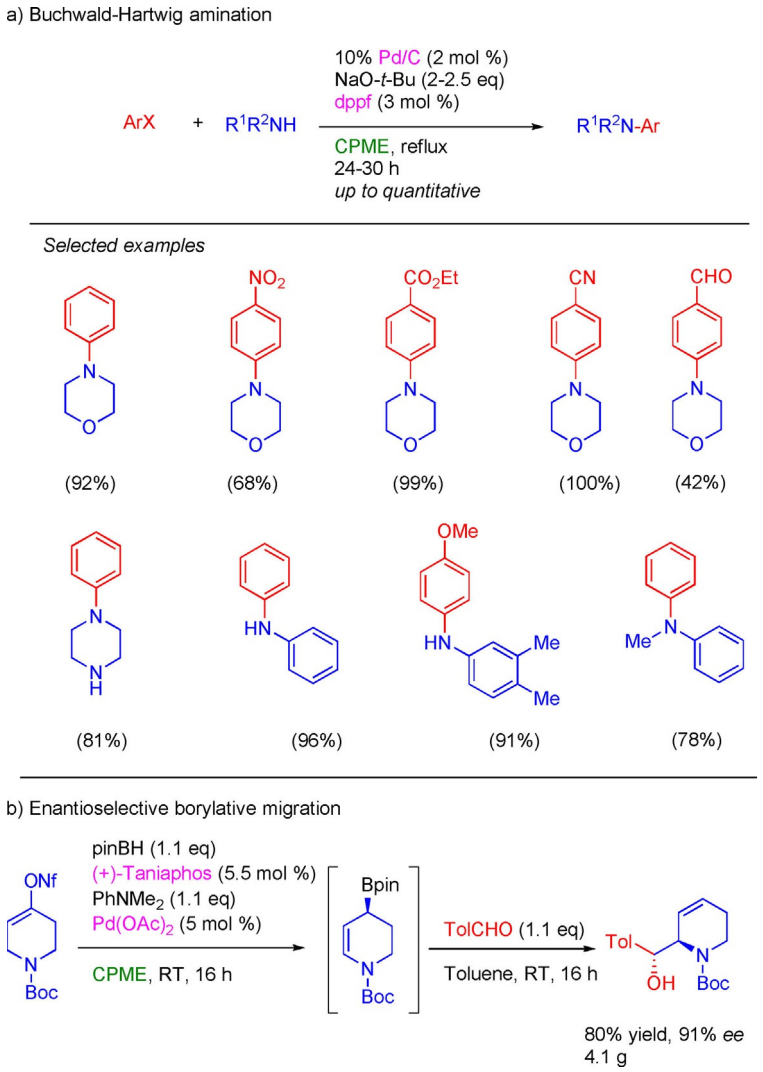
The use of CPME as a solvent has also been extended to C–H activation chemistry, as demonstrated by Buchwald in the intramolecular Pd-catalyzed difluoroalkylation of (hetero)arenes for the construction of 3,3-difluoro-2-oxindoles starting from readily available chlorodifluoroacetanilides (Scheme 24).[61] The reaction is strictly dependent on the nature of the phosphine ligand, and highly sterically hindered phosphines have been shown to be ideal; furthermore, the reaction shows an impressive level of functional-group tolerance, as observed in the case of variously functionalized materials.

Molander et al. use CPME as the solvent of choice in the Pd-catalyzed cross-coupling reactions of potassium 2-(trifluoroboratomethyl)-2,1-borazaronaphthalenes with (hetero)aryl chlorides (Scheme 25).[62] This cross-coupling reaction is characterized by a broad substrate scope and gives good to excellent yields of valuable borazaronaphthyl arylmethanes.

Chirik describes a method for the chemoselective α-diimine Ni-catalyzed perborylation of the benzylic C(sp^3)–H bonds of methyl- and alkylarenes in CPME (Scheme 26).[63] The combination of benzylic perborylation with a new base-mediated deborylative conjugate addition–alkylation sequence enables a one-pot procedure for a highly diastereoselective carbon–carbon bond-forming process, in which multiple, simple precursors are combined to generate diastereopure products containing quaternary stereocenters.

Cramer et al. disclose a highly enantioselective Ni^0-catalyzed reductive [3+2] cycloaddition of α,β-unsaturated aromatic mesityl enoates and internal alkynes for the asymmetric synthesis of cyclopentenones (Scheme 27).[64] Ligands, represented by chiral, bulky, C_1-symmetric N-heterocyclic carbene **L1** and non-C_2-symmetric chiral carbene ligand **L2**, enable the transformation to occur at 50 °C by employing CPME as the solvent.

In 2013, Minami and co-workers performed selective C–CN activation for the addition of polyfluorobenzonitriles to alkynes without C–H or C–F bond cleavage (Scheme 28).[65] The fluo-



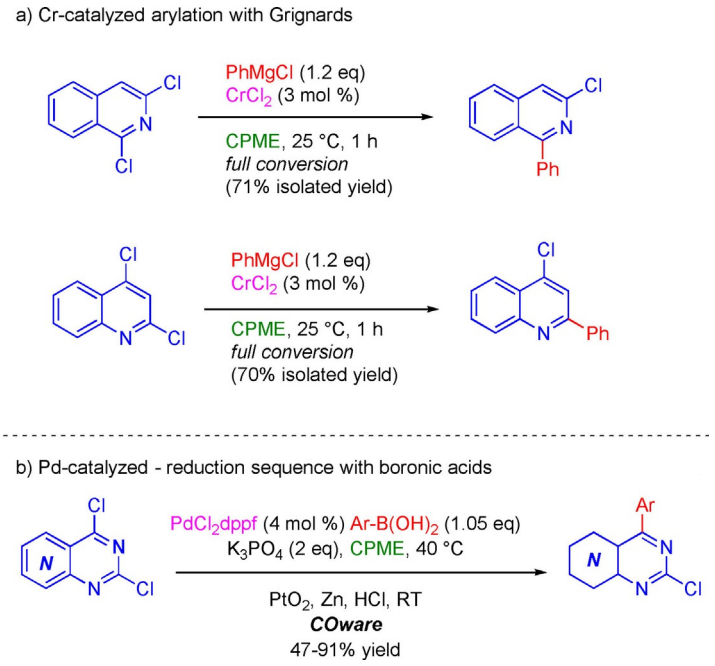
Scheme 21. Pd-catalyzed C–N and C–B bond formation in CPME. Tf = triflyl, pinBH = pinacolborane, (+)-Taniaphos = (R_P)-1-[(*R*)-α-(dimethylamino)-2-(diphenylphosphino)benzyl]-2-diphenylphosphinoferrocene, tol = tolyl.

rine atoms bound to the aryl group significantly enhance the reactivity of the C–CN bond toward oxidative addition to the nickel(0) complex. This study highlights the role of a Ni/BPh_3 catalyst system in CPME for accessing a variety of fluorinated organic compounds.

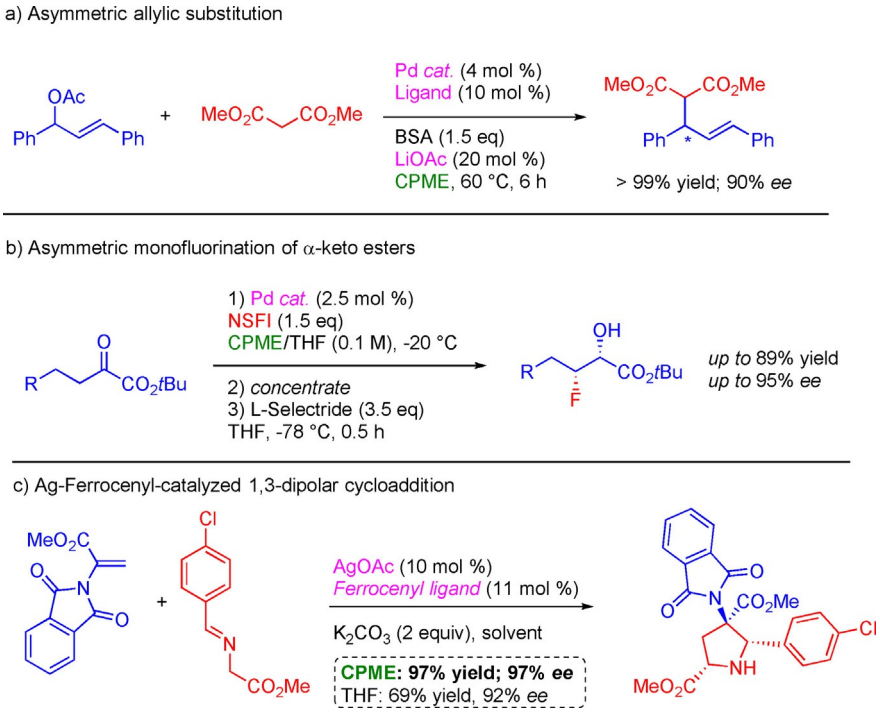
In 2014, Molander and Argintaru described the use of air- and moisture-stable potassium organotrifluoroborates for the Ni-catalyzed alkenylation of alkyl electrophiles (Scheme 29).[66] Through this general method, highly substituted *E*- and *Z*-alkenyltrifluoroborates as well as vinyl- and propenyltrifluoroborates can be employed and no erosion of stereochemistry or regiochemistry is observed during the transformation. Various functional groups are tolerated on both the nucleophilic and electrophilic partners. The combination of the nonprotic solvent CPME with a tertiary alcohol reduces undesired protodeboronation and increases the yield of the desired cross-coupled product.

Chen has demonstrated the use of CPME as the solvent of choice to perform the Ni(acac)$_2$-catalyzed 1,2-addition of aryl- and alkylboronic acids to tryptanthrins to access quaternary indoloquinazolinone-type alcohols in 30–90% yield (Scheme 30).[67] Importantly, this reaction shows good functional-group tolerance and a remarkably broad substrate scope that includes substrates bearing halogens.

Additional examples of transition-metal chemistry in CPME involve the use of iridium, gold, and cobalt catalysis. For example, Carraux et al. recount the development of a new route to α-aminoboronates through the iridium-catalyzed allylic amination of boronated substrates (Scheme 31).[68] The best yield of the desired product results by using CPME as the reaction medium with a catalytic amount of 1,5-diazabiciclo[5.4.0]undec-7-ene (DBU). The use of a trifluoroborato group in place of a boronic ester allows control of the regioselectivity of this method. Cyclic amines can be successfully employed as nucleophiles to afford the corresponding products in 60–91% yield. Additionally, Li et al. has designed the first example of a bidentate N,B-type boryl ligand to promote a C(sp^2)–H borylation reaction in CPME.[69] A symmetric pyridine-containing tetraamino-



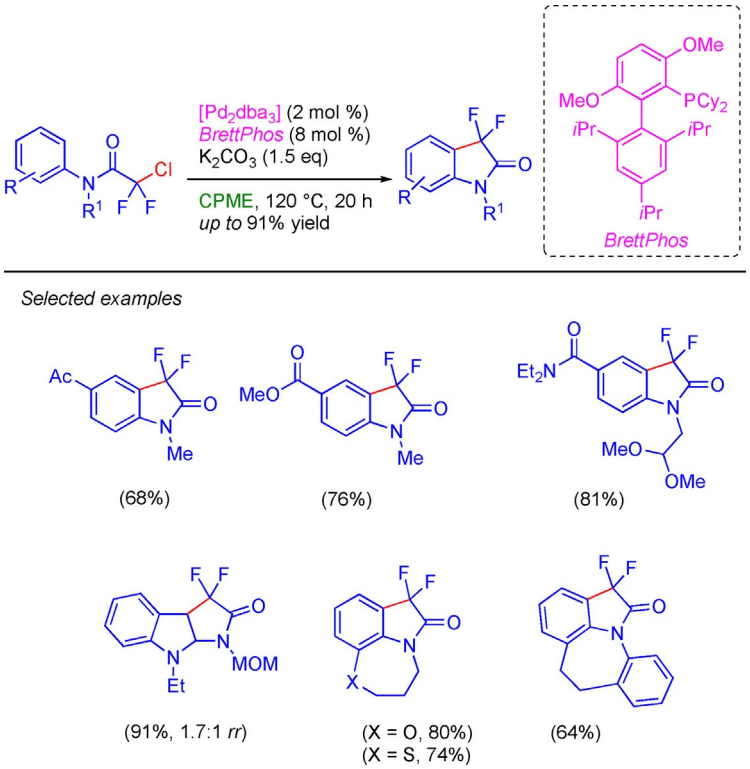
Scheme 22. Arylation of azaheterocycles in CPME. dppf = 1,1′-bis(diphenylphosphino)ferrocene.



