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PPh_3-Assisted Esterification of Acyl Fluorides with Ethers via C(sp^3)–O Bond Cleavage Accelerated by TBAT

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Abstract: We describe the (triphenylphosphine (PPh_3)-assisted methoxylation of acyl fluorides with cyclopentyl methyl ether (CPME) accelerated by tetrabutylammonium difluorotriphenysilicate (TBAT) via regiospecific C–OMe bond cleavage. Easily available CPME is utilized not only as the solvent, but a methoxylating agent in this transformation. The present method is featured by C–O and C–F bond cleavage under metal-free conditions, good functional-group tolerance, and wide substrate scope. Mechanistic studies revealed that the radical process was not involved.

Keywords: Acyl fluorides; cyclopentyl methyl ether (CPME); tetrabutylammonium difluorotriphenysilicate (TBAT); carbon-oxygen bond cleavage; esterification

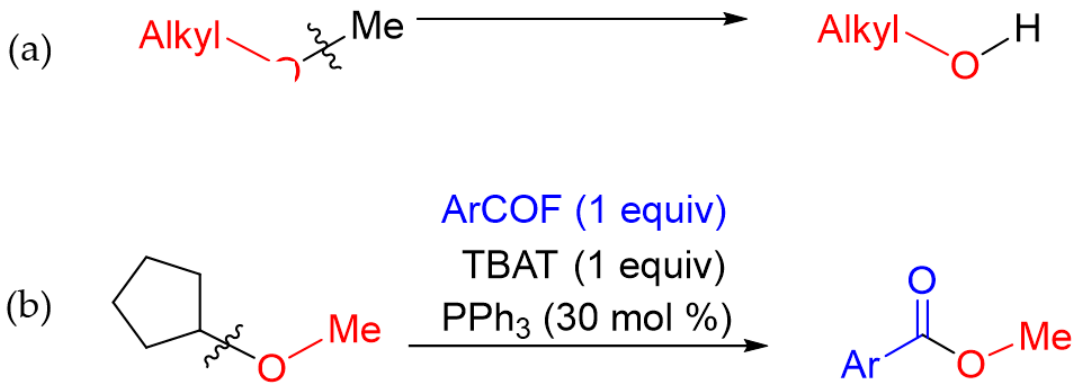
1. Introduction

The C−O bond cleavage in ethers is one of the most fundamental transformations in organic synthesis and has been widely applied in the manufacturing of fine chemicals as well as the synthesis of polyfunctional molecules [1–5]. Particularly, the preparation and degradation of ethers have often been considered important synthetic strategies for the protection/deprotection of hydroxyl groups. Although numerous studies on demethylation in aromatic methyl ethers have been reported [6–10], demethylation of viable aliphatic surrogates has been relatively less explored. Typically, various reagents have been utilized to convert aliphatic methyl ethers into the corresponding alcohols via demethylation (Scheme 1a), employing $BF_3{\cdot}Et_2O/(CH_3CO)_2O$ [11], BCl_3 [12], BBr_3 [13], $BF_3{\cdot}Et_2O$/EtSH [14], Me_3SiI [15], hydrobromic acid/phase-transfer-catalysts [16], BBr_3/NaI/15-crown-5 [17], $(CH_3)_2BBr$ [18], $AlCl_3$/NaI/CH_3CN [19], or BI_3/*N*,*N*-diethylaniline [20].

On the other hand, since 2005, cyclopentyl methyl ether (CPME) [21,22] has become the common solvent in organic reactions [23–25]. Compared with other conventional ethereal solvents such as diethyl ether (Et_2O), tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), 1,4-dioxane, methyl *tert*-butyl ether (MTBE), and 2-MeTHF, CPME displays many advantages, such as low cost, high-boiling point (106 °C), low polarity, lower miscibility with water (1.1 g/100 g), low tendency to form peroxides, narrow explosion range, and stability under strong acidic and basic conditions. With these characteristics of CPME in mind, the utility of CPME as a potential reactant in various organic transformations are attractive. However, to the best of our knowledge, the selective C−O bond cleavage in CPME [26] and the utilization of released methoxy group as a methoxylating agent [27] has been unexplored.

Numerous examples for utilization of acyl fluorides in synthetic organic chemistry have been reported [28], while recently, unique reactivity of acyl fluorides has been extensively disclosed due

to their strong electrophilicity and high stability [29,30]. Transformations of acyl fluorides into other valuable molecules have been well demonstrated by others [31–36] and our group [37–40]. As a part of our ongoing interest in the functionalization of acyl halides, we herein report the nucleophilic methoxylation of acyl fluorides with CPME assisted by PPh_3 via both C−OMe and C−F bonds cleavage under metal-free conditions (Scheme 1b).



Scheme 1. C−O cleavage in alkyl methyl ethers. (**a**) Conventional demethylation of aliphatic methyl ethers (deprotection), (**b**) This work.