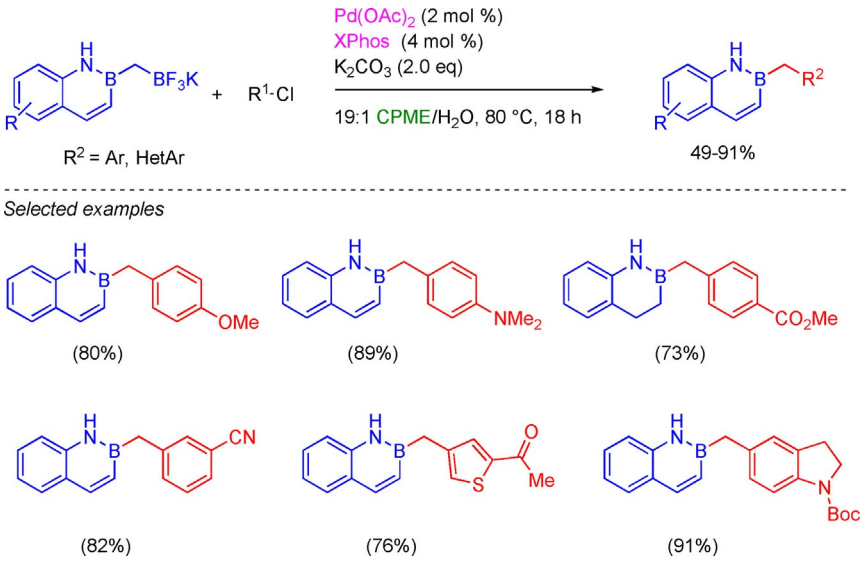
Scheme 23. Pd- and Ag-catalyzed asymmetric processes in CPME. BSA = bis(trimethylsilyl)acetamide, NSFI = *N*-fluorobenzenesulfonimide.

diborane compound is readily prepared and is able to generate a highly active catalyst in situ through B–B oxidative addition onto iridium for C–H borylation of a broad range of (hetero)arene substrates, including highly electron-rich and/or sterically hindered ones.

Hong et al. propose Au-catalyzed chemoselective methods for the synthesis of *N*-sulfonyl enaminones (Scheme 32).[70] In this case, CPME also contributes to stabilize the Au catalyst at high reaction temperatures. These reactions represent the first examples of the transition-metal-catalyzed synthesis of enamines from sulfonamides and alkynes. Two different isomers are obtained in a chemocontrolled manner by employing the different properties of Au^{I} and Au^{III} catalysts. Upon using Au^{I}, predominantly proton-assisted carbonyl activation followed by



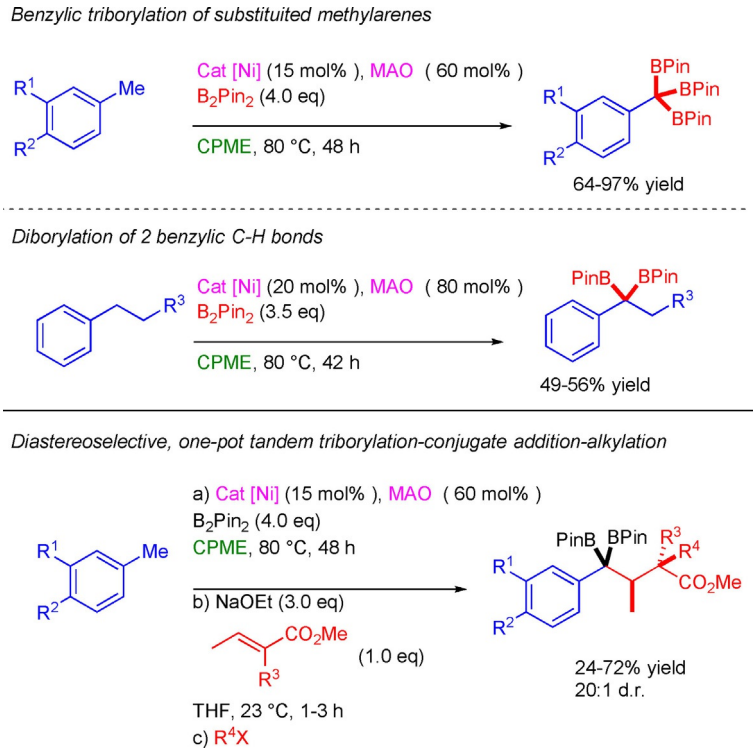
Scheme 24. Buchwald's intramolecular Pd-catalyzed C–H activation en route to difluorooxindoles.



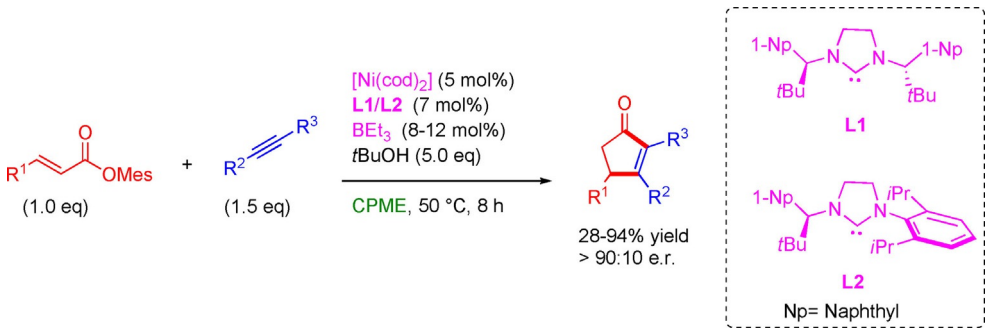
Scheme 25. Molander's cross-coupling of (hetero)aryl chlorides and α-boryl organotrifluoroborates. XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

Meyer–Schuster rearrangement is observed. A wide range of substrates afford moderate to excellent yields and selectivities.

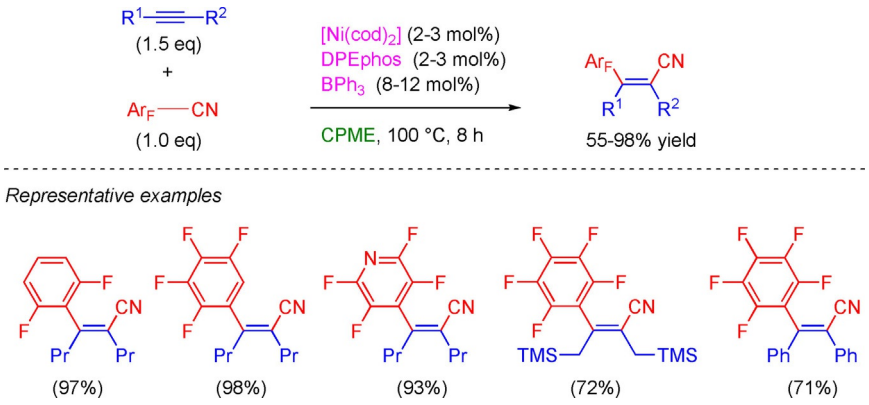
Beller has achieved the direct reductive cobalt-catalyzed C–H alkylation and selective alkenylation of indoles by using carboxylic acids in the presence of molecular hydrogen in CPME (Scheme 33).[71] Several substituted indole derivatives react with acetic acid, phenylacetic acid, and diphenylacetic acid. This protocol enables the direct functionalization of indoles with readily available and stable carboxylic acids by using a catalytic system based on the combination of $Co(acac)_3$ and 1,1,1-tris(diphenylphosphinomethyl)ethane (Triphos) in the presence of $Al(OTf)_3$ as a co-catalyst. The effect of CPME is remarkable, as it allows the catalyst loading to be lowered (2 mol%) with excellent results.



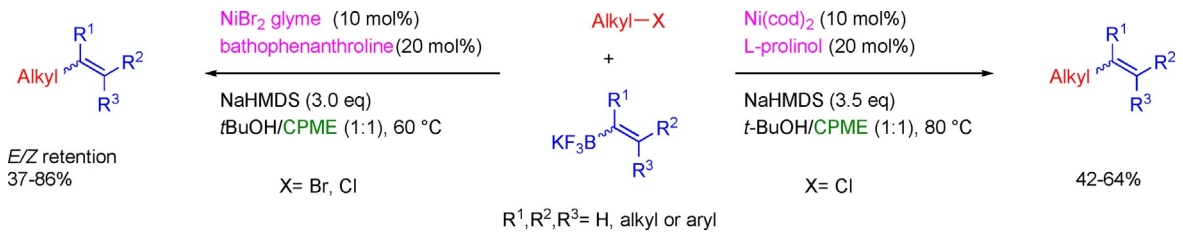
Scheme 26. Diastereoselective C–C bond formation through the Ni-catalyzed coupling of benzyltriboronates, enoates, and alkyl halides in CPME. MAO = methylaluminoxane.



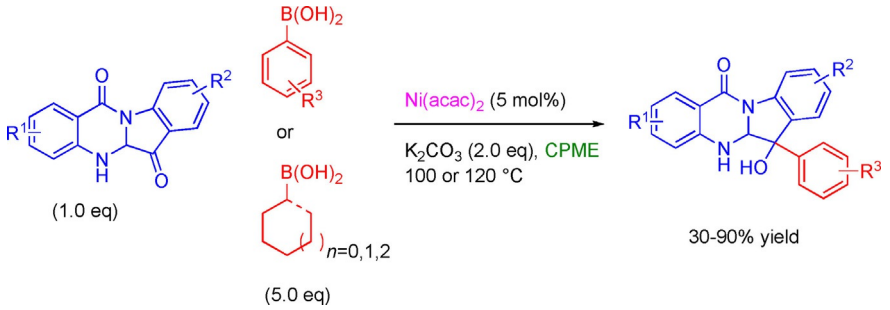
Scheme 27. Ni-catalyzed annulation of alkynes with NHC ligands in CPME.