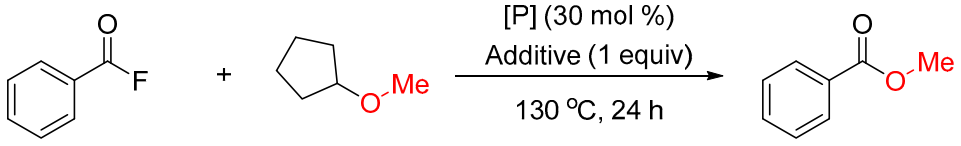
2. Results and Discussion

When we conducted the reaction of benzoyl fluoride (**1a**) with CPME (**2a**), giving rise to methyl benzoate (**3a**) in the presence of a catalytic amount of PPh_3, various additives were screened. As shown in Table, tetrabutylammonium difluorotriphenylsilicate (TBAT) [41] as the additive sufficiently increased the yield of **3a** in 74% yield (Table 1, entry 1). PPh_3 showed superior result than other monodentate phosphine ligands (entries 2–5). Compared to TBAT, several tetrabutylammonium halides such as tetrabutylammonium fluoride, -chloride, -bromide, and -iodide were tested, but they were found to be inferior (entries 6–9). Markedly, tetrabutylammonium trifluoromethanesulfonate (NBu_4OTf) did not work at all (entry 10). With regard to other fluoride sources, poor results were obtained when potassium fluoride (KF) or cesium fluoride (CsF) was employed (entries 11–12). Interestingly, in the presence of 18-crown-6, KF gave 34% of **3a** (entry 13), which might prove the importance of a naked fluoride ion. Notably, no trace of **3a** was detected with fluorotriphenysilane (entry 14) or without TBAT (entry 15), indicating that TBAT uniquely accelerated this methoxylation event (Table S1). Careful control experiments resulted in an unexpected accelerating effect on methoxylation with 30 mol % of PPh_3 (entry 1 *vs* entry 16), suggesting that an addition of PPh_3 can enhance the electrophilicity of acyl fluorides, to some extents (Table S2) [42]. It is noteworthy that the identical reaction with benzoyl chloride afforded the lower yield of **3a** (entry 17), suggesting a unique feature of acyl fluoride in this transformation.

With the optimized reaction conditions in hand, we investigated the scope and limitation of the methoxylation of an array of acyl fluorides **1** with CPME. As shown in Figure 1, this protocol displayed remarkable tolerance towards the substitution pattern and a steric effect. Both electron-donating and sterically encumbering substituents in any positions of the aryl ring gave good results. Another interesting feature of this reaction is that alkyl aryl ethers such as **3c** and **3d** were inert under the conditions. Acyl fluorides bearing electron-donating groups provided the corresponding products **3e**–**3g** in 64–90% isolated yields. When acyl fluorides with electron-withdrawing groups were employed, except for 4-nitrobenzoyl fluoride (**1i**), the desired products **3h**, **3j**, and **3k** were obtained in good yields. Particularly, an ester group can also be tolerated, affording the target product **3l** in 75% yield, which is noteworthy because the esters are known to be incompatible with Me_3SiI [15]. Either more sterically hindered (**3n**) or more electron-rich (**3o**) products were successfully formed in this transformation. Polyaromatic products including naphthalenes (**3p**–**3q**) and anthracene (**3r**) motifs also exhibited moderate to good levels of reactivity. Moreover, oxygen- (**3s** and **3t**), sulfur-containing heterocycles

(**3u**) did not interfere toward the ester formation. To our delight, the primary and tertiary alkylated acyl fluorides also could accommodate under optimal conditions, afforded corresponding ester **3v** and **3w** in moderate yields.

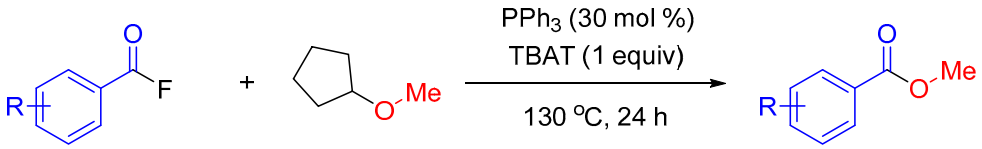
Table 1. Optimization of the reaction conditions.



1a **2a** **3a**

Entry	[P]	Additive	Yield of 3a (%) [1]
1	PPh_3	TBAT	74 (74)
2	$P(OPh)_3$	TBAT	40
3	PCy_3	TBAT	50
4	P^tBu_3	TBAT	45
5	$P(4\text{-}F\text{-}C_6H_4)_3$	TBAT	55
6	PPh_3	NBu_4F	46
7	PPh_3	NBu_4Cl	30
8	PPh_3	NBu_4Br	14
9	PPh_3	NBu_4I	25
10	PPh_3	NBu_4OTf	0
11	PPh_3	KF	12
12	PPh_3	CsF	14
13	PPh_3	18-crown-6/KF	34
14	PPh_3	Ph_3SiF	0
15	PPh_3	-	0
16	-	TBAT	53
17 [2]	PPh_3	TBAT	50

[1] Determined by gas chromatography (GC) analysis of the crude mixture using *n*-dodecane as an internal standard. An isolated yield is given in parentheses. [2] Benzoyl chloride was employed instead of **1a**.