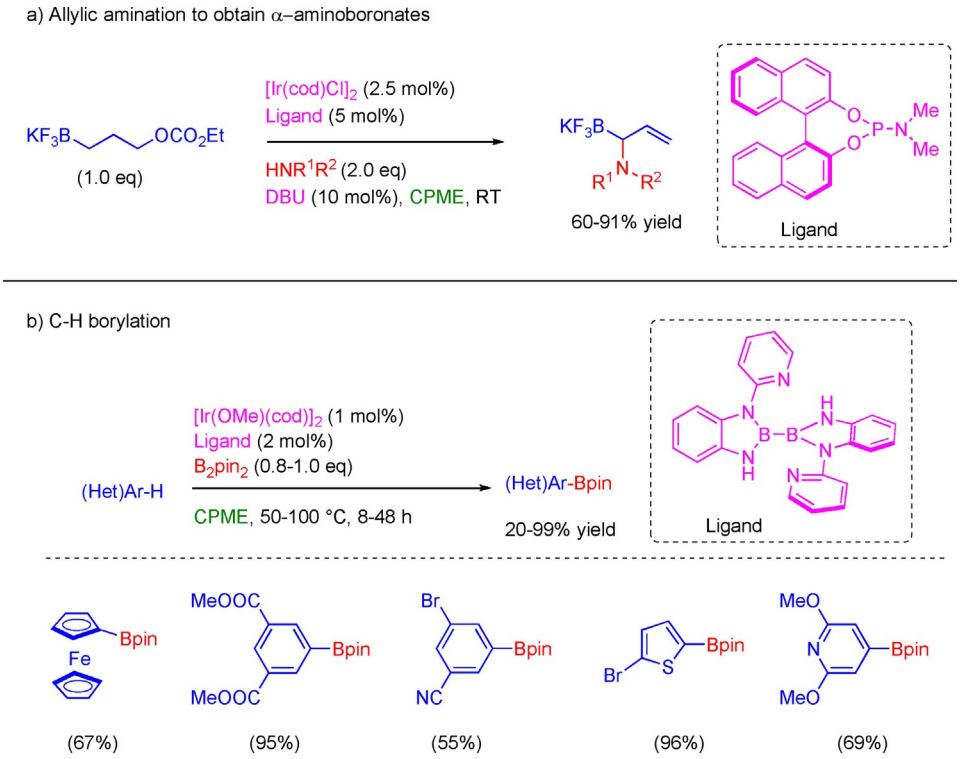
Scheme 28. Ni-catalyzed/Lewis acid polyfluoroarylcyanation of alkynes. Ar_F = perfluorinated aryl group, DPEphos = bis[(2-diphenylphosphino)phenyl] ether.



Scheme 29. Stereospecific Ni/Lewis acid catalyzed cross-coupling of potassium alkenyltrifluoroborates with alkyl halides. HMDS = hexamethyldisilazide.



Scheme 30. Ni-catalyzed addition of boronic acids to carbonyls in CPME.

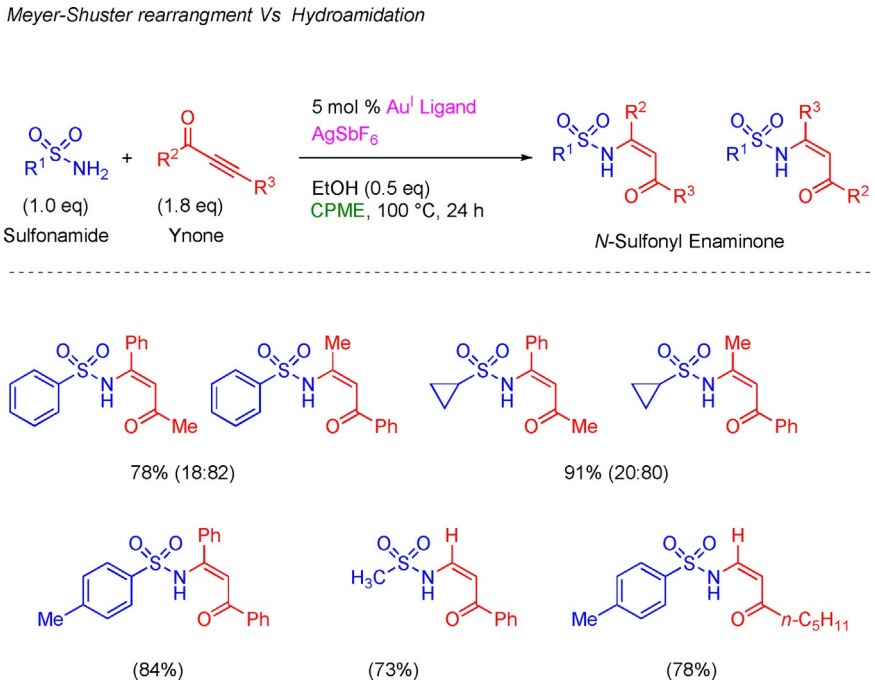


Scheme 31. Ir-catalyzed transformations in CPME.

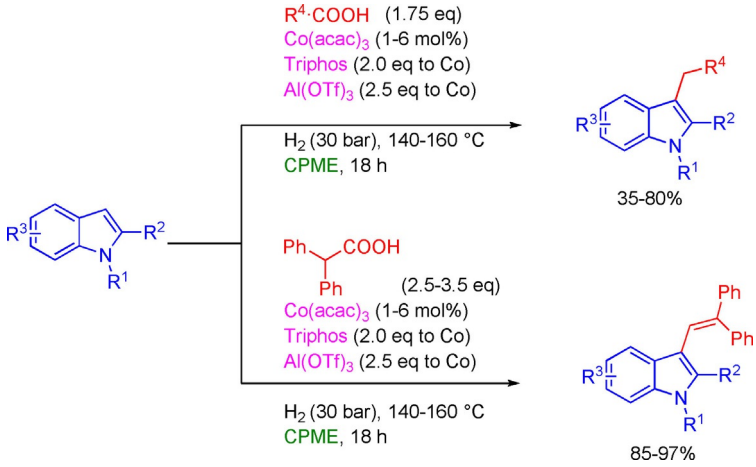
2.3. Use of CPME in organocatalysis

The phenyl sulfenate anion has been introduced as a new and versatile organocatalyst in the conversion of benzyl halides into symmetric *trans*-stilbenes; CPME has been proven to be superior to toluene, THF, and dioxane as the reaction medium (Scheme 34).[72]

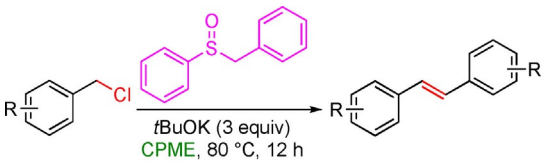
As illustrated in Scheme 35, the sulfenate anion behaves as both a good leaving group and a good nucleophile. Indeed, α-deprotonation of a catalytic amount of benzylic sulfoxide **A** followed by alkylation with a benzyl halide affords α-substituted sulfoxide **D**, which thereafter affords desired *trans*-stilbene and sulfenate anion **F**. As a result of its good nucleophilicity, anion



Scheme 32. Au-catalyzed coupling of alkynones and sulfonamides in CPME.



Scheme 33. Co-catalyzed reductive C–H alkylation of indoles with carboxylic acids and molecular hydrogen in CPME.



Scheme 34. Synthesis of symmetric *trans*-stilbenes.

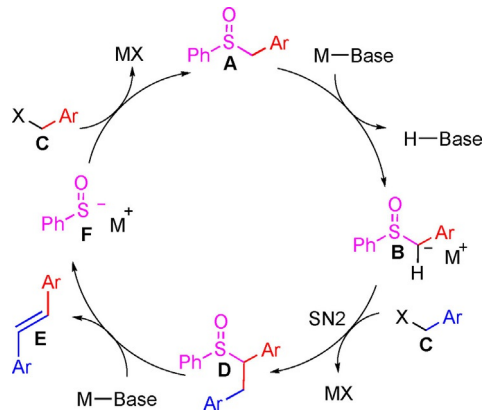
F reacts with the benzyl halide to regenerate the starting material, thus completing the catalytic cycle.

Theoretical calculations, taking into account the effect CPME, validate the proposed mechanism by employing the conductor polarizable continuum model (CPCM), implemented in the Gaussian09 package. The energy barrier calculated for each step at the DFT/M06-2X(6-311++G**) level shows a thermodynamically convenient process with the formation of sulfoxide **D** (Scheme 35, Figure 1) as the only real energy barrier (rate-determining step). Furthermore, the activation energy of this step (20.6 kcal mol^{-1}) indicates favorable kinetic conditions by performing the reaction in CPME at 80 °C (**TS1**, Figure 1).[73]

Under similar conditions, and to circumvent the problem that the first catalytic cycle installs a phenyl group on the *trans*-stilbene independent of the benzyl chloride under investigation, *tert*-butyl phenyl sulfoxide has successfully been employed as a traceless sulfenate anion precatalyst: indeed, mixing the precatalyst with the base in CPME cleanly affords the phenyl sulfenate anion together with isobutylene as a gaseous byproduct.[74]

Finally, the above-described procedure has successfully been applied to the coupling polymerization of compounds bearing two chloromethyl substituents on the same or on different linked aromatic rings, as depicted in Scheme 36. Such a benzylic chloromethyl coupling polymerization links the monomers by C=C bond formation, always employing CPME (or MTBE) as the preferred solvent.[75]

Several novel macroporous polystyrene-bound 1,5,7-triazabicyclo[4.4.0]dec-5-enes (PS-TBDs) have recently been prepared



Scheme 35. Proposed mechanism for the phenyl sulfenate anion catalyzed coupling of benzyl halides to symmetric stilbenes.

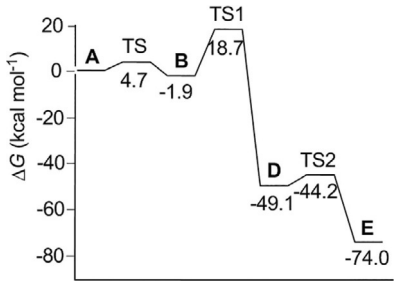
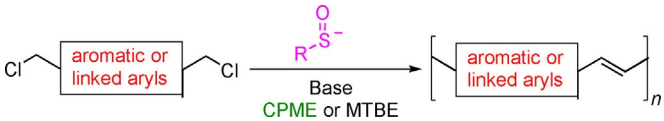


Figure 1. Free-energy profile [kcal mol^{-1}] for the conversion of benzyl chloride into *trans*-stilbene catalyzed by sulfenate anions calculated with DFT/M06-2X(6-311++G**) in CPME (CPCM model).

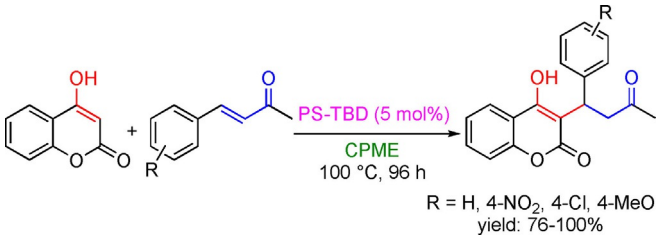
in the presence of different porogens, and their efficiency as basic organocatalysts has been tested in the Michael addition of 4-hydroxycoumarin to α,β-unsaturated ketones for the synthesis of biologically active 4-hydroxy-3-(3-oxo-1-arylbutyl)-2*H*-chromen-2-ones. Among other reaction media, CPME has been proven as the best choice, and it affords good to excellent conversions of the starting materials and additionally allows easy recovery and reuse of the catalysts (Scheme 37).[76]

Because of their capability to interact with different substrates as hydrogen-atom donors and/or acceptors, several modified and unmodified cinchona alkaloids have found wide application as asymmetric organocatalysts in a variety of reactions successfully performed in CPME.

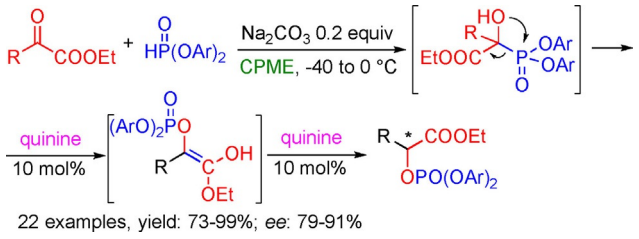
Indeed, CPME is superior to toluene as the reaction medium in the Na_2CO_3/quinine-catalyzed protonation of α-keto ester enolates prepared through the phospha-Brook rearrangement. According to the authors, the hydrophosphonyled α-keto esters are effectively coordinated by the organocatalyst, which thus promotes both the phospha-Brook rearrangement and



Scheme 36. Sulfenate anion catalyzed benzylic chloromethyl coupling polymerization.



Scheme 37. Synthesis of 4-hydroxy-3-(3-oxo-1-arylbutyl)-2*H*-chromen-2-ones.

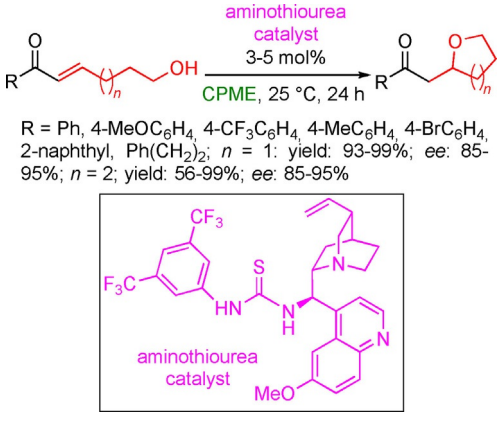


Scheme 38. Enantioselective protonation of α-keto esters enolates.

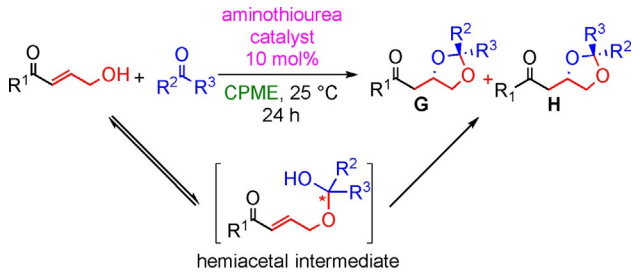
the enantiodetermining protonation step (Scheme 38). Interestingly, by substituting quinine with quinidine, the reaction products are obtained in good yields with excellent and opposite enantioselectivity.[77]

After a wide screening, CPME has been identified as the best solvent to synthesize several chiral oxacyclic frameworks through an enantioselective intramolecular oxy-Michael addition catalyzed by a thiourea derived from a cinchona alkaloid. This asymmetric methodology has successfully been applied to the synthesis of 2-substituted chiral tetrahydrofurans and tetrahydropyrans with high product yields and high *ee* values (Scheme 39).[78] According to the authors, the thiourea and tertiary amino groups of the catalyst cooperate as a hydrogen-bond donor and hydrogen-bond acceptor, respectively, and thus simultaneously activate both the electrophilic and nucleophilic centers of the substrate.

Under similar conditions, the organocatalyzed reaction of γ-hydroxy-α,β-unsaturated ketones with aldehydes and ketones

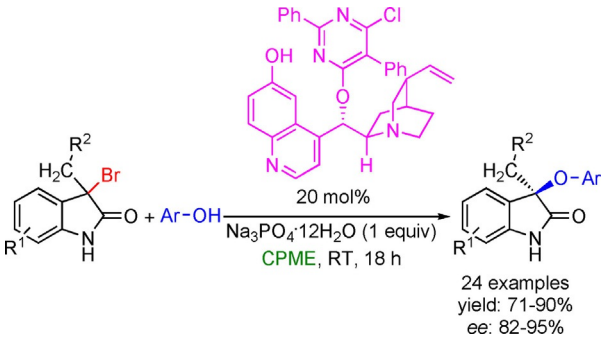


Scheme 39. Asymmetric synthesis of 2-substituted chiral tetrahydrofurans and tetrahydropyrans.



R^1 = Ph, 4-MeOC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 2-MeC$_6$H$_4$, 4-BrC$_6$H$_4$, 1-naphthyl, 2-thienyl, Ph(CH$_2$)$_2$, R^2 = *cyclo*-C$_6$H$_{11}$, Et, *i*Pr, *t*Bu , CF$_3$; R^3 = H, Ph: yield: 71-99%, *ee*: 90-98% (**G**), 31-91 (**H**), *dr* (**G**/**H**) = 1.2:1 - 4.7:1.

Scheme 40. Asymmetric synthesis of 4-substituted-1,3-dioxolanes.



Scheme 42. Asymmetric stereoablative aryloxylation of 3-bromooxindoles.

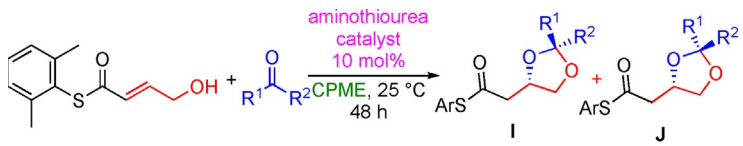
affords the corresponding chiral 1,3-dioxolanes in good to very good yields with the same level of enantioselectivity, most probably through the formation of hemiacetal intermediates (Scheme 40).[78b,79]

Further application of the last protocol has led to the asymmetric synthesis of protected β,γ-dihydroxy carboxyl derivatives, as depicted in Scheme 41. After screening several solvents (THF, Et_2O, benzene, CH_2Cl_2), the authors conclude that CPME is the best medium in terms of both the yield and stereoselectivity.[78b,80]

CPME has proved to be an efficient solvent for the enantioselective installation of chiral tetrasubstituted stereocenters at the C3 position of oxindole, a key step in the synthesis of a wide variety of biologically active compounds. Accordingly, an ether derived from a cinchona alkaloid has successfully been applied to the asymmetric stereoablative aryloxylation of 3-bromooxindoles. Under the optimized conditions, CPME is a better solvent than CH_2Cl_2, $CHCl_3$, THF, and 1,4-dioxane in terms of yield and selectivity (Scheme 42).[81]

During the development of an enantioselective approach for the synthesis of a gastrin/cholecyctokinin-B receptor antagonist, Nakamura, Shibata et al. reported optimized conditions leading to the asymmetric decarboxylative addition of malonic acid *S*-phenyl monothioesters to ketimines derived from isatins catalyzed by an 8-quinolinesulfonamide derivative of a cinchona alkaloid (Scheme 43).[82]

In the presence of a different sulfonamide of the same cinchona alkaloid and pentafluorobenzoic acid, CPME is superior to a variety of solvents (e.g., toluene, CH_2Cl_2, THF, MTBE, etc.) in promoting the enantioselective decarboxylative aldol condensation of aromatic and heteroaromatic aldehydes with α-amino-substituted malonic acid half oxyesters (Scheme 44).[83]



R^1 = Me, Et, *i*Pr, *t*Bu, *cyclo*-C$_6$H$_{11}$, R^2 = H, yield: 73-99%, *ee*: 95-99% (**I**), 81-97% (**J**); d.r. (**I**/**J**) = 3.4:1-4.4:1; R^1 = Ph, R^2 = CF$_3$: yield: 99%; *ee*: 69% (**I**), 72% (**J**); d.r. (**I**/**D**) = 1.1:1.

Scheme 41. Asymmetric synthesis of β,γ-dihydroxy carboxyl derivatives.

N-3,5-Bis(*tert*-butylbenzyl)cinchoninium bromide catalyzes the asymmetric 1,4-addition of glycinate Schiff bases to 4,4,4-trifluoro-1-arylbut-2-en-1-ones to afford, after treatment with concentrated HCl, β-trifluoromethylated pyrrolines in good to very good yields with the same levels of enantio- and diastereoselectivities. Under the optimized conditions, CPME is a better solvent than toluene, mesitylene, CH_2Cl_2, Et_2O, and THF (Scheme 45).[84]

Employing CPME as a reaction medium, *N*-acylimidazoles react with *tert*-butyldimethylsilyl 2-(bromomethyl)phenyl ether in the presence of a chiral triazolium pre-catalyst, CsF, 18-crown-6, and KOAc to afford a variety of dihydrocoumarins enantioselectively (Scheme 46).[85]

Under the optimized conditions, deprotonation of the precatalyst affords the corresponding N-heterocyclic carbene (NHC), which thereafter reacts with the *N*-acylimidazole to generate a nucleophilic NHC–enolate. This NHC–enolate reacts with in situ-generated electrophilic *o*-quinomethide (generated by the reaction of the protected silyl ether with CsF), which thus releases the organocatalyst and affords the desired dihydrocoumarins (Scheme 47).

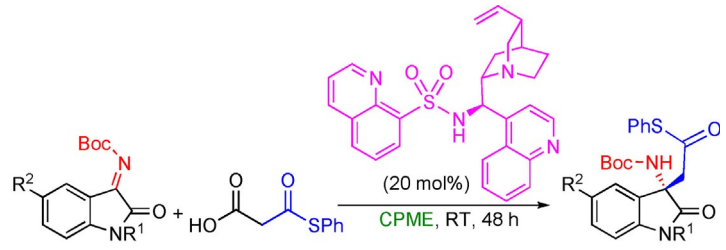
2.4. Use of CPME in acid-catalyzed reactions

As a result of its peculiar stability towards Brønsted and Lewis acids,[7] CPME is recognized as a particularly well-suited solvent to perform a variety of reactions under acidic conditions.