1 **2a** **3**

Figure 1. *Cont.*

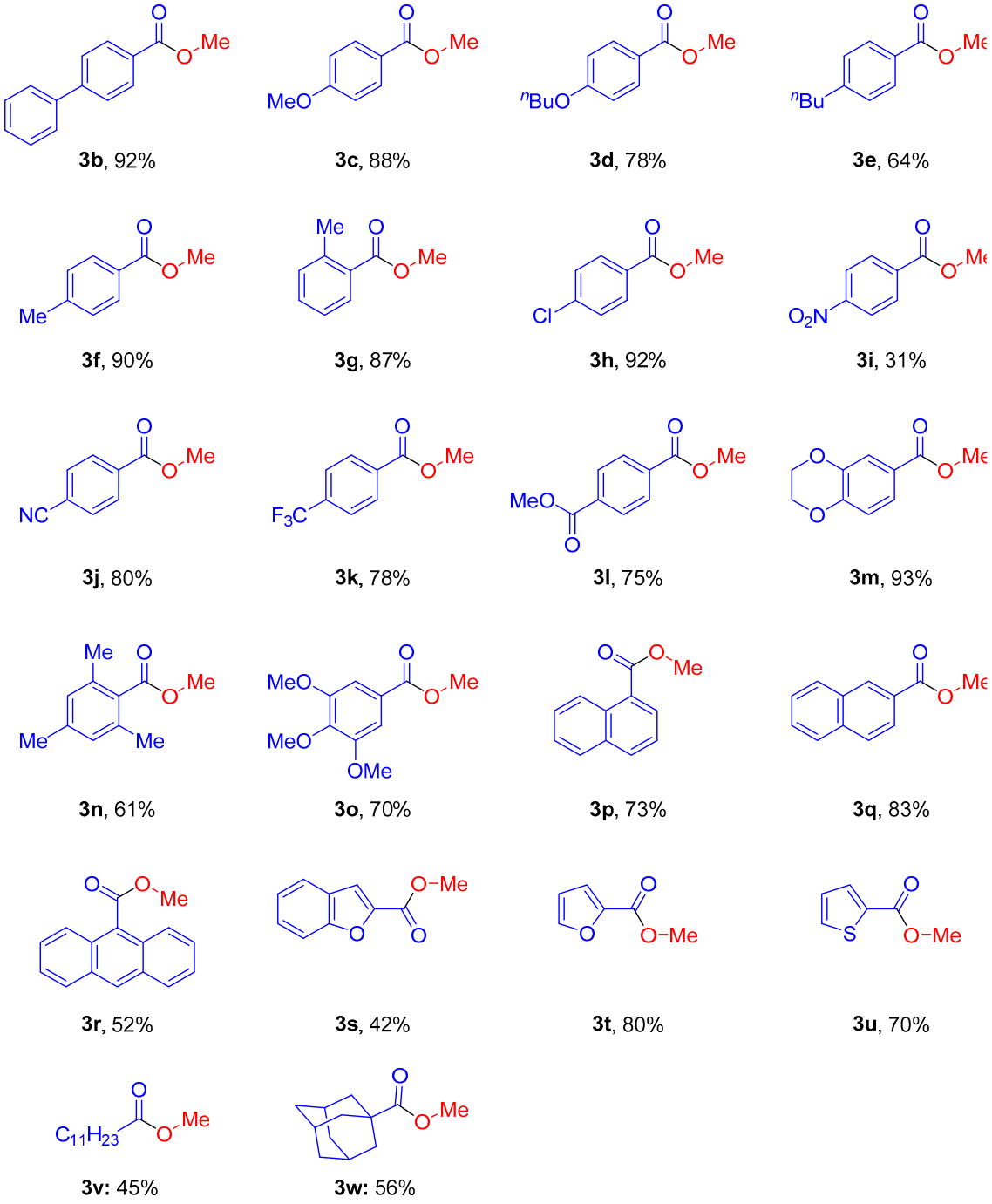
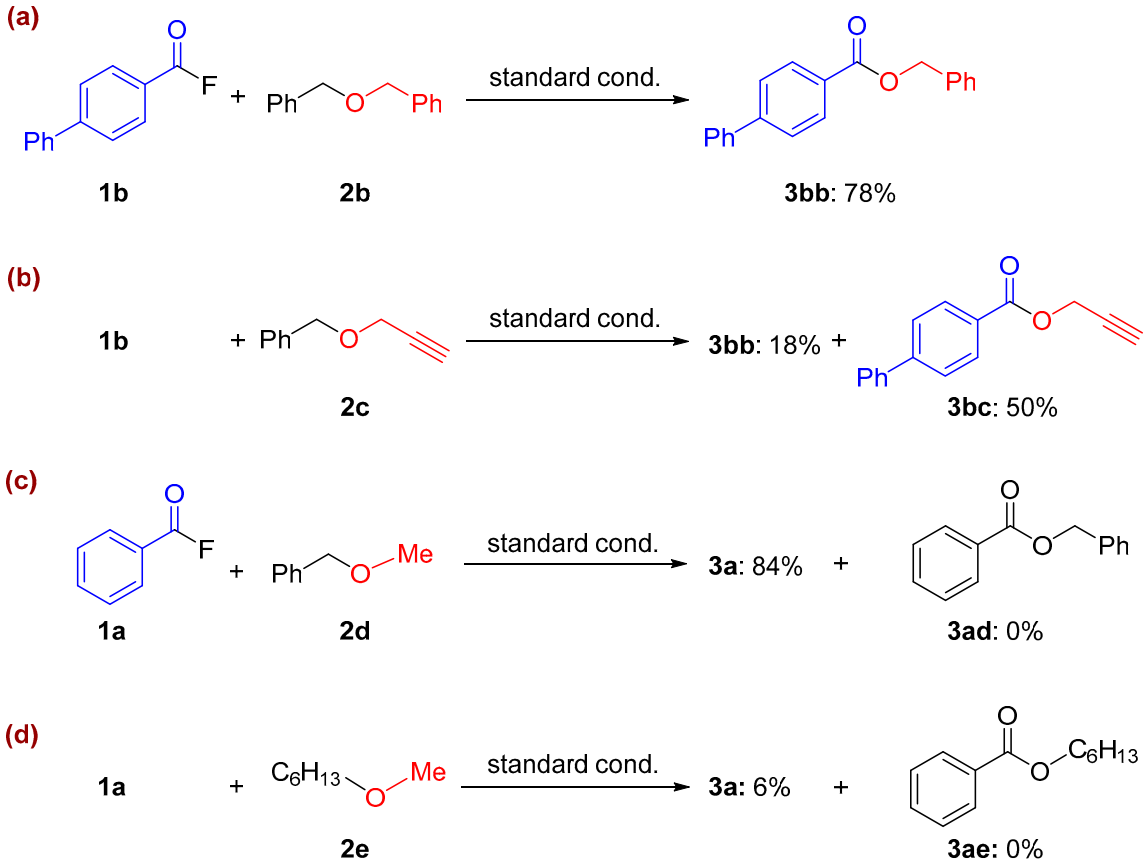


Figure 1. Methoxylation of acyl fluorides **1** with CPME (**2a**) [a,b]. [a] Reaction conditions: acyl fluorides **1** (0.2 mmol), **2a** (2 mL), PPh_3 (0.06 mmol), TBAT (0.2 mmol), 130 °C, 24 h. [b] Isolated yields.

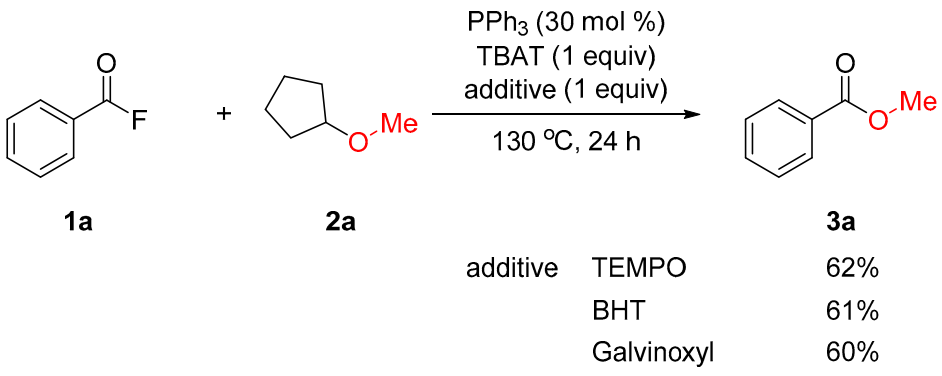
Given a regiospecific cleavage of C–O bond in CPME, we reasoned that other ethers could also be applied in alkoxylation of acyl fluorides (Scheme 2). Dibenzyl ether (**2b**) was also a good substrate, resulting in the formation of **3bb** in 78% yield (Scheme 2a). When benzyl propargyl ether (**2c**) was employed, a propargyl group was installed preferentially into the product to afford **3bc** in 50% yield, along with 18% of **3bb** (Scheme 2b). Subsequently, unsymmetrical benzyl methyl ether (**2d**) smoothly gave **3a** in 84% yield with a high regiospecificity (Scheme 2c). In a sharp contrast, *n*-hexyl methyl ether failed to undergo the reaction, leading to only 6% of **3a** and no competitive product **3ae** was detected (Scheme 2d). Although the cleavage patterns highly depend on the reagents added [1–5],

the regiospecific C–O bond cleavage in this transformation can be explained by the stability of the resulting carbocations.