Taking advantage of the commercial availability of a 4 N solution of HCl in CPME, Watanabe et al. detail the development of an efficient synthesis of imino ether hydrochloride (Pinner salts), which are key intermediates for the transformation of nitriles into esters and amidines (Scheme 48).[86]

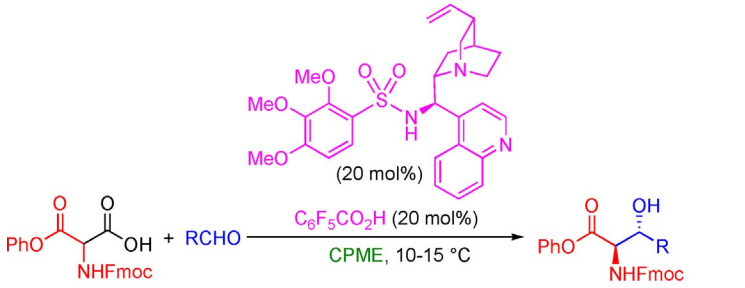
As a major advantage over known procedures, the employment of CPME as a solvent allows a particularly easy workup procedure that leads to isolation of the reaction products by simple filtration. As a further application, the same reagent can be employed in the deprotection of *N*-Boc-protected amino acids to give the corresponding amino acid hydrochlorides, which are usually insoluble in CPME.[86]

According to Ellman et al.,[87] CPME is a particularly useful solvent for reactions involving *tert*-butanesulfinamide as a chiral auxiliary in the asymmetric synthe-



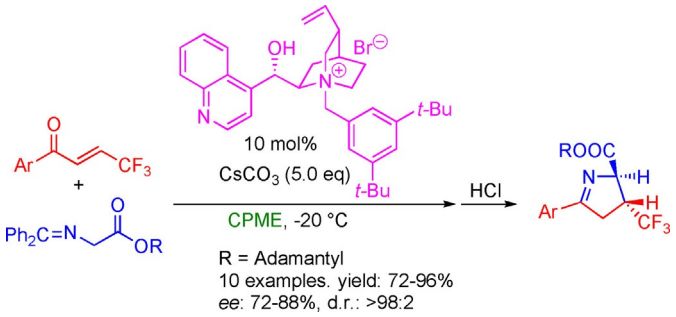
R^1 = Me, Et, *i*Pr, *cyclo*-C_5H_9, CH_3OCH_2, $PhCH_2OCH_2$, $CH_2{=}CHCH_2$, $(EtO)_2CHCH_2$, $PhCH_2$, 4-$CH_3OC_6H_4CH_2$, R^2 = H: yield: 58-90%, *ee*: 74-83%; $R^1 = R^2$ = Me: yield: 80%, *ee*: 80%; R^1 = Me, R^2 = OMe: yield: 81%, *ee*: 78%.

Scheme 43. Decarboxylative addition of malonic acid *S*-phenyl monoester to ketimines derived from isatins.



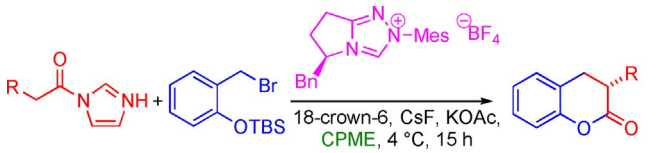
14 examples, yield: 23-99%
er up to 95:5, d.r. up to 90:10

Scheme 44. Enantioselective synthesis of *anti*-β-hydroxy-α-amino esters. Fmoc = 9-fluorenylmethoxycarbonyl.



R = Adamantyl
10 examples. yield: 72-96%
ee: 72-88%, d.r.: >98:2

Scheme 45. Asymmetric synthesis of β-trifluoromethylated pyrrolines.



15 examples, yield: 56-80%, e.r.: 75:25 - 93:7

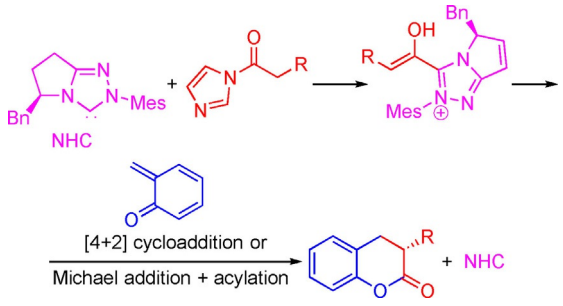
Scheme 46. Enantioselective synthesis of dihydrocoumarins. TBS = *tert*-butyldimethylsilyl, Bn = benzyl, Mes = mesityl.

sis of amines.[88] Indeed, the high bp and stability towards Lewis acids of CPME make it possible to obtain the corresponding *N*-*tert*-butanesulfinyl imines of poorly electrophilic and sterically hindered ketones in good yields, within short reaction times, and with very high enantiomeric excess (*ee*) values; this is a significant improvement over similar reactions run in a solvent with a lower bp, such as THF (Scheme 49).[87b]

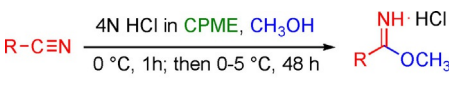
On the other hand, once imines are diastereoselectively transformed into the corresponding *N*-*tert*-butanesulfinyl amines, further reaction with HCl in CPME affords the hydrochlorides of the corresponding amines, which can be easily separated by filtration from a CPME solution of the configurationally unstable *tert*-butanesulfinyl chloride. The latter reacts with aqueous NH_3 to afford racemic *tert*-butanesulfinamide in quantitative yield. Alternatively, dynamic kinetic resolution of the sulfinyl chloride with ethanol in CPME and in the presence of a base and a catalytic amount of quinidine affords the corresponding ethyl ester, which can easily be converted into the corresponding amide in high yield with a high *ee* (Scheme 50).[87a]

CPME is superior to other solvents such as CH_2Cl_2, EtOAc, and THF to set up an efficient and ecosustainable modification of the Miyakoshi synthesis of β-nitro ketones. The desired products, notably including a β-nitro-β-substituted ketone, are obtained by the nitration of α,β-unsaturated ketones with a commercially available solid-supported nitrite (SSN) by employing CH_3COOH as a proton donor (Scheme 51).[89]

The ability of CPME to form a positive azeotrope with H_2O allows it to be used as an alternative to solvents with a higher environmental impact, such as toluene, in reactions run under

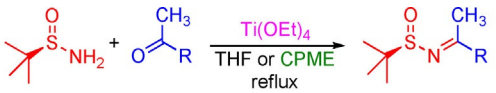


Scheme 47. Proposed reaction mechanisms for the NHC-catalyzed enantioselective synthesis of dihydrocoumarins. Mes = mesityl.



3 examples, yield: 86-91%

Scheme 48. Pinner reaction with HCl in CPME.



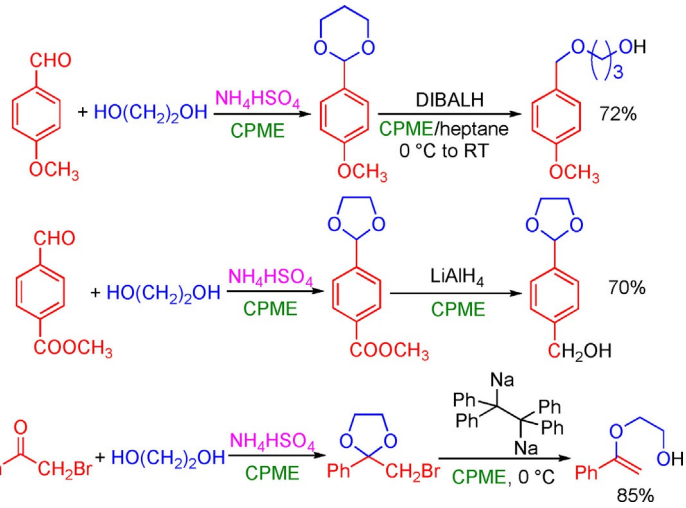
R = 4-$CH_3O(C_6H_4)$, reaction conditions: THF, 24 h, 79% yield, >99.5% *ee*; CPME, 6h, 90% yield, >99.5% *ee*. R = $(CH_3)_3C$, reaction conditions: THF, 48 h, 78% yield, >99.5% *ee*; CPME, 6h, 95% yield, >99.5% *ee*.

Scheme 49. Synthesis of *N-tert*-butanesulfinyl imines.

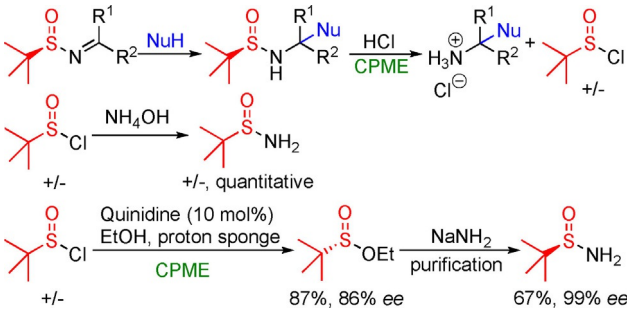
Dean–Stark conditions. Accordingly, a variety of aldehydes and ketones can efficiently be converted into the corresponding 1,3-dioxanes and 1,3-dioxolanes under azeotropic distillation conditions in the presence of ammonium salts as heterogeneous and recyclable acidic catalysts by keeping the diols to a low excess amount. Easy workup of the reaction mixture and the stability of the solvent towards strong nucleophiles allows further transformation of the crude products, always employing CPME as a solvent, as depicted in Scheme 52.[11b]

More recently, the employment of a comparable solvent/catalyst system has successfully been applied to the protection of functionalized and unfunctionalized alcohols and phenol as tetrahydropyranyl ethers, both representing alternatives to the employment of less environmentally friendly solvents, such as hydrocarbons, chloroalkanes, and dipolar aprotic solvents, and allowing a subsequent one-pot reaction of the products with strong nucleophiles (Scheme 53).[11a]

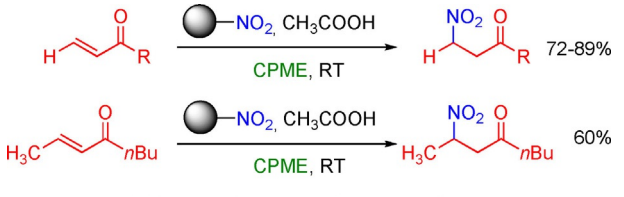
Chiral phosphoric acids catalyze the asymmetric addition of naphthols to *p*-quinone methides generated in situ by the dehydration of *p*-hydroxybenzyl alcohols. After evaluating the catalytic activities of different acids in Et_2O in the presence of 4 Å molecular sieves, the authors note that the yields and enantioselectivities could be significantly improved by using CPME as a solvent (Scheme 54).[90] The authors suggest that the observed good reactivity and high *ee* values are due to the occurrence of a pseudo-intramolecular transition state, in which the chiral phosphoric acid activates both the paraquinone methide electrophile and the naphthol nucleophile by hydrogen bonding.



Scheme 52. Acetalization of aldehydes and ketones under Dean–Stark conditions and further transformation of the reaction products.



Scheme 50. Recovery of racemic or optically pure *tert*-butanesulfinamide.



R = $Ph(CH_2)_2$, *n*-C_8H_{17}, 4-PhC_6H_4, Ph, 4-$CH_3OC_6H_4$, 4-$CF_3C_6H_4$, cyclo-C_6H_{11}, 2-furyl, $Cl(CH_2)_5$, Et, *n*Bu

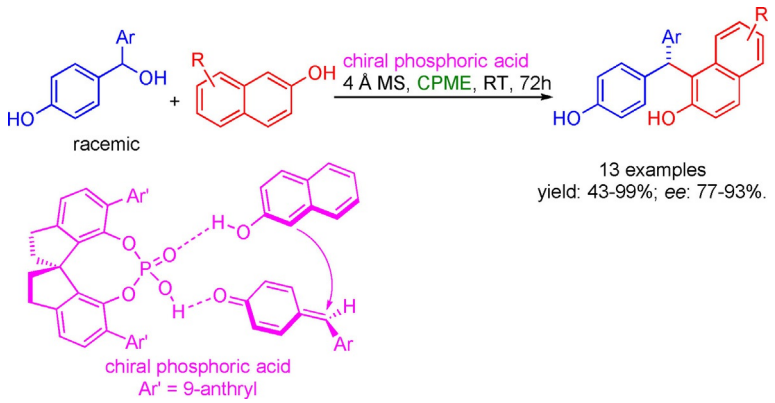
Scheme 51. Nitration of α,β-unsaturated ketones with SSN.