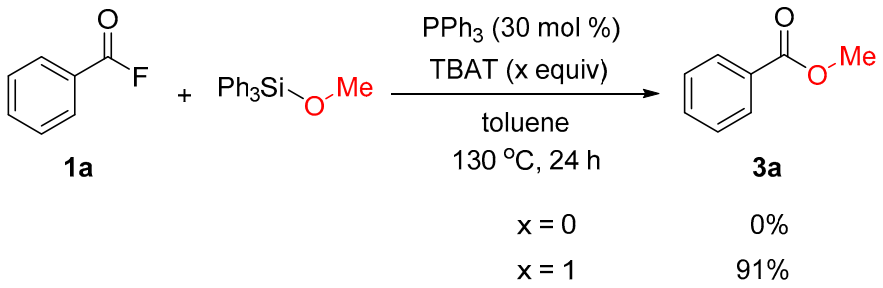
Scheme 2. (**a**) Alkoxylation of **1b** with dibenzyl ether (**2b**). (**b**) Alkoxylation of acyl fluorides **1b** with benzyl propargyl ether (**2c**). (**c**) Alkoxylation of acyl fluorides **1a** with benzyl methyl ether (**2d**). (**d**) Alkoxylation of acyl fluorides **1a** with hexyl methyl ether (**2e**).

To clarify the reaction mechanism, we performed the methoxylation in the presence of radical scavengers (Scheme 3). Consequently, in the presence of equimolar amount of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), 2,6-di-tert-butyl-4-methylphenol (BHT), or 9,10-dihydroanthracene (DHA), the reaction proceeded with comparable efficiency to that without a radical scavenger, ruling out a radical pathway of this transformation.



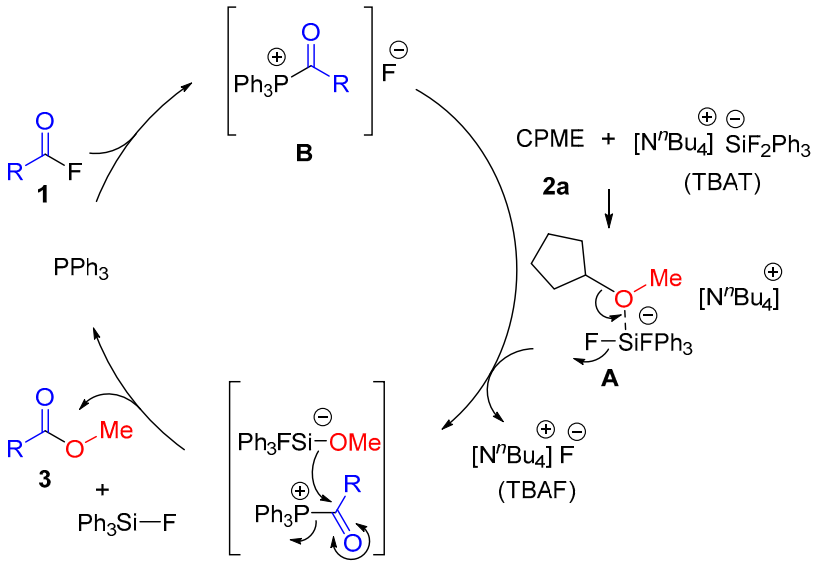
Scheme 3. Methoxylation of **1a** with **2a** in the presence of radical scavengers.

Next, we hypothesized that this PPh_3-assisted transformation might proceed via methoxytriphenylsilane (Ph_3SiOMe) as the intermediate [43]. When we carried out the reaction using Ph_3SiOMe instead of CPME under the optimized conditions (Scheme 4), no desired product **3a** was formed in the absence of TBAT, along with the recovered **1a** (91%) and Ph_3SiOMe (95%). In a sharp contrast, the reaction of **1a** with Ph_3SiOMe in the presence of TBAT, 91% of **3a** was obtained. These results indicate that the reaction of TBAT with CPME generates many nucleophilic pentacoordinate silicates [44]. Hypervalent silicates are the key organosilicon species to promote the nucleophilic substitution step, which is normally reluctant with less nucleophilic tetracoordinate organosilicon compounds [45].



Scheme 4. Methoxylation of **1a** with Ph_3SiOMe.