R = $Cl(CH_2)_6$, $Br(CH_2)_{11}$, $Ph(CH_2)_2$, 4-$Br(C_6H_4)CH_2$, 4-$Cl(C_6H_4)CH_2$, 4-$CH_3O(C_6H_4)CH_2$, 4-$MeOCO(C_6H_4)CH_2$, (-)-Menthol, (+/-)-Linalool, 4-$CH_3CO(CH_2)_2C_6H_4$, 4-*t*BuC_6H_4; yield: 84-92%

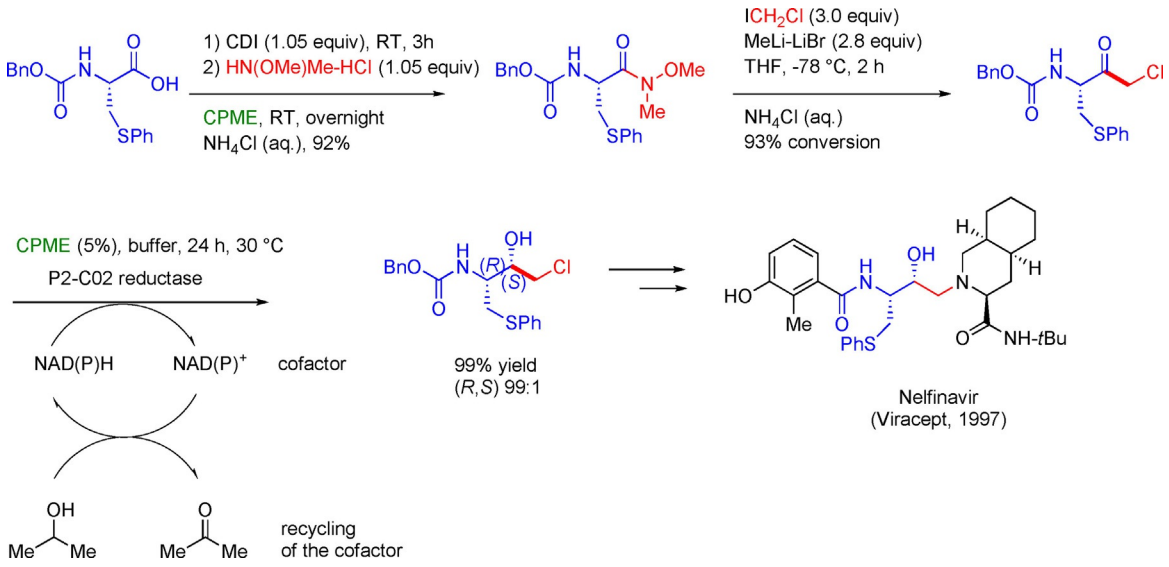
Scheme 53. Tetrahydropyranylation of alcohols and phenols in CPME.

2.5. Use of CPME in biocatalysis

Although organic solvents are often used in biocatalysis to solubilize substrates, from a sustainability perspective it is questionable if the recovery of the products and the removal of the same biocatalysts[91] fully adhere to the green chemistry philosophy. In this scenario, because of its limited miscibility in water, CPME constitutes a very promising reaction medium for biocatalysis, as two-phase reaction systems are possible and they foster product recovery. Pace and co-workers disclose the design of an effective diazomethane-free preparation of the HIV protease inhibitor nelfinavir[92] that is paved on the merging of two different chemical concepts: 1) homologation of a Weinreb amide with a lithium carbenoid;[93] 2) enzymatic reduction of the obtained α-haloketone (Scheme 55).[94] Notably, for both processes, CPME plays a significant role: it is an excellent medium for preparing the Weinreb amide[95] acylating



Scheme 54. Asymmetric addition of 2-naphthols to in situ generated *para*-quinone methides and suggested transition state.



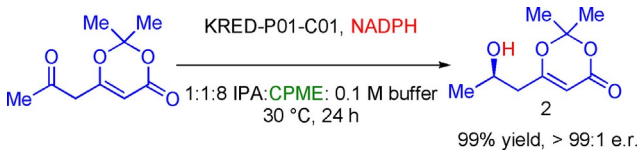
Scheme 55. Pace's synthesis of nelfinavir by Weinreb amide homologation and bioreduction in the presence of CPME as an additive. CDI = 1,1′-carbonyldiimidazole.

agent from the acid and is—by far—the ideal co-solvent for accomplishing the reduction.

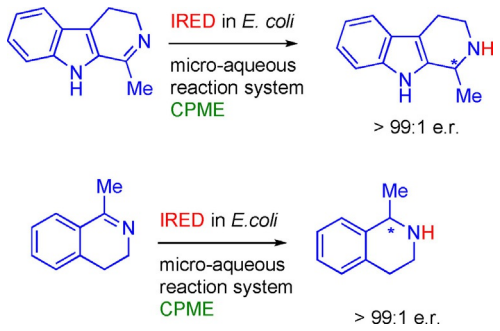
As a co-solvent, CPME has also found great utility in the optimization of a biocatalytic method for the enantioselective reduction of β-keto dioxinone bearing sp^3 carbon atoms adjacent to the stereogenic center. Scheidt et al. report an effective enantioselective strategy that overcomes the typical limitations observed with previously known methods, such as the need for a sp^2 center adjacent to the newly formed stereogenic center to get high stereoselectivity (Scheme 56).[96] Therefore, the use of CPME in phosphate buffer with 10% isopropyl alcohol (IPA) in the presence of an engineered ketoreductase allow β-hydroxydioxynones to be obtained from β-keto dioxinones in quantitative yields with an enantiomeric ratio (e.r.) of 99:1 by using a lower catalyst loading. Conversely, more hydrophobic "non-green" solvents, such as hexane and toluene, decrease the yield.

CPME has also been successfully employed as a solvent to accomplish the reduction of iminic-type functionalities such as β-carboline harmane and 1-methyl-3,4-dihydroisoquinoline to the corresponding amines in the presence of whole cells featuring imine reductases (IREDs) from *Streptomyces aurantiacus* and *Paenibacillus elgii* B69 (Scheme 57).[97] Under the optimized reaction conditions, good conversions (up to 96%) of 20 mM solutions of these hardly water soluble substrates are obtained, and the products are delivered with excellent enantiomeric excess values (>99%).

Petrenz et al. provide optimized reaction parameters for the chemoenzymatic dynamic kinetic resolution of *rac*-benzoin in batch and continuous mode (Scheme 58).[98] This investigation highlights that an immobilized lipase exhibits 1.6-fold higher activity and up to 1.5-fold higher half-life time in a more environmentally benign solvent such as CPME than in different solvents such as toluene and 2-MeTHF. Interestingly, this observation is consistent with the improved enzyme activity and enantioselectivity reported by Mine in 2005 for the transesterification of *rac*-solketal in CPME with the lipase from *Pseudomonas cepacia*.[99] Similarly, the authors use the solvent in a screening



Scheme 56. CPME in a biocatalytic approach to access β-hydroxydioxynones.



Scheme 57. Bioreduction of C=N functionalities in CPME.

for the preparation of the key enantiopure precursor of ivabradine, an alternative drug for the treatment of stable angina pectoris. The lipase-catalyzed kinetic resolution by alkoxycarbonylation of a racemic primary amine works well in terms of conversion and enantioselectivity in both CPME and 2-MeTHF.[100]

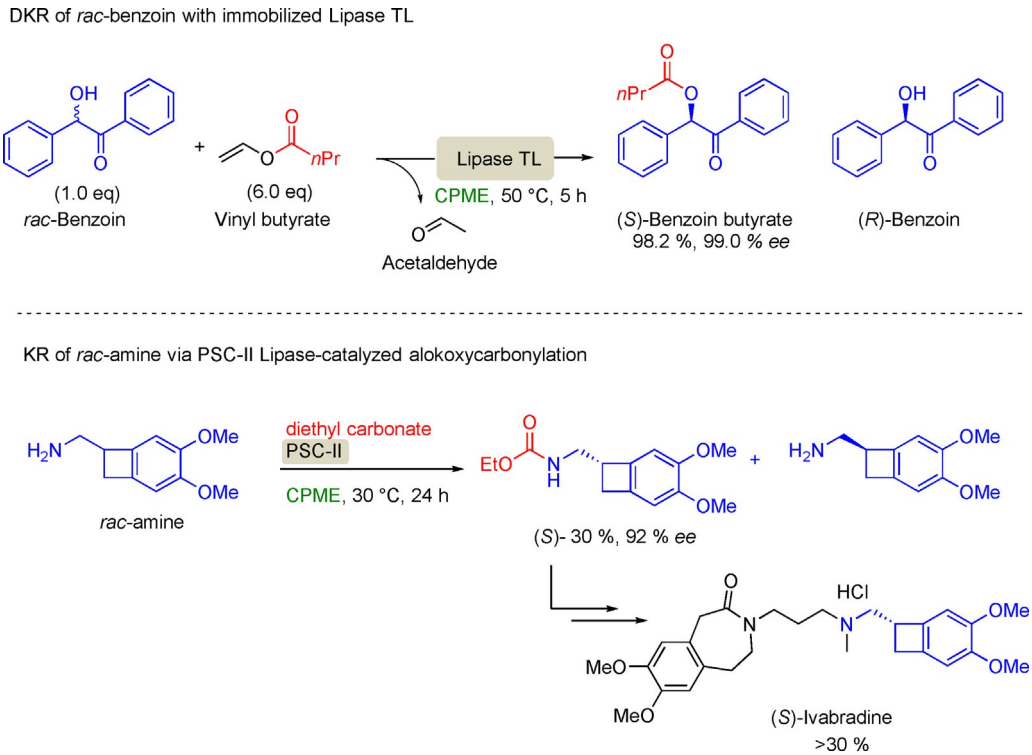
2.6. Use of CPME in reactions in biphasic systems

Because of its high hydrophobicity, CPME has found wide application in a variety of reactions performed in a CPME/H_2O biphasic reaction medium. Accordingly, the asymmetric alkylation of dipeptide-derived azlactones mediated by optically pure tetraaminophosphonium chlorides can be realized in a biphasic environment consisting of an organic solvent and a saturated aqueous solution of K_3PO_4. Under these conditions, CPME is superior to solvents such as Et_2O, MTBE, and toluene, and the desired products are delivered in higher yields with higher diastereomeric ratios (d.r. values). Owing to the ability of azlactones to be employed in the formation of new peptide bonds, this approach enables the asymmetric synthesis of oligopeptides containing quaternary α-amino acid residues at prerequisite positions (Scheme 59).[101]

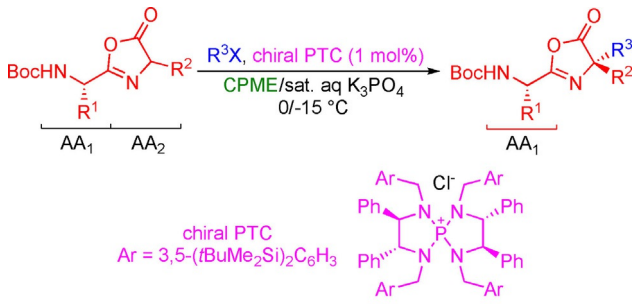
Similar installation of a chiral quaternary carbon center at the α position of cyclohexanones is a key step in the synthesis of biologically active compounds, such as morphine and strychnine. Starting with 2-arylcyclohexanones, their asymmetric alkylation is achieved in a CPME/H_2O biphasic system in the presence of a chiral ammonium bromide as a phase-transfer catalyst (PTC) (Scheme 60).[102]

The same biphasic system has significant benefits with respect to known commercial processes in the alkylation step leading to a new synthesis of darifenacin·HBr (Scheme 61).