A plausible reaction mechanism is outlined in Scheme 5. Initially, CPME (**2a**) interacts with TBAT to form a hypervalent silicate **A**, which is supposed to cleave C–OMe bond, affording silicate $[Ph_3FSiOMe]^-$. Meanwhile, acyl fluorides **1** react with PPh_3 to generate phosphonium **B** which can be more electrophilic to participate in methoxylation by nucleophilic attack of a methoxide ion to a carbonyl group, giving the desired product **3** and Ph_3SiF which was confirmed by $^{19}F\{^1H\}$ nuclear magnetic resonance (NMR) spectrum. Although a role of a catalytic amount of PPh_3 has not been clarified, the formation of phosphonium might accelerate a nucleophilic attack of a methoxide to **1**.



Scheme 5. Proposed mechanism.

3. Experimental Sections

3.1. General

Unless otherwise noted, all the reactions were carried out under an argon atmosphere using standard Schlenk techniques. Glassware was dried in an oven (150 °C) and heated under reduced

pressure prior to use. Solvents were employed as eluents for all other routine operation, as well as dehydrated solvent were purchased from commercial suppliers and employed without any further purification. For thin layer chromatography (TLC) analyses throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. Silica gel column chromatography was carried out using Silica gel 60 N (spherical, neutral, 40–100 μm) from Kanto Chemicals Co., Inc. (Tokyo, Japan) NMR spectra (^{1}H and ^{19}F{^{1}H}) were recorded on Varian INOVA-600 (600 MHz) or Mercury-400 (400 MHz) spectrometers (Agilent Technologies International Japan, Ltd., Tokyo, Japan). Chemical shifts (δ) are in parts per million relative to $CDCl_3$ at 7.26 ppm for ^{1}H. The ^{19}F{^{1}H} NMR spectra were measured by using CCl_3F (=0.00 ppm) as an external standard. The NMR yields were determined using dibromomethane as an internal standard. The GC yields were determined by GC analysis of the crude mixture, using *n*-dodecane as an internal standard.

3.2. Experimental Method

3.2.1. Representative Procedure for the Synthesis of Acyl Fluorides from Acyl Chlorides

To a 50 mL of Schlenk tube charged with a magnetic stir bar, were successively added acyl chlorides (4 mmol), 18-crown-6 (52.9 mg, 0.2 mmol, 5 mol %), KF (2.32 g, 40 mmol, 10 equivalents), and THF (20 mL). After the reaction mixture was stirred at 40 °C for 24 h, insoluble inorganic solid (KF or KCl) was filtered, and the volatiles were removed using a rotary evaporator. The crude product was purified by bulb-to-bulb distillation to afford the corresponding acyl fluorides **1** [46].

3.2.2. Representative Procedure for the Synthesis of Acyl Fluorides from Carboxylic Acids

To a 20 mL of Schlenk tube charged with a magnetic stir bar, were successively added carboxylic acids (3.0 mmol) and CH_2Cl_2 (15 mL). After the mixture was stirred at 0 °C for 30 min, Deoxo-Fluor® reagent (608 μL, 1.1 equivalents, 3.3 mmol) was slowly added to the reaction mixture. After the reaction mixture was stirred at 0 °C for 30 min, the solution was slowly poured into saturated $NaHCO_3$, extracted with CH_2Cl_2 (3 × 15 mL), and dried over $MgSO_4$. The crude product was purified by flash chromatography on silica gel to afford the corresponding acyl fluorides **1** [47].

3.2.3. Synthesis of Methoxytriphenylsilane

To methanol (2 mL), were added chlorotriphenylsilane (1.179 g, 4 mmol) and triethylamine (607.1 mg, 6 mmol, 1.5 equiv). The reaction mixture was stirred under argon for 72 h until full conversion. Next, the reaction mixture was evaporated to dryness, dissolved in diethyl ether (100 mL), and washed with H_2O (1 × 5 mL, 2 × 2.5 mL). Organic phase was dried over sodium sulfate and evaporated. The crude product was purified by flash chromatography (*n*-hexane: EtOAc = 40:1) to afford methoxytriphenylsilane in 95% yield [48].

3.2.4. General Methods for the Synthesis of Benzyl Ethers **2b**–**2d**

To a solution of the corresponding alcohol (20 mmol) in DMF (20 mL), was added sodium hydride (1.2 g, 30 mmol, 60% in paraffin oil, 1.5 equivalents) at 0 °C under argon. After the reaction mixture was stirred for 30 min, benzyl bromide (2.95 mL, 30 mmol, 1.5 equivalents) was added to the reaction mixture at 0 °C and the solution was stirred at room temperature for 5 h. Then the reaction mixture was quenched with H_2O (10 mL) and extracted with Et_2O (20 mL × 2). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by silica-gel column chromatography (*n*-hexane: EtOAc = 40:1) to give the corresponding benzyl ether derivatives **2b**–**2d** [49].

3.2.5. Representative Procedure for Methoxylation of Acyl Fluorides **1** with CPME (**2a**)

To a 20 mL Schlenk tube containing PPh_3 (15.7 mg, 0.06 mmol, 30 mol %,) and TBAT (108 mg, 0.2 mmol, 1 equivalents), were added [1,1′-biphenyl]-4-carbonyl fluoride (**1b**) (40.0 mg, 0.2 mmol,)

and CPME (2.0 mL). Subsequently, the resulting mixture was heated at 130 °C. After 24 h, cyclopentyl methyl ether (**2a**) was removed by a rotary evaporator (for the high-boiling-point ethers were removed by bulb-to-bulb distillation), and the residue was purified by column chromatography (*n*-hexane: EtOAc = 20:1) to afford methyl [1,1′-biphenyl]-4-carboxylate (**3b**) (39 mg, 0.184 mmol) in 92% yield. Spectroscopic data for methyl esters matched with those previously reported in the literature, and ^{1}H and ^{19}F{^{1}H} NMR spectra of representative starting materials and the prepared products are shown in Supplementary Materials.

3.3. Characterization Data of Starting Materials and Products

Methoxytriphenylsilane [48]. Yield: 95% (1.1 g); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H), 7.37–7.47 (m, 9H), 7.60–7.67 (m, 6H).

((Prop-2-yn-1-yloxy)methyl)benzene (**2c**) [49]. Yield: 80% (2.34 g); colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.47 (s, 1H), 4.18 (d, *J* = 2.4 Hz, 2H), 4.62 (s, 2H), 7.29–7.33 (m, 1H), 7.34–7.39 (m, 4H).

Methyl benzoate (**3a**) [50]. Yield: 74% (20.2 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 7.42-7.47 (m, 2H), 7.53–7.58 (m, 1H), 8.02-8.07 (m, 2H).

Methyl [1,1′-biphenyl]-4-carboxylate (**3b**) [51]. Yield: 92% (39.1 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 3H), 7.40 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.61–7.68 (m, 4H), 8.11 (d, *J* = 8.2 Hz, 2H).

Methyl 4-methoxybenzoate (**3c**) [50]. Yield: 88% (29.2 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 3.88 (s, 3H), 6.91 (d, *J* = 8.9 Hz, 2H), 7.99 (d, *J* = 9.0 Hz, 2H).

Methyl 4-butoxybenzoate (**3d**) [52]. Yield: 78% (32.5 mg); colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.4 Hz, 3H), 1.46–1.53 (m, 2H), 1.78 (ddt, *J* = 9.1, 7.7, 6.5 Hz, 2H), 3.88 (s, 3H), 4.01 (s, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 7.92–8.03 (m, 2H).

Methyl 4-butylbenzoate (**3e**) [53]. Yield: 64% (24.6 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.31–1.40 (m, 2H), 1.55–1.67 (m, 2H), 2.63–2.68 (m, 2H), 3.90 (s, 3H), 7.24 (dt, *J* = 8.6, 0.6 Hz, 2H), 7.90–7.98 (m, 2H).

Methyl 4-methylbenzoate (**3f**) [50]. Yield: 90% (27.0 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.90 (s, 3H), 7.24 (dt, *J* = 8.0, 0.6 Hz, 2H), 7.89–7.97 (m, 2H).

Methyl 2-methylbenzoate (**3g**) [54]. Yield: 87% (26.2 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (s, 3H), 3.89 (s, 3H), 7.22–7.26 (m, 2H), 7.39 (td, *J* = 7.5, 1.3 Hz, 1H), 7.91 (dd, *J* = 8.2, 1.2 Hz, 1H).

Methyl 4-chlorobenzoate (**3h**) [50]. Yield: 92% (31.4 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.95–8.00 (m, 2H).

Methyl 4-nitrobenzoate (**3i**) [55]. Yield: 31% (11.3 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 8.19–8.23 (m, 2H), 8.26–8.31 (m, 2H).

Methyl 4-cyanobenzoate (**3j**) [56]. Yield: 80% (25.8 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 3H), 7.71–7.77 (m, 2H), 8.10–8.17 (m, 2H).

Methyl 4-(trifluoromethyl)benzoate (**3k**) [50]. Yield: 78% (32.0 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 3H), 7.69–7.73 (m, 2H), 8.11–8.18 (m, 2H).

Dimethyl terephthalate (**3l**) [55]. Yield: 75% (29.0 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 6H), 8.10 (s, 4H).

Methyl 2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylate (**3m**) [57]. Yield: 93% (36.1 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 4.25–4.28 (m, 2H), 4.29–4.32 (m, 2H), 6.86–6.90 (m, 1H), 7.52–7.58 (m, 2H).

Methyl 2,4,6-trimethylbenzoate (**3n**) [58]. Yield: 61% (21.8 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 9H), 3.89 (s, 3H), 6.85 (s, 2H).