At variance with earlier methods performed with organic solvents such as toluene, THF, and CH_3CN, the employment of a CPME/H_2O biphasic system allows easier monitoring of the reaction and easier purification of the reaction product. Finally,



Scheme 58. Lipase-catalyzed kinetic resolution processes in CPME.



AA_1 = Leu, Val, Pro, Gly, Phe; AA_2 = Phe, Trp, Leu; R^3X = AllylBr, $HCCCH_2Br$, $PhCH_2Br$, MeO_2CCH_2Br, $NCCH_2Br$, $MeOCH_2Cl$; yield: 66-98%; d.r. = 91:9-98:2

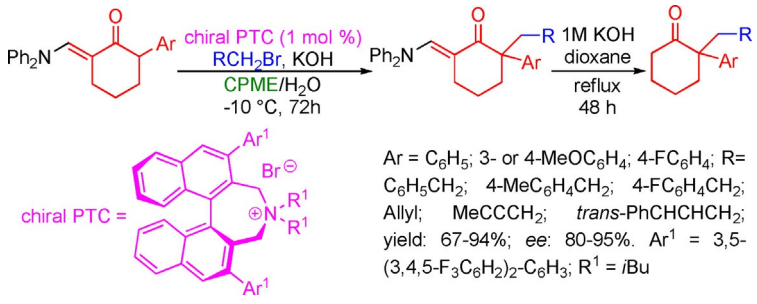
Scheme 59. Asymmetric alkylation of dipeptide-derived azlactones under phase-transfer conditions.

the high recovery percentage of CPME represents a distinct economic and environmental advantage of this procedure, also in view of its low enthalpy of vaporization.[103]

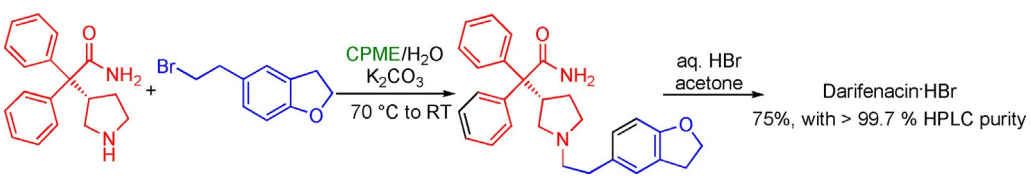
CPME has successfully been employed as a low-impact co-solvent to improve the yield and selectivity in the acid-catalyzed dehydration of xylose (or hydrolysis–dehydration of xylose-rich vegetal biomasses) to furfural. Indeed, in a biphasic system furfural is immediately extracted into the organic phase, which thus strongly inhibits the formation of otherwise inevitable byproducts.[104]

According to these premises, as an environmentally more friendly option, CPME is preferred over several other solvents to improve the yield of furfural. Indeed, the H_2SO_4-catalyzed dehydration of xylose in a biphasic CPME/aqueous NaCl system leads to the formation of furfural in approximately 60% yield at 85% conversion, whereas in the absence of the co-solvent, these values are 40 and 75%, respectively (Scheme 62 a).[104]

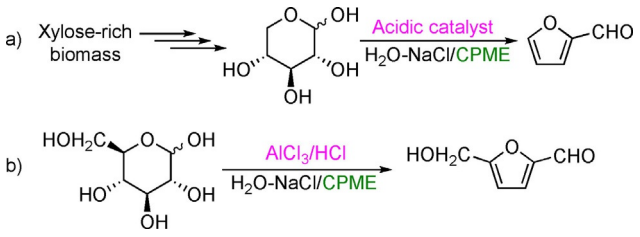
Furthermore, CPME has been chosen as a co-solvent in subsequent works aimed at developing the reaction under micro-



Scheme 60. Asymmetric alkylation of 2-arylcyclohenanones.



Scheme 61. A new synthesis of darifenacin·HBr.



Scheme 62. a) Dehydration of xylose to furfural. b) Isomerization/dehydration of glucose to 5-hydroxymethylfurfural.

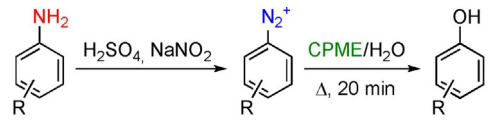
wave irradiation in the presence of efficient and environmentally more friendly homogeneous[105] and heterogeneous catalysts.[106]

Under related conditions, glucose and various disaccharides and polysaccharides are converted into 5-hydroxymethylfurfural through an isomerization (to fructose)/dehydration route that is synergistically catalyzed by an $AlCl_3$/HCl catalyst (Scheme 62 b).[107]

Likewise, 3-(4-nitrophenoxy)phenyldiazonium hydrogensulfate is hydrolyzed to the corresponding 3-(4-nitrophenoxy)phenol, an industrially important raw material in polymer synthesis. Indeed, diazotation and hydrolysis of 3-(4-nitrophenoxy)aniline in pure H_2O affords the desired product in modest yield, together with a tar byproduct probably formed through a diazo-coupling reaction. On the other side, CPME is superior to more than 20 organic solvents in performing the same reaction in a two-phase organic solvent/H_2O system to afford 3-(4-nitrophenoxy)phenol in almost quantitative yield (Scheme 63). Similarly, a variety of substituted phenols are synthesized in satisfactory to excellent yields.[108]

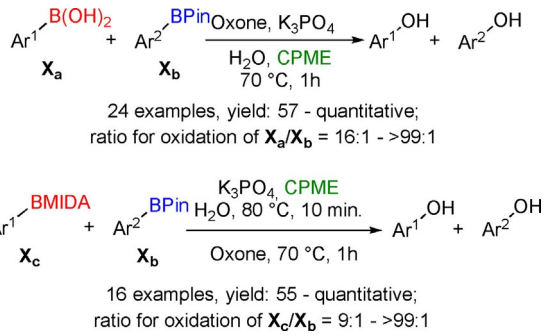
The employment of the oxidizing basic biphasic system Oxone/K_3PO_4/H_2O/solvent allows the conversion of aryl organoboronic acids into the corresponding H_2O-soluble trihydroxyboronates, which can subsequently be oxidized to the corresponding phenols in the aqueous phase. It is noted that CPME is the best solvent out of a group of 11 solvents tested, and it allows the quantitative oxidation of boronic acids and very high chemoselectivities in the presence of the corresponding boronic acid pinacol (BPin) esters, which are not extracted into the H_2O layer and, therefore, survive oxidation (Scheme 64).[109] No conversion is observed in a purely organic solvent (i.e., THF), and practically no selectivity is observed in the absence of base.

Under optimized conditions, it is also possible to oxidize arylboronic acid *N*-methyliminodiacetic acids (BMIDA) esters chemoselectively in the presence of



R = H, 3-(4-NO_2-C_6H_4O), 3-C_6H_5O, 3-$C_6H_5CH_2O$, 3-*i*Pr; 3-Me; 3-MeO; 3-Ac; 3-NO_2, 3-CF_3, 3-COOH, 2-Me-4-COOH, 4-Me-2-COOH; yield: 56-98%.

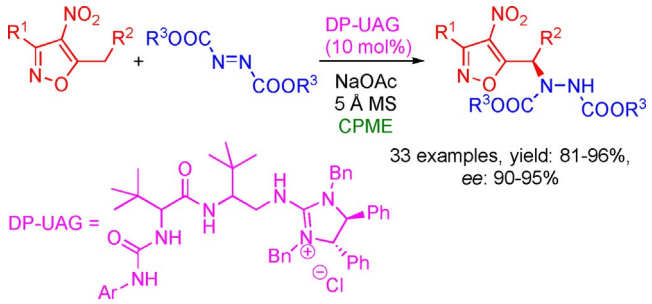
Scheme 63. Hydrolysis of diazonium salt in CPME/H_2O.



Scheme 64. Chemoselective oxidation of arylboronic derivatives.

BPin esters through a two-step, one-pot controlled hydrolysis–oxidation reaction path (16 examples).

Finally, it is notable that a dipeptide-based urea–amide–guanidinium (DP-UAG) can successfully be employed as a solid–liquid phase-transfer catalyst in the enantioselective vinylogous amination of 5-alkyl-4-nitroisoxazoles (Scheme 65).[110] Under the optimized conditions, CPME is superior to other solvents, including toluene, Et_2O, and THF.



Scheme 65. Enantioselective vinylogous amination of 5-alkyl-4-nitroisoxazoles.

2.7. Use of CPME in oxidation processes

The chemical stability of CPME to oxidation can be exploited in the epoxidation of alkenes with hydrogen peroxide catalyzed by polyoxometalate nanoparticles. Indeed, within a set of 18 ecofriendly solvents plus MeCN and $CHCl_3$, tris-dodecyltrimethylammonium [$PW_{12}O_{40}$] in CPME and 2-MeTHF give the best results in terms of turnover frequency (TOF) (Figure 2).[111]

Moreover, CPME is the best choice to ensure that the catalyst nanoparticles remain in suspension. The described procedure has successfully been extended to various olefins with competitive rates, good yields, and high selectivities, and the nanoparticles can be easily separated from the reaction product and recycled over five consecutive steps.[111]

The oxidation of ynamides to α-keto imides has been realized by a combination of *N*-iodosuccinimide (NIS), DMSO, and air, and the best results are afforded in CPME, possibly also because of its inherent stability to the acidity developed during the reaction (Table 2).[112]

The substrate scope can be extended to nine additional examples, and the products are obtained in moderate to acceptable yields; furthermore the oxidation of diarylalkynes to the corresponding 1,2-diketones is also possible (seven examples).

Mizuno et al. describe optimized reaction conditions to convert terminal alkynes and tertiary amines into propargylamines.[113] Such a cross-dehydrogenative coupling occurs in the presence of a catalytic amount of $ZnBr_2$ and a manganese oxide based octahedral molecular sieve (OMS-2) under an oxygen atmosphere. The proposed mechanism involves OMS-2 as a single-electron-transfer (SET) acceptor and a tertiary amine (employed in excess amount) as a base to deprotonate the alkyne. Reoxidation of OMS-2 by molecular oxygen completes the catalytic cycle (Scheme 66).

Mashima et al. delineate an investigation into the dehydrogenative coupling of primary alcohols with amines that occurs through the intermediate formation of aldehydes and hemiaminals and thereafter leads to the formation of the corresponding amides and/or imines.[114] The authors carefully screen different Ru catalysts, bases, and additives and note that CPME is the best solvent for the highly chemoselective synthesis of amides. A different set of reaction conditions lead to the chemoselective synthesis of imines (Scheme 67).

2.8. Use of CPME in radical-mediated reactions

Owing to its relatively high bp and stability towards hydrogen-atom abstraction, CPME is an effective reaction medium for radical reactions. Accordingly, the AIBN- or 2,2′-azobis(2,4-dimethylvaleronitrile) (V-65)-promoted hydrostannation, hydrosilylation, and hydrothiolation of several alkenes and alkynes can successfully be run in CPME (Scheme 68).[12]

Furthermore, CPME has successfully been applied as a reaction medium in multistep reactions consisting of hydrostannation followed by Pd-catalyzed coupling and organometallic addition to afford highly efficient one-pot processes within a wide range of reaction temperatures (from +90 to −78 °C).[12]

Finally, CPME is efficient in promoting the radical reduction of a few bromides and in the Barton–McCombie radical deoxygenation of several thiocarbonates (Scheme 69).[12] The last reaction has found further applications in the related deoxygenation of some intermediates in the synthesis of natural products.[115]

Noteworthy, the ecofriendly nature of CPME has found successful application in the atom-transfer radical polymerization

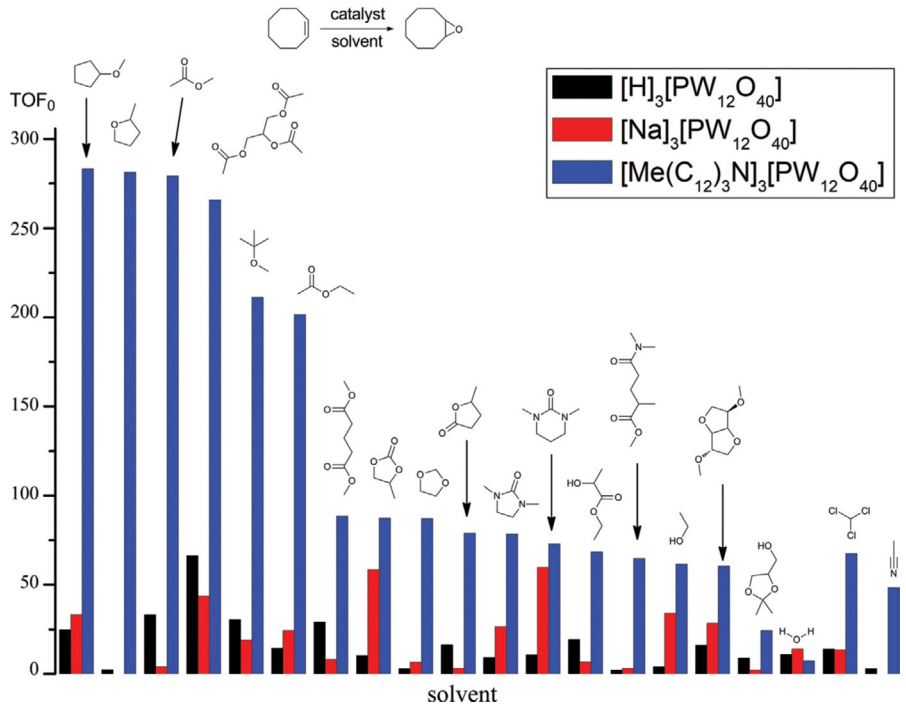
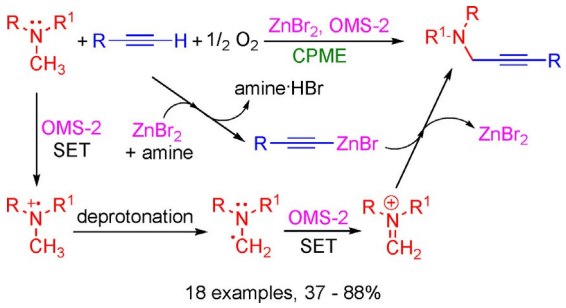


Figure 2. Initial turnover frequency (TOF_0) observed for the epoxidation of cyclooctene in various solvents.

Table 2. Oxidation of ynamides to α-keto imides.[a]

Entry	Solvent	Yield [%]
1	CPME	84
2	CPME	0[b]
3	CPME	85[c]
3	THF	51
4	DMSO	74
5	DMF	63
6	acetone	68
7	2-propanol	39
8	toluene	58

[a] Ts = tosyl. [b] Reaction run under an argon atmosphere. [c] Reaction run under an O_2 atmosphere.

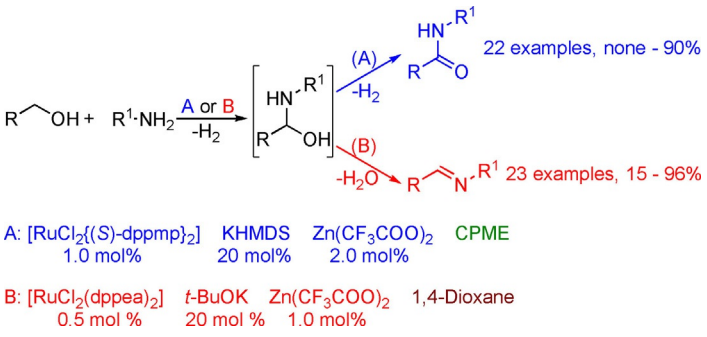


Scheme 66. Aerobic cross-dehydrogenative coupling of terminal alkynes with tertiary amines.

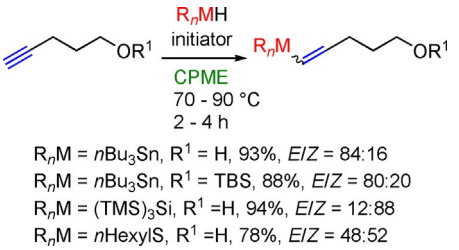
of several vinyl monomers promoted by supplemental activators and reducing agents such as Fe^0, Cu^0, and $Na_2S_2O_4$.[116]

2.9. Use of CPME in amidation-type reactions

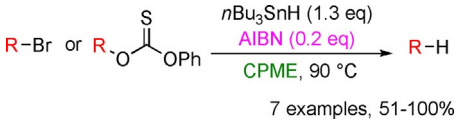
The formation of amide bonds under environmentally friendly conditions is a topic of great interest for both academia and the pharmaceutical industry. Accordingly, the activation of carboxylic acids with borate esters appears as a particularly interesting procedure, owing to both its effectiveness and ease of workup.[117] Within a broad solvent screening, CPME, probably thanks to its relatively high boiling



Scheme 67. Chemoselective dehydrogenative coupling of alcohols and amines. dppmp = (*S*)-2-[(diphenylphosphenyl)methyl]pyrrolidine, dppea = 2-diphenylphospinoethylamine.

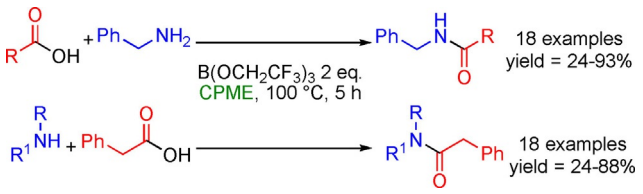


Scheme 68. Radical additions of nBu$_3$SnH, (TMS)$_3$SiH, and n-HexylSH to alkynes. TBS = *tert*-butyldimethylsilyl, initiator = AIBN or V-65.



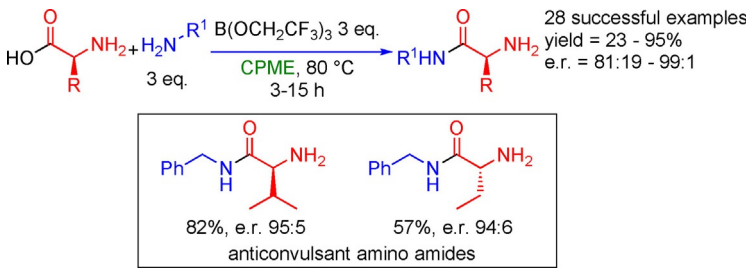
Scheme 69. Barton–McCombie radical deoxygenation of thiocarbonates.

point, has been proven to be a highly effective reaction medium to perform the $(CF_3CH_2O)_3B$-promoted amidation of a wide set of functionalized carboxylic acids and amines of pharmaceutical interest "specifically selected by researchers […] as difficult substrates". Under optimized reaction conditions, 18 out of 21 acids and 18 of 21 amines afford the desired products in fair to good yields (Scheme 70).[118]



Scheme 70. Borate ester-mediated amidation.

A slightly modified procedure has successfully been applied to the direct amidation of unprotected amino acids with a range of amines; the lack of significant self-reaction of the amino acid is a notable feature of this procedure, and good yields are obtained for the majority of the common proteogenic α-amino acids and for several unnatural amino acids. Additionally, two anticonvulsant amino amides can be synthesized in good yields with good enantiomeric ratios (Scheme 71).[119]



Scheme 71. Amidation of amino acids with various amines.

Finally, in-depth investigation by Albericio and co-workers is worth mentioning to highlight the reaction conditions under which CPME (or, even better, 2-MeTHF) can be employed as a green alternative in peptide synthesis. After screening a wealth of reaction conditions, including different coupling reagents, additives, and resins, the authors conclude that the best results for both solvents can be obtained by using *N*,*N*′-diisopropylcarbodiimide as a coupling reagent with ethyl 2-cyano-2-hydroxyimino acetate (OxymaPure) as an additive on, preferably, polystyrene or polyethylene glycol resins.[120]

2.10. Use of CPME in chromatography

Chromatographic purification of reaction products consumes the largest quantity of solvents employed in the synthesis of fine chemicals. Accordingly, the replacement of chlorinated solvents with equally efficient, albeit environmentally friendly, solvents is a topic of major concern for both academia and the pharmaceutical industries.

It is, therefore, notable that MeOH/CPME solvent mixtures offer considerable potential as a replacement of similar MeOH/CH_2Cl_2 binary eluents within the chromatographic purification of a large set of compounds of interest in medicinal chemistry.[121] Successful application of the same solvent mixtures to the resolution of enantiomers by supercritical fluid chromatography on chiral stationary phases has also been described.[122] Finally, CPME has been indicated to be an effective alternative to $CHCl_3$ in the liquid-phase chromatography of lipids.[123]

3. Outlook and Perspective

The wide variety of examples collected in this Review show that the physicochemical properties of CPME (low toxicity, high boiling and low melting points, hydrophobicity, relatively low latent heat of vaporization, and chemical stability towards a wide range of conditions) make it a good solvent for a vast array of reactions, spanning from the different fields of catalysis to organometallic chemistry and biphasic reactions.

Furthermore, its noteworthy stability towards hydrogen-atom abstraction allows its (seemingly safe) use in a wide range of oxidation and radical reactions. To widen this kind of application, it would be even more useful if researchers involved in this chemistry would verify the possible formation of peroxides in the reaction solvent.

Additionally, the versatility of this solvent has been turned into an advantage in several examples, for which its utilization in the setup of one-pot, multistep syntheses, a field worthy of further exploitation in the future, has been reported.

At the same time, a significant contribution to more sustainable laboratory waste management could derive from its broader use as a substitute for chlorinated solvents in the chromatographic purification of reaction products.

Finally, it is notable that CPME is currently produced from nonrenewable sources with a 100% atom-economical and highly efficient synthesis that

outperforms a potential derivation from renewable sources. However, recent progress in the conversion of furfural into cyclopentanol,[124] a potential precursor of CPME, suggests the future realization of a favorable biobased production of this solvent; this event could improve its "greenness", which would thus promote the even wider use of CPME in organic synthesis.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: ethers · green chemistry · organometallic chemistry · solvent effects · synthetic methods

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