Methyl 3,4,5-trimethoxybenzoate (**3o**) [59]. Yield: 70% (31.7 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (d, *J* = 1.0 Hz, 12H), 7.29 (s, 2H).

Methyl 1-naphthoate (**3p**) [54]. Yield: 73% (27.2 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 3H), 7.48–7.56 (m, 2H), 7.62 (ddd, *J* = 8.6, 6.8, 1.5 Hz, 1H), 7.89 (ddd, *J* = 8.2, 1.4, 0.7 Hz, 1H), 8.02 (ddd, *J* = 8.3, 1.4, 0.7 Hz, 1H), 8.19 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.89–8.95 (m, 1H).

Methyl 2-naphthoate (**3q**) [60]. Yield: 83% (31.0 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (s, 3H), 7.57 (dddd, *J* = 19.6, 8.1, 6.9, 1.4 Hz, 2H), 7.88 (dt, *J* = 8.0, 1.2 Hz, 2H), 7.95 (ddt, *J* = 8.0, 1.4, 0.7 Hz, 1H), 8.07 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.62 (dd, *J* = 1.6, 0.8 Hz, 1H).

Methyl anthracene-9-carboxylate (**3r**) [54]. Yield: 52% (24.6 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (s, 3H), 7.47-7.57 (m, 4H), 8.03 (dd, *J* = 8.4, 4.1 Hz, 4H), 8.54 (s, 1H).

Methyl benzofuran-2-carboxylate (**3s**) [61]. Yield: 42% (14.8 mg); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.31 (ddd, *J* = 7.9, 7.2, 0.8 Hz, 1H), 7.46 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.54 (t, *J* = 0.7 Hz, 1H), 7.59 (dq, *J* = 8.3, 0.8 Hz, 1H), 7.69 (ddd, *J* = 7.9, 1.4, 0.7 Hz, 1H).

Methyl furan-2-carboxylate (**3t**) [62]. Yield: 80% (20.2 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 6.47 (dd, *J* = 3.5, 1.8 Hz, 1H), 7.14 (dd, *J* = 3.5, 0.9 Hz, 1H), 7.54 (dd, *J* = 1.7, 0.9 Hz, 1H).

Methyl thiophene-2-carboxylate (**3u**) [54]. Yield: 70% (20 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H), 7.10 (dd, *J* = 5.0, 3.7 Hz, 1H), 7.55 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.80 (dd, *J* = 3.7, 1.3 Hz, 1H).

Methyl dodecanoate (**3v**) [63]. Yield: 45% (19.4 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85–0.90 (m, 3H), 1.23–1.30 (m, 16H), 1.62 (td, *J* = 7.1, 3.0 Hz, 2H), 2.27–2.32 (m, 2H), 3.66 (s, 3H).

Methyl (3r,5r,7r)-adamantane-1-carboxylate (**3w**) [64]. Yield: 56% (21.8 mg); white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.68–1.73 (m, 6H), 1.88–1.89 (m, 6H), 1.99–2.02 (m, 3H), 3.64 (s, 3H).

Benzyl [1,1′-biphenyl]-4-carboxylate (**3bb**) [65]. Yield: 78% (45.1 mg); white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.40 (s, 2H), 7.33–7.43 (m, 4H), 7.45–7.49 (m, 4H), 7.61–7.64 (m, 2H), 7.65–7.68 (m, 2H), 8.13–8.17 (m, 2H).

Prop-2-yn-1-yl [1,1′-biphenyl]-4-carboxylate (**3bc**) [66]. Yield: 50% (23.6 mg); white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.54 (t, *J* = 2.4 Hz, 1H), 4.96 (d, *J* = 2.5 Hz, 2H), 7.39-7.43 (m, 1H), 7.45–7.50 (m, 2H), 7.61–7.64 (m, 2H), 7.66–7.70 (m, 2H), 8.12–8.18 (m, 2H).

4. Summary

In summary, we report the PPh_3-assisted methoxylation via the regiospecific cleavage of the inert C−OMe bond in CPME. This protocol demonstrated the utility of CPME as a methoxylating reagent, good functional group tolerance, and metal-free conditions. Furthermore, the regiospecific cleavage of aliphatic ethers, even in the presence of aromatic ethers, is quite difficult to achieve by conventional reagents. We believe that our study constitutes an important contribution towards a more practical use of readily available aliphatic ethers as coupling partners. Further explorations of related transformations via C−O scission are currently underway in our laboratory.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4344/9/7/574/s1. Details of screening the amounts of TBAT and PPh3 (Table S1), the effect of PPh_3 (Table S2), and ^{1}H and ^{19}F{^{1}H} NMR spectra of representative starting materials and final products.

Author Contributions: Z.W. developed above reactions and wrote the manuscript; Z.W. and X.W. prepared starting materials and expanded the substrates scope; Y.N. supervised the project and revised the manuscript.

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